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Cost-effectiveness of total knee replacement in addition to non-surgical treatment: 2-year outcome from a randomized trial

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Abstract

Objective: To assess the 24-month cost-effectiveness of total knee replacement (TKR) plus non-surgical treatment compared to non-surgical treatment alone.

Methods: 100 adults with moderate to severe knee osteoarthritis found eligible for TKR by an orthopedic surgeon in secondary care were randomized to TKR plus 12 weeks of supervised non-surgical treatment (exercise, education, diet, insoles and pain medication) or to supervised non-surgical treatment alone. Including quality-adjusted life years (QALYs) data from baseline, 3, 6, 12 and 24 months, effectiveness was measured as change at 24 months. Healthcare costs and transfer payments were derived from national registries. Incremental health care costs, and incremental cost-effectiveness ratios (ICERs) were calculated. A probabilistic sensitivity analysis was conducted and the probability of cost-effectiveness was estimated at the 22,665 Euros/QALY threshold defined by the National Institute for Health and Care Excellence.

Results: TKR plus non-surgical treatment was more expensive (mean of 23,076 vs. 14,514 Euros over 24 months) but also more effective than non-surgical treatment alone (mean 24-month improvement in QALY of 0.195 vs. 0.056). While cost-effective in the unadjusted scenario (ICER of 18,497 Euros/QALY), TKR plus non-surgical treatment was not cost-effective compared to non-surgical treatment alone in the adjusted, base-case scenario (ICER of 32,611 Euros/QALY) with a probability of cost-effectiveness of 23.2%. When including deaths, TKR plus non-surgical treatment was still not cost-effective (ICERs of 46,277 to 64,208 Euros/QALY).

Conclusions: From a 24-month perspective, TKR plus non-surgical treatment is not cost-effective compared to non-surgical treatment alone in patients with moderate to severe knee osteoarthritis. Further research assessing the long-term cost-effectiveness of TKR is needed.

Trial registration: ClinicalTrials.gov (NCT01410409).

Keywords: Osteoarthritis; Therapeutics; Randomized controlled trial; Knee Replacement; Medical economics

Strengths and limitations of this study

- This is study is the first economic evaluation of total knee replacement that is based on a randomized trial of surgical and non-surgical treatment thereby providing highly comparable treatment groups.
- Cost data was retrieved from the Danish health registries which contain detailed, high-quality information on health sector costs, social costs, and prescription medication on individual patients, and effectiveness data was systematically and rigorously collected in the randomized trial.
- The 24-month time horizon limits conclusions on the long-term cost-effectiveness of total knee replacement

INTRODUCTION

Knee osteoarthritis (OA) is one of the leading contributors to the global burden of disease[1] with considerable pain and functional limitations for the individual[2]. The disease has been estimated to affect 250 million people worldwide[3], with total European costs estimated to be 817 billion Euros per year[4]. Over the last 20 years, the prevalence of knee OA has increased substantially[5] and is expected to continue to increase[1] and amplify the societal burden.

In patients with end-stage knee OA, total knee replacement (TKR) is considered an effective[6] and cost-effective[7] treatment. However, approximately 20% continue to have chronic pain after otherwise successful surgery[8] and, in addition, the procedure is associated with a risk of serious adverse events[9]. Furthermore, clinical guidelines reflecting high-quality evidence from recent decades highlight non-surgical treatments as an effective and less costly treatment for patients with knee OA[10]. As the number of TKR procedures performed each year has increased dramatically since the 1970s[11], with around 600,000 annual procedures in the United States alone[12], evidence of the effectiveness and cost-effectiveness of TKR in comparison to non-surgical treatments is warranted[7].

In 2015, a randomized trial assessing the effectiveness of TKR plus non-surgical treatment as compared with non-surgical treatment alone was published[13]. Being the first of its kind, the study provided high-quality evidence on the effects of TKR and, at the same time, offered a unique opportunity to study the cost-effectiveness of TKR in two highly comparable treatment groups, thereby making an important contribution to previous non-randomized analyses of TKR cost-effectiveness[7,14].

The purpose of the current study was to report the 24 months cost-effectiveness of TKR plus non-surgical treatment as compared to non-surgical treatment alone using quality-adjusted life years

(QALYs) data from the randomized trial and the unique Danish health registries which contain detailed information on health sector costs, social costs, and prescription medication on the trial participants. We hypothesized that TKR plus non-surgical treatment would be a more cost-effective procedure compared to non-surgical treatment alone due to greater improvements in quality of life counterbalancing the expected additional cost related to the surgery.

METHODS

Study design

This was a pre-planned baseline to 24 months cost-utility analysis from a parallel group assessor-blinded randomized trial (1:1 ratio) that conforms to the CHEERS statement for reporting health economic evaluations[15]. Costs were collected from a limited societal perspective (i.e. health care costs and public transfer payments), with QALYs used as the outcome measure. Individual-level data were obtained from the clinical trial and linked with data from national registries for use in the analyses.

A brief presentation of the trial methods is provided below. Full details about the process for recruitment, criteria for eligibility, the randomization procedure, allocation concealment and detailed description of the interventions have been published previously [16].

Ethics

The study was designed to follow the principles of the Declaration of Helsinki and ethics approval was obtained from the local Ethics Committee of The North Denmark Region (N-20110024) and the study was registered at ClinicalTrials.gov (NCT01410409).

Participants

One hundred patients diagnosed with symptomatic and moderate to severe radiographic knee OA considered eligible for TKR by the orthopedic surgeon were included in the study. The study had three major exclusion criteria: 1) mean pain the previous week above 60 mm on a 100-mm visual

analogue scale, 2) previous knee replacement on the same side, and 3) need for bilateral simultaneous TKR.

Setting and time horizon

Patients were recruited between September 2011 and December 2013 from one of two specialized, public outpatient clinics at Aalborg University Hospital, Denmark (Frederikshavn and Farsoe), and all patients provided informed written consent before being enrolled. To have identical time periods for the whole population, we compared resource use and costs 1 year before randomization (pre-period) to resource use and costs 2 years after randomization for each individual patient.

Randomization procedure and allocation concealment

The randomization schedule was generated a priori in permuted blocks of eight, stratified by site, and the allocation numbers were concealed in sealed, opaque envelopes prepared by an independent staff member. One research assistant at each of the two sites had access to the envelopes, opening them only after informed consent and baseline outcomes had been obtained.

Comparators

Patients were randomly assigned (1:1) to 1) undergo TKR plus 12 weeks of supervised non-surgical treatment or 2) receive only the 12 weeks of supervised non-surgical treatment.

Total knee replacement

A total cemented prosthesis with patellar resurfacing (NexGen, CR-Flex, fixed bearing or LPS-Flex, fixed bearing, Zimmer, Warsaw, Indiana, USA) was inserted by high-volume orthopedic specialists

using the surgical methods recommended by the manufacturer[17]. Surgery was performed by the surgeon in charge of the assessment at the time of recruitment.

Supervised non-surgical treatment

The 12-week individualized, non-surgical treatment program included exercise, patient education, and insoles, with dietary advice and/or pain medication prescribed if indicated. The treatments were delivered by physiotherapists and dieticians at Aalborg University Hospital, Denmark.

Exercise

The NEuroMuscular EXercise training program (NEMEX), previously found feasible in patients with moderate to severe knee OA awaiting joint replacement [18], was administered in 60-min group-based sessions twice weekly supervised by a physiotherapist. To increase long-term adherence, after 12 weeks of exercise, the patients undertook a transition period of 8 weeks where the exercise program was increasingly performed at home.

Patient education

Patient education was delivered as two 60-minute group-based educational sessions which actively engaged the patients in their treatment. The sessions focused on disease characteristics, advice about treatment and self-help. Sessions were held in groups of up to 16 patients and were facilitated by the project physiotherapist.

Dietary advice

Patients with a body mass index ≥25 at baseline had four individual 1-hour consultations with a dietician with the overall aim of reducing body weight by at least 5%[19]. The program was based on motivational interviewing[20].

Insoles

Patients received individually fitted full-length Formthotics Original Dual Medium (perforated) insoles with medial arch support (Foot Science International, Christchurch, New Zealand). A 4° lateral wedge was added to the insoles if patients had a knee-lateral-to-foot position (the knee moves over, or lateral, to the 5th toe in three or more of five trials)[21].

Pain medication

Paracetamol 1 g four times daily, ibuprofen 400 mg three times daily, and pantoprazole 20 mg daily were prescribed by the orthopedic surgeon if indicated. Prescriptions were reassessed every 3 weeks and the patients were instructed to contact the study team if they were uncertain about the need for continued pain medication.

Booster sessions

After the 12-week non-surgical program and the 8-week transition period and until the 12-month follow up, a physiotherapist phoned the patients monthly to support exercise adherence. Patients consulting the dietician were telephoned twice by the dietician to encourage dietary adherence.

Patient and public involvement

While no patients were involved in this cost-effectiveness analysis, the specific content of the non-surgical treatment was guided by feedback from patients to ensure feasibility and acceptance.

Measurement of resource use and costs

Information on resource use and costs, including health care costs and public transfer income for each patient, was retrieved from Danish national registries. In Denmark, the Danish Civil Registration System assigns every citizen a personal identification number (central personal

registration number), which allows for the linking of information between national registries at the individual level. This enables identification of the patients in the trial and calculations of costs associated with these individuals. Health care costs comprised expenses associated with inpatient services, outpatient visits, primary care services and prescription medication. Inpatient services were assessed as both including and excluding TKR surgeries during the study period. Inpatient and outpatient costs are available from the National Patient Registry (NPR), which contains information on all kinds of patient contacts including diagnoses and diagnostic and treatment procedures. Linking the data with the Danish Case Mix System (Diagnosis-Related Groups) enabled estimation of associated costs. Primary care included visits to the general practitioner, medical specialist, physiotherapist, chiropractor, laboratory work and others. Resources related to utilization of the primary care services were derived from the Danish National Health Insurance Service Register. Costs were estimated for all prescription medication; pain medication (ATC-codes N02A, N02B and M01A) and non-pain medication (i.e. anything else besides pain medication), respectively. Medication costs were calculated by multiplying the retail price with the prescribed quantity, available from the Danish Medicines Agency.

Non protocol-driven resources, e.g. costs of recruitment, were included. As both groups received the same supervised non-surgical treatment (as described above), this cost was not included for either group. The cost of the non-surgical treatment was estimated to be between 560 € (actual cost of the non-surgical treatment in the trial) to 1646 € (estimated cost of the non-surgical treatment in private practice in Denmark) per person.

To increase the international applicability of the study, costs were adjusted to 2015-equivalent price levels using the consumer price index and converted to Euros (1 € = 7.45 DKK). 1 Euro corresponded to 1.13 US dollars at the 2017 average exchange rate.

Public transfer income was calculated as the number of weeks a person was receiving sick leave pay, disability pension, early retirement and unemployment benefits (including activated persons). About half of the participants were older than 64 years (56%), and retired (age pension). This information was available from national registries from Statistics Denmark.

Measurement of effectiveness

A generic measure of health in terms of QALYs gained was used as the effectiveness measure. This is a composite measure that considers both the quantity and quality of life of an individual. The maximum achievable QALY is 1, reflecting one year of full health, whereas a QALY value of 0 reflects death. Health-related quality of life (HRQoL) was measured using the three-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), including the score on the descriptive index (ranging from −0.59 to 1.00) and the score on the visual analogue scale (ranging from 0 to 100)[22], at baseline, at 3 months, 6 months, 12 months, and at the 24 months follow-up. The baseline to 12 months EQ-5D data was previously published in the primary RCT report [13], but has not previously been used for cost-effectiveness analyses. The EQ-5D-3L has five digits measuring mobility, self-care, usual activities, pain discomfort and anxiety/depression. The descriptive index is based on a Danish "time trade-off" value set[23], which is a method used to evaluate the relative amount of time patients would be willing to sacrifice to avoid a certain poor health state. The patients completed the EQ-5D at baseline and all follow-up visits at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark.

Analytical methods

Missing data

Missing data were handled by using multiple imputation, which enables individuals with incomplete data to be included in the analysis. The underlying assumption when using multiple imputation is that data are missing at random, i.e. the probability of missing values is *not* dependent on unobserved data. Missing values occurred on utilities at 24 months, and thus, QALY values were imputed at 24 months.

Costs in the pre-period, Year 1, and Year 2

The costs of the two groups were compared by using arithmetic means for each period. The statistical significance of the difference between groups was assessed using the bootstrapped t-test.

Cost-effectiveness analyses

Regression analyses were used to estimate incremental costs and QALYs. Costs in the regression analyses only included health care costs. Because costs are normally right-skewed and QALYs left-skewed, a gamma distribution was assumed in the regression analyses. Both regression analyses were adjusted for covariates in the base-case analysis, i.e. the cost regression was adjusted for age, sex and baseline costs and the QALY regression was adjusted for age, sex and baseline QALY. Two additional scenarios were also considered: one not taking covariates into account, i.e. without adjustment (Scenario 1), and the other not considering either covariates or missing values/imputations (Scenario 2).

QALY gains or losses were calculated as the difference in QALYs from baseline to 24 months taking into account changes in utility over time, i.e. from baseline to 3 months, 6 months, 12 months and 24 months follow-up, respectively. Hence, the calculation was processed as follows:

$$QALY\ gained = (QALY\ 3\ months - QALY\ baseline) * 0.25 + (QALY\ 6\ months - QALY\ baseline) * 0.25 + (QALY\ 12\ months - QALY\ baseline) * 0.5 + (QALY\ 24\ months - QALY\ baseline)\_discounted * 1$$

Costs and effects were discounted by 3%.

Sub-analysis

A sub-analysis, including deaths during the study period, was conducted for each scenario (Base-case scenario, Scenario 1 and Scenario 2).

Sensitivity analyses

A probabilistic sensitivity analysis was carried out for each scenario in the primary analysis and the sub-analysis, respectively. The probabilistic sensitivity analysis takes into account all parameter uncertainty at once. Incremental costs and QALYs were used to simulate 10,000 random draws resulting in a scatterplot reflecting the probability of cost-effectiveness. In Denmark, no officially set willingness-to-pay threshold exists. Instead, we used a threshold of 22,665 Euros/QALY or lower corresponding to the decision rule defined by the National Institute for Health and Care Excellence (NICE) (£ 20,000)[24].

All analyses were performed using SAS 9.1.3 (SAS Institute, North Carolina, USA) and the significance level was set to 0.05.

RESULTS

Patient characteristics

The baseline characteristics of the two groups of patients and patient flow are presented in Table 1 and Fig 1, respectively.

******* PLACE TABLE 1 AND FIGURE 1 AROUND HERE *******

Out of the 100 patients randomized, 24 months follow-up data were available for 47/50 (94%) in the non-surgical group and 43/50 (86%) in the TKR plus non-surgical group. Administrative data yielded that 16 out of 50 patients (32%) from the non-surgical group had a TKR before the 24 months follow-up: 13 patients from baseline to 12 months and three patients between 12 and 24 months. Mean duration (range) from initiating the non-surgical treatment to the TKR was 8.7 (2.6 to 21.5) months. One of the 50 patients (2%) in the TKR plus non-surgical group decided not to undergo TKR anyway. One patient in the TKR plus non-surgical group had three revision surgeries ending up with the prosthesis being removed and the knee fused following a deep infection. Due to severe knee stiffness during the rehabilitation period after TKR, three patients in the TKR plus non-surgical group and one patient in the non-surgical group who had TKR later required manipulation of the knee under anesthesia. The mean follow-up time was 24.0 and 24.3 months in the TKR plus non-surgical group and the non-surgical group, respectively.

Table 2 shows health care costs and public transfer income given as weeks in the pre-period, year 1 (12 months) and year 2 (24 months), respectively. The groups had similar health care costs during the year prior to randomization (2,695 vs. 2,644 Euros). At 12 months after randomization, health care costs in the TKR plus non-surgical group were more than double those of the non-surgical

group (16,343 vs. 7,028 Euros), mostly due to the surgical procedure. Although not statistically significant, the costs in the TKR plus non-surgical group were lower at the 24 months follow-up (6,733 vs. 7,486 €) because some patients in the non-surgical group underwent TKR. No significant between-group differences were found in weeks of incurring public transfer income.

******* PLACE TABLE 2 AROUND HERE *******

The non-surgical group experienced a gain in QALYs of 0.056 from baseline to 24 months while the TKR plus non-surgical group experienced a gain of 0.195, with the largest increases in QALYs in both groups from baseline to 3 months (see Table 3 for QALY values at the different time points).

******* PLACE TABLE 3 AROUND HERE *******

Incremental costs and QALYs for each scenario are presented in Table 4. In all scenarios, TKR plus non-surgical treatment was more expensive, but also more effective in terms of QALY gain. Incremental cost-effectiveness ratios (ICERs) and the probability of cost-effectiveness at the willingness-to-pay threshold for each scenario are also presented in Table 4. In the Base-case (adjusted) scenario, TKR plus non-surgical treatment costed 32,611 Euros per QALY gained, which is above the threshold for willingness-to-pay defined by NICE (22,665 Euros/QALY). However, in the unadjusted Scenario 1 and unadjusted and without imputation of missing values (scenario 2) the ICERs were below the threshold (19,917 Euros/QALY and 18,497 Euros/QALY, respectively). The probability of cost-effectiveness of TKR plus non-surgical treatment was only 23.2% in the (adjusted) Base-case scenario but increased to 58.3% and 61.9% in Scenarios 1 and 2, respectively.

***** PLACE TABLE 4 AROUND HERE *****

Sub-analysis including deaths

Three persons died in the TKR plus non-surgical treatment group and one person in the non-surgical treatment only group. Including deaths in the analysis decreased the QALY gained in both groups. The non-surgical group experienced a gain in QALYs of 0.040 from baseline to 24 months while the TKR plus non-surgical group experienced a gain of 0.136, with the largest increases in QALYs in both groups from baseline to 3 months (see Table 5 for QALY values at the different time points).

***** PLACE TABLE 5 AROUND HERE *****

Including deaths in the regression analysis changed the estimates of incremental costs and QALYs (Table 6). TKR plus non-surgical treatment was still more expensive and more effective for all scenarios but in all three scenarios the ICER exceeded the NICE threshold. In the Base-case scenario, the ICER was more than twice as high as the threshold for willingness-to-pay defined by NICE (22,665 Euros/QALY), and the probability of cost-effectiveness was only 7.8%. In Scenario 1 and 2 the probability of cost-effectiveness was 12.4% and 13.8%, respectively.

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DISCUSSION

TKR plus non-surgical treatment was more expensive, but also more effective than non-surgical treatment alone. The cost-utility analysis demonstrated that TKR plus non-surgical treatment was

not cost-effective compared to non-surgical treatment alone from a 24-month limited societal perspective when adjusting for covariates and imputing missing values. Results were sensitive to changes, as the treatment was cost-effective in the unadjusted scenario.

Given the extensive burden of knee OA[3,4], there is considerable societal demand for evidence on cost-effective evidence-based treatments[25]. The current study provides the first direct comparison of two different treatment strategies in terms of cost-effectiveness for patients with moderate to severe symptomatic and radiographic knee OA. The cost-utility analysis was conducted alongside a randomized trial, which demonstrated that TKR plus non-surgical treatment compared to non-surgical treatment alone was twice as effective in terms of pain relief and functional improvements[13,26]. Therefore, we hypothesized that TKR would be a cost-effective procedure due to higher improvements in quality of life counterbalancing the expected additional cost related to the procedure. However, in contrast to our hypothesis, TKR plus non-surgical treatment was not found to be cost-effective compared to non-surgical treatment alone from a 24 months perspective. The cost per QALY gained exceeded the threshold defined by NICE by approximately 10,000 Euros [24]. However, without adjustment for covariates and imputation of missing values the cost per QALY was just cost-effective according to the threshold (ICER of 18,497 Euros/QALY).

Our results from the Base-case scenario contrast with findings in a recent systematic review[27]. The review included four studies examining the cost-effectiveness of TKR compared to non-surgical procedures and all four concluded that TKR was a cost-effective option. However, as opposed to our study, none of the previous studies were based on a randomized trial. Two of the previous studies used a Markov model to assess the long-term and lifetime cost-effectiveness of TKR[28,29]. The remaining two were cohort-based studies examining short-term cost-effectiveness of TKR[30,31]. A recent cohort-based cost-effectiveness analysis, not included in the systematic review, concluded that TKR was not cost-effective at a group level over 8 years, while it would be cost-effective if it

was restricted to patients with more severe symptoms[14]. In contrast, we did not find that TKR was cost-effective in addition to non-surgical treatment in patients with more severe symptoms. Our study provides the first cost-effectiveness analysis of TKR in addition to non-surgical treatment using two comparable treatment groups, thereby providing an important addition to the above mentioned non-randomized studies.

One could argue that extending the time horizon might have led to a different conclusion. If the positive effect of the surgery persists beyond the 24 months, TKR plus non-surgical treatment might eventually end up being a cost-effective option. However, as indicated by a previous report[32], improvements in symptoms might decline from 1 to 5 years after TKR, questioning the assumptions underlining a potential long-term cost-effectiveness of TKR. This is supported by the observed change in QALY over time in this trial. Both patients undergoing TKR plus non-surgical treatment and patients undergoing non-surgical treatment only experienced the greatest gain in QALYs from baseline to 3 months. The QALY remained stable until the 24 months follow-up in the TKR plus non-surgical group, while the non-surgical treatment only had a small (0.044) decrease in QALY. If TKR plus non-surgical treatment was to become cost-effective in the longer term, the decrease in QALY in the non-surgical group would need to continue. In the TKR plus non-surgical group, three people died during the period, while only one person died in the non-surgical group. When including the deaths in the analysis, TKR plus non-surgical treatment was still more effective than non-surgical treatment alone, though not as effective as in the primary analysis. This is because death corresponds to a QALY value of zero, thereby attenuating the effect of the surgery. The short time horizon and the different findings in the analysis without adjustment for covariates and imputation of missing values and the sub-analysis including deaths emphasize the susceptibility of the results and highlight the need for further analyses in the field.

Strengths and limitations

All treatments, in particular surgical treatment, are associated with placebo effects[33]. As our study did not include a sham surgery control group, we were not able to evaluate the proportion of the 24 months treatment effects attributable to contextual factors[34]. Neither did we include a group receiving TKR without the non-surgical treatment, leaving us without the possibility of evaluating the additional effect and cost of the non-surgical treatment. Furthermore, as one of the exclusion criteria was mean pain the previous week above 60 mm on a 100-mm visual analogue scale, our results might not be generalizable to patients with more severe pain at baseline. However, 42% of the patients reported pain higher than 60 mm when asked about worst pain during the previous 24 hours and the mean pain intensity in our trial of 49 on a 0-100 worst to best scale is comparable to a range of previous clinical studies evaluating pain severity prior to TKR[35-37]. The study strengths include the highly comparable treatment groups as a result of the randomization and the use of data from the unique Danish registries, which comprise data deemed to be of high quality. Linkage between these registries and the Danish Civil Registration system allowed for retrieving data on an individual level, which is a unique feature of this study.

CONCLUSIONS

From a 24 months perspective, TKR plus non-surgical treatment is not cost-effective compared to non-surgical treatment alone in patients with moderate to severe osteoarthritis eligible for TKR. However, as TKR plus non-surgical treatment was just cost-effective when not adjusting for covariates and imputing missing values, further confirmatory studies with longer follow-up are needed.

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Author contributions

Study conception and design. Skou, Kjellberg, Roos, Laursen, Arendt-Nielsen, Rasmussen, Simonsen

Recruitment of patients: Laursen, Simonsen.

Acquisition of data. Skou, Kjellberg

Analysis and interpretation of data. Skou, Kjellberg, Roos, Laursen, Arendt-Nielsen, Ibsen, Larsen, Rasmussen, Simonsen

Drafting the article or revising it critically for important intellectual content. Skou, Kjellberg, Roos, Laursen, Arendt-Nielsen, Ibsen, Larsen, Rasmussen, Simonsen

Final approval of the article. Skou, Kjellberg, Roos, Laursen, Arendt-Nielsen, Ibsen, Larsen, Rasmussen, Simonsen

All authors had full access to all the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the Funder/Sponsor

The funders played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript or decision to submit the manuscript for publication.

Conflict of interest

Dr. Roos is deputy editor of Osteoarthritis and Cartilage, the developer of the Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures and co-founder of Good Life with Osteoarthritis in Denmark (GLA:D), a not-for profit initiative hosted by the University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Dr. Skou is associate editor of Journal of Orthopaedic & Sports Physical Therapy, he has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all outside the submitted work. He is co-founder of GLA:D, a not-for profit initiative hosted by the University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Ms. Ibsen is partner in the company i2minds, who specialize in collecting, processing and analyzing data and information.

The authors report no other conflict of interest.

Data sharing

The data that support the findings of this study are available from Statistics Denmark but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors OS and ML upon reasonable request and with permission of Statistics Denmark.

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Figure legends

Fig 1. Flow of patients in the randomized controlled trial of patients eligible for total knee replacement. TKR=Total knee replacement; K-L score= Kellgren-Lawrence score; VAS=Visual Analogue Scale.

Tables

Table 1. Baseline characteristics in the randomized controlled trial of patients eligible for total knee replacement (TKR)

Baseline characteristics	TKR-+non-surgical group (n=50)	Non-surgical group (n=50)
Women, n (%)	32 (64)	30 (60)
Age (years), mean (SD)	65.8 (8.7)	67.0 (8.7)
Body Mass Index, mean (SD)	32.3 (6.2)	32.0 (5.8)
Bilateral knee pain, n (%)	18 (36)	17 (34)
Radiographic knee OA severity (Kellgren-Lawrence), n (%)		
Grade 1	0 (0)	0 (0)
Grade 2	7 (14)	5 (10)
Grade 3	21 (42)	21 (42)
Grade 4	22 (44)	24 (48)
KOOS scores		
Pain	48.6 (17.5)	49.5 (13.1)
Symptoms	54.0 (15.0)	58.3 (15.2)
ADL	55.0 (17.0)	53.5 (14.2)
Sport/Rec	18.0 (14.7)	16.7 (15.1)
QOL	32.3 (15.3)	32.7 (13.3)
$KOOS_4$	47.4 (13.4)	48.5 (11.4)
Timed Up and Go test, seconds	9.4 (2.4)	8.6 (2.1)
20-meter walk test, seconds	13.4 (3.7)	12.2 (2.6)
Used pain medication in the last week, yes n (%)	33 (67)	29 (58)

Radiographic severity: Radiographic knee osteoarthritis severity on the Kellgren-Lawrence scale; $KOOS_4$: The mean score of four out of five of the Knee injury and Osteoarthritis Outcome Score subscales covering Pain, Symptoms, Function in daily living (ADL), Sport/Rec: Function in sport and recreation. and Quality of life (QOL), with scores ranging from 0 to 100 (worst to best scale).

Table 2. Average health costs and public transfer income (measured as weeks) for the TKR plus non-surgical treatment group and the non-surgical treatment group prior to the study, at 1 and 2 follow up.

Health costs	Pre-period			Year 1 (0-12 months)			Year 2 (12-24 months)		
	TKR+non-surgical (N=50)	Non-surgical (N=50)	*p* value	TKR+non-surgical (N=50)	Non-surgical (N=50)	p-value	TKR+non-surgical (N=50)	Non-surgical (N=50)	*p* value
	€	€		€	€		€	€	
Hospital sector									
Inpatient (incl. TKRs)	515	546	1.000	13,149	4,016	<0.001*	3,845	3,881	1.000
Inpatient (excl. TKRs)	515	546	1.000	3,412	1,515	0.980	3,436	2,278	1.000
Outpatient	1,132	1,234	1.000	2,035	2,188	1.000	1,887	2,772	1.000
Primary sector, all	448	421	1.000	454	351	0.550	382	361	1.000
General practitioner	270	238	1.000	325	193	0.010*	246	201	0.900
Medical specialist	126	122	1.000	84	91	1.000	91	90	1.000
Physiotherapy	37	42	1.000	24	45	0.980	25	44	1.000
Chiropractic	3	5	1.000	5	5	1.000	6	3	1.000
Lab work and other	12	14	1.000	17	18	1.000	15	24	1.000
Prescription medication, all	599	443	1.000	704	472	0.950	620	471	1.000
Other medication	534	377	1.000	607	382	0.920	572	403	1.000
Pain medication	65	66	1.000	97	91	1.000	48	69	1.000
NSAID (N02B + M01A)	51	50	1.000	53	66	1.000	33	52	0.980
Opioids (N02A)	13	13	1.000	45	21	0.250	14	14	1.000
All health costs (incl. TKRs)	2,695	2,644	1.000	16,343	7,028	<0.001*	6,733	7,486	1.000
All health costs (excl. TKRs)	2,695	2,644	1.000	6,606	4,527	1.000	6,325	5,882	1.000
Public transfer income	**Pre-period**			**Year 1 (0-12 months)**			**Year 2 (12-24 months)**		
	TKR+non-surgical	Non-surgical	*p* value	TKR+non-surgical	Non-surgical	*p* value	TKR+non-surgical	Non-surgical	*p* value
	Weeks	Weeks		Weeks	Weeks		Weeks	Weeks	
Observations (N)	19	15		19	15		19	15	
Total public transfer income	12.9	9.2	1.000	13.2	9.1	0.980	11.6	6.8	0.910
Unemployment	5.2	1.0	0.470	3.5	0.5	0.570	5.7	0.2	0.080
Sick pay	3.1	0.0	0.140	5.3	0.7	0.200	1.7	0.8	1.000
Disability pension	0.9	1.0	1.000	1.0	1.0	1.000	1.0	1.2	1.000
Early retirement	3.8	7.1	0.930	3.4	6.9	0.950	3.2	4.7	1.000

TKR=Total knee replacement. Significant differences ($p<0.05$) are indicated with an asterisk.

Table 3. Primary analysis excluding deaths. QALYs for the TKR plus non-surgical treatment group and the non-surgical treatment group at baseline and at 3 months, 6 months, 12 months and 24 months follow-up.

	TKR+non-surgical group						Non-surgical group					
QALY	Baseline	3 months	6 months	12 months	24 months	24 months (discounted)	Baseline	3 months	6 months	12 months	24 months	24 months (discounted)
Mean	0.658	0.848	0.866	0.858	0.878	0.853	0.680	0.780	0.755	0.795	0.758	0.736
SD	0.160	0.145	0.141	0.180	0.155	0.151	0.148	0.118	0.158	0.153	0.199	0.193
Median	0.723	0.824	0.824	0.919	1.000	0.971	0.723	0.776	0.776	0.776	0.776	0.753
25th	0.655	0.776	0.776	0.774	0.723	0.702	0.655	0.723	0.718	0.723	0.723	0.702
75th	0.723	1.000	1.000	1.000	1.000	0.971	0.771	0.824	0.824	1.000	0.838	0.814
N	47	39	41	41	43	43	49	45	48	48	47	47

TKR=Total knee replacement; QALY= quality-adjusted life-years; discounted= i.e. future QALY value converted to present QALY value.

Table 4. Primary analysis excluding deaths. Incremental cost-effectiveness ratios (ICERs) and probability of cost-effectiveness of TKR plus non-surgical treatment vs non-surgical treatment alone for each scenario.

Analysis	Incremental cost	95% CI	Incremental effect	95% CI	ICER	Probability of cost-effectiveness at € 22,665
	€		QALY		€ / QALY	%
Base-case	6,070	1,857 to 10,283	0.186	0.078 to 0.294	32,611	23.2
Scenario 1	4,640	-200 to 9,480	0.233	0.088 to 0.378	19,917	58.3
Scenario 2	4,481	-668 to 9,629	0.242	0.095 to 0.390	18,497	61.9

TKR=Total knee replacement; QALY=quality-adjusted life-years; 95% CI=95% confidence interval
Base-case=Adjusted for age, sex and baseline value
Scenario 1=unadjusted; Scenario 2=unadjusted and without imputation of missing values

Table 5. Sub-analysis including deaths. QALYs for TKR plus non-surgical treatment vs non-surgical treatment alone at baseline and at 3 months, 6 months, 12 months and 24 months follow-up.

	TKR+non-surgical group						Non-surgical group					
QALY	Baseline	3 months	6 months	12 months	24 months	24 months (discounted)	Baseline	3 months	6 months	12 months	24 months	24 months (discounted)
Mean	0.661	0.845	0.865	0.861	0.821	0.797	0.681	0.780	0.757	0.795	0.742	0.721
SD	0.156	0.145	0.139	0.177	0.266	0.258	0.147	0.117	0.157	0.151	0.225	0.219
Median	0.723	0.824	0.824	0.919	1.000	0.971	0.723	0.776	0.776	0.776	0.776	0.753
25th	0.655	0.750	0.776	0.776	0.723	0.702	0.655	0.723	0.723	0.723	0.723	0.701
75th	0.723	1.000	1.000	1.000	1.000	0.971	0.771	0.824	0.824	1.000	0.831	0.807
N	50	40	42	46	46	46	50	46	49	49	48	48

TKR=Total knee replacement; QALY=quality-adjusted life-years; discounted= i.e. future QALY value converted to present QALY value.

Table 6. Sub-analysis including deaths. Incremental cost-effectiveness ratios (ICERs) and probability of cost-effectiveness of TKR plus non-surgical treatment vs non-surgical treatment alone for each scenario.

Analysis	Incremental cost	95% CI	Incremental effect	95% CI	ICER	Probability of cost-effectiveness at € 22,665
	€		QALY		€ / QALY	%
Base-case	7,880	2,894 to 12,867	0.123	-0.011 to 0.257	64,208	7.8
Scenario 1	8,585	2,442 to 14,728	0.178	0.011 to 0346	48,128	12.4
Scenario 2	8,805	2,201 to 15,409	0.190	0.023 to 0.357	46,277	13.8

TKR=Total knee replacement; QALY=quality-adjusted life-years; 95% CI=95% confidence interval
Base-case=QALY adjusted for age, sex and baseline value
Scenario 1=unadjusted; Scenario 2=unadjusted and without imputation of missing values
Dominated=Non-surgical treatment alone was both more effective and less costly than TKR plus non-surgical treatment

Supporting information captions

S1. Completed CONSORT Checklist

S2. Published study protocol

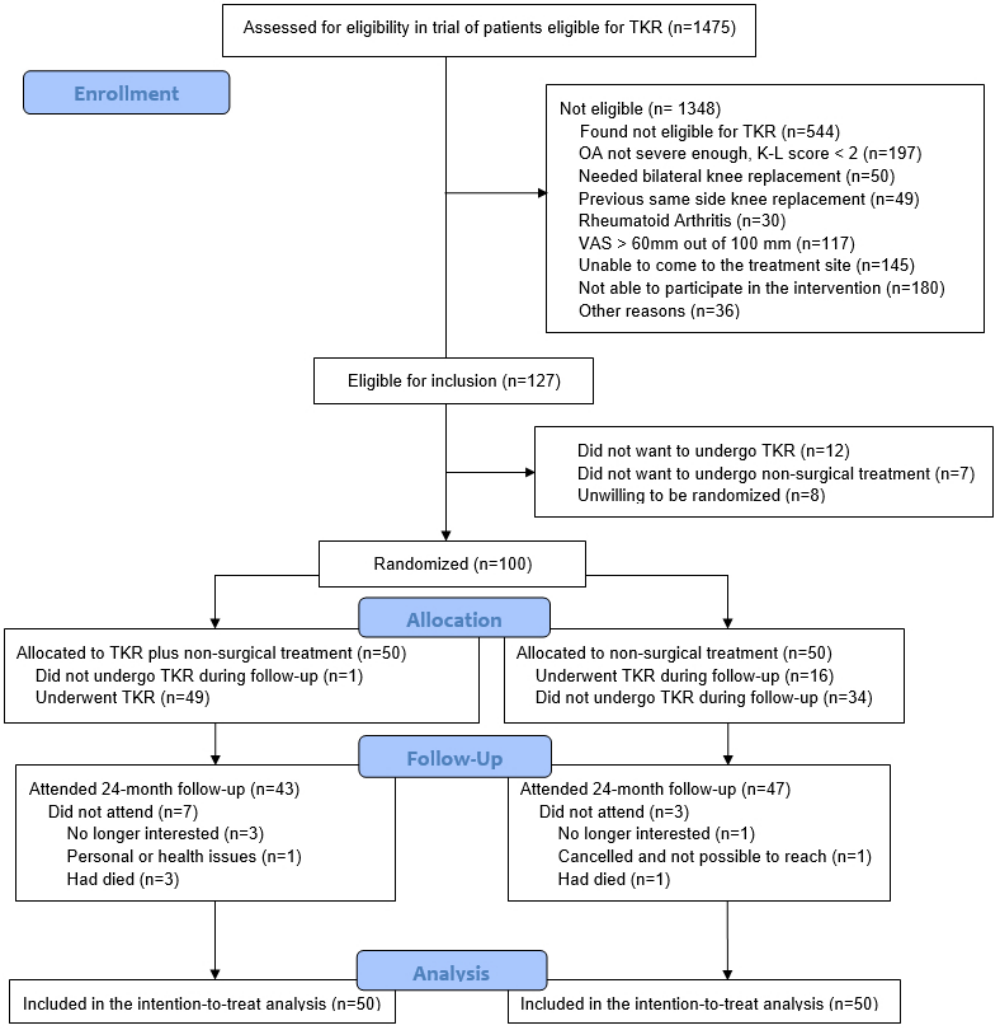

Fig 1. Flow of patients in the randomized controlled trial of patients eligible for total knee replacement. TKR=Total knee replacement; K-L score= Kellgren-Lawrence score; VAS=Visual Analogue Scale.

208x215mm (96 x 96 DPI)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6-7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6-7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	7-9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	13
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	11
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	4+6

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9-11
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7+10
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	12-13
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	12-13
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	12-13
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	14-16
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	14-16
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	14-16
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	16
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	17-19
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	21-22
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	21-22

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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BMJ Open

Cost-effectiveness of total knee replacement in addition to non-surgical treatment: 2-year outcome from a randomized trial in secondary care in Denmark

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Health economics
Keywords:	Osteoarthritis, THERAPEUTICS, Randomized controlled trial, Knee Replacement, Medical economics

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Cost-effectiveness of total knee replacement in addition to non-surgical treatment: 2-year outcome from a randomized trial in secondary care in Denmark

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Abstract

Objective: To assess the 24-month cost-effectiveness of total knee replacement (TKR) plus non-surgical treatment compared to non-surgical treatment with the option of later TKR if needed.

Methods: 100 adults with moderate to severe knee osteoarthritis found eligible for TKR by an orthopedic surgeon in secondary care were randomized to TKR plus 12 weeks of supervised non-surgical treatment (exercise, education, diet, insoles and pain medication) or to supervised non-surgical treatment alone. Including quality-adjusted life years (QALYs) data from baseline, 3, 6, 12 and 24 months, effectiveness was measured as change at 24 months. Healthcare costs and transfer payments were derived from national registries. Incremental health care costs, and incremental cost-effectiveness ratios (ICERs) were calculated. A probabilistic sensitivity analysis was conducted and the probability of cost-effectiveness was estimated at the 22,665 Euros/QALY threshold defined by the National Institute for Health and Care Excellence.

Results: TKR plus non-surgical treatment was more expensive (mean of 23,076 vs. 14,514 Euros) but also more effective than non-surgical treatment. (mean 24-month improvement in QALY of 0.195 vs. 0.056). While cost-effective in the unadjusted scenario (ICER of 18,497 Euros/QALY), TKR plus non-surgical treatment was not cost-effective compared to non-surgical treatment with the option of later TKR if needed in the adjusted (age, sex and baseline values), base-case scenario (ICER of 32,611 Euros/QALY) with a probability of cost-effectiveness of 23.2%. Including deaths, TKR plus non-surgical treatment was still not cost-effective (ICERs of 46,277 to 64,208 Euros/QALY).

Conclusions: From a 24-month perspective, TKR plus non-surgical treatment does not appear to be cost-effective compared to non-surgical treatment with the option of later TKR if needed. in

patients with moderate to severe knee osteoarthritis and moderate intensity pain in secondary care in Denmark. Results were sensitive to changes, highlighting the need for further confirmatory research also assessing the long-term cost-effectiveness of TKR.

Trial registration: ClinicalTrials.gov (NCT01410409).

Keywords: Osteoarthritis; Therapeutics; Randomized controlled trial; Knee Replacement; Medical economics

Strengths and limitations of this study

- This is the first economic evaluation of total knee replacement that is based on a randomized trial of surgical and non-surgical treatment thereby providing highly comparable treatment groups assessed and treated in a standardized and controlled setup.
- Cost data were retrieved from the Danish health registries which contain detailed, high-quality information on health sector costs, social costs, and prescription medication on individual patients, and effectiveness data were systematically and rigorously collected in the randomized trial.
- The 24-month time horizon and the selected population included limit conclusions on the long-term cost-effectiveness of total knee replacement and the generalizability to other populations
- Since nearly 1 out of 3 from the non-surgical group had TKR surgery during the 24 months, it is likely that the true additional effect and cost of TKR in addition to non-surgical treatment have been underestimated in the study.

INTRODUCTION

Knee osteoarthritis (OA) is one of the leading contributors to the global burden of disease[1] with considerable pain and functional limitations for the individual[2]. The disease has been estimated to affect 250 million people worldwide[3], with total European costs estimated to be 817 billion Euros per year[4]. Over the last 20 years, the prevalence of knee OA has increased substantially[5] and is expected to continue to increase[1] and amplify the societal burden.

In patients with end-stage knee OA, total knee replacement (TKR) is considered an effective[6] and cost-effective[7] treatment. However, approximately 20% continue to have chronic pain after otherwise successful surgery[8] and, in addition, the procedure is associated with a risk of serious adverse events[9]. Furthermore, clinical guidelines reflecting high-quality evidence from recent decades highlight non-surgical treatments as an effective and less costly treatment for patients with knee OA[10]. As the number of TKR procedures performed each year has increased dramatically since the 1970s[11], with around 600,000 annual procedures in the United States alone[12], evidence of the effectiveness and cost-effectiveness of TKR in comparison to non-surgical treatments is warranted[7].

In 2015, a randomized trial assessing the effectiveness of TKR plus non-surgical treatment as compared with non-surgical treatment alone was published[13]. Being the first of its kind, the study provided high-quality evidence on the effects of TKR and, at the same time, offered a unique opportunity to study the cost-effectiveness of TKR in two highly comparable treatment groups, thereby making an important contribution to previous non-randomized analyses of TKR cost-effectiveness[7,14].

The purpose of the current study was to report the 24 months cost-effectiveness of TKR plus non-surgical treatment as compared to non-surgical treatment with the option of later TKR if needed

using quality-adjusted life years (QALYs) data from the randomized trial and the unique Danish health registries which contain detailed information on health sector costs, social costs, and prescription medication on the trial participants. We hypothesized that TKR plus non-surgical treatment would be a more cost-effective procedure compared to non-surgical treatment with the option of later TKR if needed at 24 months due to greater improvements in quality of life counterbalancing the expected additional cost related to the surgery.

METHODS

Study design

This was a pre-planned baseline to 24 months cost-utility analysis from a parallel group assessor-blinded randomized trial (1:1 ratio) that conforms to the CHEERS statement for reporting health economic evaluations[15]. Costs were collected from a health system perspective, with QALYs used as the outcome measure. Individual-level data were obtained from the clinical trial and linked with data from national registries for use in the analyses.

A brief presentation of the trial methods is provided below. Full details about the process for recruitment, criteria for eligibility, the randomization procedure, allocation concealment and detailed description of the interventions have been published previously [16].

Ethics

The study was designed to follow the principles of the Declaration of Helsinki and ethics approval was obtained from the local Ethics Committee of The North Denmark Region (N-20110024) and the study was registered at ClinicalTrials.gov (NCT01410409).

Participants

One hundred patients diagnosed with symptomatic and moderate to severe radiographic knee OA considered eligible for TKR by the orthopedic surgeon were included in the study. The study had three major exclusion criteria: 1) mean pain the previous week above 60 mm on a 100-mm visual analogue scale, 2) previous knee replacement on the same side, and 3) need for bilateral simultaneous TKR.

Setting and time horizon

Patients were recruited between September 2011 and December 2013 from one of two specialized, public outpatient clinics at Aalborg University Hospital, Denmark (Frederikshavn and Farsoe), and all patients provided informed written consent before being enrolled. To have identical time periods for the whole population, we compared resource use and costs 1 year before randomization (pre-period) to resource use and costs 2 years after randomization for each individual patient.

Randomization procedure and allocation concealment

The randomization schedule was generated a priori in permuted blocks of eight, stratified by site, and the allocation numbers were concealed in sealed, opaque envelopes prepared by an independent staff member. One research assistant at each of the two sites had access to the envelopes, opening them only after informed consent and baseline outcomes had been obtained.

Comparators

Patients were randomly assigned (1:1) to 1) undergo TKR plus 12 weeks of supervised non-surgical treatment or 2) receive only the 12 weeks of supervised non-surgical treatment.

Total knee replacement

A total cemented prosthesis with patellar resurfacing (NexGen, CR-Flex, fixed bearing or LPS-Flex, fixed bearing, Zimmer, Warsaw, Indiana, USA) was inserted by high-volume orthopedic specialists (a surgeon performing +100 TKRs/year) using the surgical methods recommended by the manufacturer[17]. Surgery was performed by the surgeon in charge of the assessment at the time of recruitment.

Supervised non-surgical treatment

The 12-week individualized, non-surgical treatment program included exercise, patient education, and insoles, with dietary advice and/or pain medication prescribed if indicated. The treatments were delivered by physiotherapists and dieticians at Aalborg University Hospital, Denmark.

Exercise

The NEuroMuscular EXercise training program (NEMEX), previously found feasible in patients with moderate to severe knee OA awaiting joint replacement [18], was administered in 60-min group-based sessions twice weekly supervised by a physiotherapist. To increase long-term adherence, after 12 weeks of exercise, the patients undertook a transition period of 8 weeks where the exercise program was increasingly performed at home.

Patient education

Patient education was delivered as two 60-minute group-based educational sessions which actively engaged the patients in their treatment. The sessions focused on disease characteristics, advice about treatment and self-help. Sessions were held in groups of up to 16 patients and were facilitated by the project physiotherapist.

Dietary advice

Patients with a body mass index ≥25 at baseline had four individual 1-hour consultations with a dietician with the overall aim of reducing body weight by at least 5%[19]. The program was based on motivational interviewing[20].

Insoles

Patients received individually fitted full-length Formthotics Original Dual Medium (perforated) insoles with medial arch support (Foot Science International, Christchurch, New Zealand). A 4° lateral wedge was added to the insoles if patients had a knee-lateral-to-foot position (the knee moves over, or lateral, to the 5th toe in three or more of five trials)[21].

Pain medication

Paracetamol 1 g four times daily, ibuprofen 400 mg three times daily, and pantoprazole 20 mg daily were prescribed by the orthopedic surgeon if indicated. Prescriptions were reassessed every 3 weeks and the patients were instructed to contact the study team if they were uncertain about the need for continued pain medication.

Booster sessions

After the 12-week non-surgical program and the 8-week transition period and until the 12-month follow up, a physiotherapist phoned the patients monthly to support exercise adherence. Patients consulting the dietician were telephoned twice by the dietician to encourage dietary adherence.

Patient and public involvement

While no patients were involved in this cost-effectiveness analysis, the specific content of the non-surgical treatment was guided by feedback from patients to ensure feasibility and acceptance.

Measurement of resource use and costs

Information on resource use and costs, including health care costs and public transfer income for each patient, was retrieved from Danish national registries up until the 24-month follow-up. In Denmark, the Danish Civil Registration System assigns every citizen a personal identification number (central personal registration number), which allows for the linking of information between national registries at the individual level. This enables identification of the patients in the trial and

calculations of costs associated with these individuals. Health care costs comprised expenses associated with inpatient services, outpatient visits, primary care services and prescription medication. Inpatient services were assessed as both including and excluding TKR surgeries during the study period. Data on inpatient and outpatient services are available from the National Patient Registry (NPR), which contains information on all kinds of patient contacts including diagnoses and diagnostic and treatment procedures. Linking data on resource use from NPR with the Danish Case Mix System (Diagnosis-Related Groups) enabled estimation of associated costs. Primary care included visits to the general practitioner, medical specialist, physiotherapist, chiropractor, laboratory work and others. Resources related to utilization of the primary care services were derived from the Danish National Health Insurance Service Register. Costs were estimated for all prescription medication; pain medication (ATC-codes N02A, N02B and M01A) and non-pain medication (i.e. anything else besides pain medication), respectively. Medication costs were calculated by multiplying the retail price with the prescribed quantity, available from the Danish Medicines Agency.

Non protocol-driven resources, e.g. costs of recruitment, were not included. As both groups received the same supervised non-surgical treatment (as described above), this cost was not included for either group. The cost of the non-surgical treatment was estimated to be between 560 € (actual cost of the non-surgical treatment in the trial) to 1646 € (estimated cost of the non-surgical treatment in private practice in Denmark) per person.

To increase the international applicability of the study, costs were adjusted to 2015-equivalent price levels using the consumer price index and converted to Euros (1 € = 7.45 DKK). 1 Euro corresponded to 1.13 US dollars at the 2017 average exchange rate.

Public transfer income was calculated as the number of weeks a person was receiving sick leave pay, disability pension, early retirement and unemployment benefits (including activated persons). About half of the participants were older than 64 years (56%), and retired (age pension). This information was available from national registries from Statistics Denmark.

Measurement of effectiveness

A generic measure of health in terms of QALYs gained was used as the effectiveness measure of effects up until the 24-month follow-up. This is a composite measure that considers both the quantity and quality of life of an individual. The maximum achievable health utility is 1 and hence, a QALY value of 1 reflects one year of full health, whereas a QALY value of 0 reflects death. Health-related quality of life (HRQoL; health utility) was measured using the three-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), including the score on the descriptive index (ranging from −0.59 to 1.00) and the score on the visual analogue scale (ranging from 0 to 100)[22], at baseline, at 3 months, 6 months, 12 months, and at the 24 months follow-up. The baseline to 12 months EQ-5D data were previously published in the primary RCT report [13], but has not previously been used for cost-effectiveness analyses. The EQ-5D-3L has five digits measuring mobility, self-care, usual activities, pain discomfort and anxiety/depression. The descriptive index is based on a Danish "time trade-off" value set[23], which is a method used to evaluate the relative amount of time patients would be willing to sacrifice to avoid a certain poor health state. The patients completed the EQ-5D at baseline and all follow-up visits at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark.

Analytical methods

Missing data

Missing data were handled by using multiple imputation, which enables individuals with incomplete data to be included in the analysis. The underlying assumption when using multiple imputation is that data are missing at random, i.e. the probability of missing values is *not* dependent on unobserved data. Missing data were imputed using multiple imputation in SAS, and the assumption of data missing at random was also tested and confirmed in SAS. Missing utility values occurred at 3, 6, 12 and 24 months, and thus, utilities were imputed at these time points using utilities from available time points.

Costs in the pre-period, Year 1, and Year 2

The costs of the two groups were compared by using arithmetic means for each period. The statistical significance of the difference between groups was assessed using the bootstrapped t-test.

Cost-effectiveness analyses

Regression analyses were used to estimate incremental costs and QALYs and data were analyzed in accordance with intention-to-treat principle. Costs in the regression analyses only included health care costs. Because costs are normally right-skewed and QALYs left-skewed, a gamma distribution was assumed in the regression analyses. Both regression analyses were adjusted for covariates in the base-case analysis, i.e. the cost regression was adjusted for age, sex and baseline costs and the QALY regression was adjusted for age, sex and baseline QALY. Two additional scenarios were also considered: one not taking covariates into account, i.e. without adjustment (Scenario 1), and the other not considering either covariates or missing values/imputations (Scenario 2).

QALY gains or losses were calculated as the area under the curve, i.e. taking changes in utility over time into account.

Costs and effects were discounted by 3%.

Sub-analysis

A sub-analysis, including deaths during the study period, was conducted for each scenario (Base-case scenario, Scenario 1 and Scenario 2).

Sensitivity analyses

A probabilistic sensitivity analysis was carried out for each scenario in the primary analysis and the sub-analysis, respectively. The probabilistic sensitivity analysis takes into account all parameter uncertainty at once. Incremental costs and QALYs were used to simulate 10,000 random draws resulting in a scatterplot reflecting the probability of cost-effectiveness. In Denmark, no officially set willingness-to-pay threshold exists. Instead, we used a threshold of 22,665 Euros/QALY or lower corresponding to the decision rule defined by the National Institute for Health and Care Excellence (NICE) (£ 20,000)[24].

A cost-effectiveness acceptability curve illustrating the cost-effectiveness at different thresholds and a cost-effectiveness plane showing the uncertainty around the ICER were produced (both excl. deaths).

All analyses were performed using SAS 9.1.3 (SAS Institute, North Carolina, USA) and the significance level was set to 0.05.

RESULTS

Patient characteristics

The baseline characteristics of the two groups of patients and patient flow are presented in Table 1 and Fig 1, respectively. Below 8% (n=117) of patients assessed for eligibility were excluded due to pain intensity above 60mm out of 100mm.

******* PLACE TABLE 1 AND FIGURE 1 AROUND HERE *******

Out of the 100 patients randomized, 24 months follow-up data were available for 47/50 (94%) in the non-surgical group and 43/50 (86%) in the TKR plus non-surgical group. Administrative data yielded that 16 out of 50 patients (32%) from the non-surgical group had a TKR before the 24 months follow-up: 13 patients from baseline to 12 months and three patients between 12 and 24 months. Mean duration (range) from initiating the non-surgical treatment to the TKR was 8.7 (2.6 to 21.5) months. One of the 50 patients (2%) in the TKR plus non-surgical group decided not to undergo TKR anyway. One patient in the TKR plus non-surgical group had three revision surgeries ending up with the prosthesis being removed and the knee fused following a deep infection. Due to severe knee stiffness during the rehabilitation period after TKR, three patients in the TKR plus non-surgical group and one patient in the non-surgical group who had TKR later required manipulation of the knee under anesthesia. The mean follow-up time was 24.0 and 24.3 months in the TKR plus non-surgical group and the non-surgical group, respectively.

Table 2 shows health care costs and public transfer income given as weeks in the pre-period, year 1

(12 months) and year 2 (24 months), respectively. The groups had similar health care costs during the year prior to randomization (2,695 vs. 2,644 Euros). At 12 months after randomization, health care costs in the TKR plus non-surgical group were more than double those of the non-surgical group (16,343 vs. 7,028 Euros), mostly due to the surgical procedure. Although not statistically significant, the costs in the TKR plus non-surgical group were lower at the 24 months follow-up (6,733 vs. 7,486 €) because some patients in the non-surgical group underwent TKR. No significant between-group differences were found in weeks of incurring public transfer income.

******* PLACE TABLE 2 AROUND HERE *******

The non-surgical group experienced a gain in health utilities of 0.056 from baseline to 24 months while the TKR plus non-surgical group experienced a gain of 0.195, with the largest increases in health utilities in both groups from baseline to 3 months (see Table 3 for utility values at the different time points).

******* PLACE TABLE 3 AROUND HERE *******

Incremental costs and QALYs for each scenario are presented in Table 4. In all scenarios, TKR plus non-surgical treatment was more expensive, but also more effective in terms of QALY gain. Incremental cost-effectiveness ratios (ICERs) and the probability of cost-effectiveness at the willingness-to-pay threshold for each scenario are also presented in Table 4. In the Base-case (adjusted) scenario, TKR plus non-surgical treatment costed 32,611 Euros per QALY gained, which is above the threshold for willingness-to-pay defined by NICE (22,665 Euros/QALY). However, in the unadjusted Scenario 1 and unadjusted and without imputation of missing values (scenario 2) the ICERs were below the threshold (19,917 Euros/QALY and 18,497 Euros/QALY, respectively). The

probability of cost-effectiveness of TKR plus non-surgical treatment was only 23.2% in the (adjusted) Base-case scenario but increased to 58.3% and 61.9% in Scenarios 1 and 2, respectively.

******* PLACE TABLE 4 AROUND HERE *******

Cost-effectiveness acceptability curve showing the probability of TKR plus non-surgical treatment being cost-effective at different thresholds is presented in Figure 2. The probability of cost-effectiveness was below 60% up until a threshold of approx. 40,000 Euros/QALY. To reach a probability of cost-effectiveness greater than 90%, a threshold of minimum 60,000 Euros/QALY was needed.

******* PLACE FIGURE 2 AROUND HERE *******

Cost-effectiveness plane illustrating the uncertainty around the ICER is presented in Supplementary appendix figure 1.

Sub-analysis including deaths

Three persons died in the TKR plus non-surgical treatment group and one person in the non-surgical treatment only group. Including deaths in the analysis decreased the QALY gained in both groups. The non-surgical group experienced a gain in health utilities of 0.040 from baseline to 24 months while the TKR plus non-surgical group experienced a gain of 0.136, with the largest increases in health utilities in both groups from baseline to 3 months (see Supplementary appendix table 1 for utility values at the different time points).

Including deaths in the regression analysis changed the estimates of incremental costs and QALYs (Supplementary appendix table 2). TKR plus non-surgical treatment was still more expensive and more effective for all scenarios but in all three scenarios the ICER exceeded the NICE threshold. In

the Base-case scenario, the ICER was more than twice as high as the threshold for willingness-to-pay defined by NICE (22,665 Euros/QALY), and the probability of cost-effectiveness was only 7.8%. In Scenario 1 and 2 the probability of cost-effectiveness was 12.4% and 13.8%, respectively.

DISCUSSION

TKR plus non-surgical treatment appear to be more expensive, but also more effective than non-surgical treatment after 24 months in patients with knee OA eligible for TKR and moderate intensity pain. The cost-utility analysis suggested that TKR plus non-surgical treatment was not cost-effective compared to non-surgical treatment with the option of later TKR if needed from a 24-month health system perspective in secondary care in Denmark when adjusting for covariates and imputing missing values. Results were sensitive to changes, as the treatment was cost-effective in the unadjusted scenario, highlighting the need for further research with 5 to 10-year time horizons.

Given the extensive burden of knee OA[3,4], there is considerable societal demand for evidence on cost-effective evidence-based treatments[25]. The current study provides the first direct comparison of two different treatment strategies in terms of cost-effectiveness after 24 months for patients with moderate to severe symptomatic and radiographic knee OA. The cost-utility analysis was conducted alongside a randomized trial, which demonstrated that TKR plus non-surgical treatment compared to non-surgical treatment was twice as effective in terms of pain relief and functional improvements after 12 and 24 months[13,26]. Therefore, we hypothesized that TKR would be a cost-effective procedure after 24 months due to higher improvements in quality of life counterbalancing the expected additional cost related to the procedure. However, in contrast to our hypothesis, TKR plus non-surgical treatment was not found to be cost-effective compared to non-surgical treatment with the option of later TKR if needed from a 24 months perspective in secondary care in Denmark. The cost per QALY gained exceeded the threshold defined by NICE by approximately 10,000 Euros [24]. However, without adjustment for covariates and imputation of missing values the cost per QALY was just cost-effective according to the threshold (ICER of 18,497 Euros/QALY).

Our results from the Base-case scenario contrast with findings in a recent systematic review[27]. The review included four studies examining the cost-effectiveness of TKR compared to non-surgical procedures and all four concluded that TKR was a cost-effective option. However, as opposed to

our study, none of the previous studies were based on a randomized trial and the content of the non-surgical treatment was neither as comprehensive nor aligned with evidence-based recommendations as the non-surgical treatment in our study. Two of the previous studies used a Markov model to assess the long-term and lifetime cost-effectiveness of TKR[28,29]. The remaining two were cohort-based studies examining short-term cost-effectiveness of TKR[30,31]. A recent cohort-based cost-effectiveness analysis, not included in the systematic review, concluded that TKR was not cost-effective at a group level over 8 years, while it would be cost-effective if it was restricted to patients with more severe symptoms[14]. In contrast, we did not find that TKR was cost-effective in addition to non-surgical treatment after 24 months in patients with moderate intensity pain. Our study provides the first cost-effectiveness analysis of TKR in addition to recommended non-surgical treatment using two comparable treatment groups, thereby providing an important addition to the above mentioned non-randomized studies.

One could argue that extending the time horizon might have led to a different conclusion. If the positive effect of the surgery persists beyond the 24 months, TKR plus non-surgical treatment might eventually end up being a cost-effective option. Though the mean utility fluctuates slightly over time in both groups, there seems to be an overall improvement in the TKR plus non-surgical group as compared to non-surgical treatment only. Assuming that this between-group difference is at least maintained and a potential increased cost in the non-surgical group due to future TKR surgery, this could improve the cost-effectiveness ratios in favor of TKR plus non-surgical treatment. However, as indicated by a previous report[32], improvements in symptoms might decline from 1 to 5 years after TKR, questioning the assumptions underlining a potential long-term cost-effectiveness of TKR. In the TKR plus non-surgical group, three people died during the period, while only one person died in the non-surgical group. When including the deaths in the analysis, TKR plus non-surgical treatment was still more effective than non-surgical treatment, though not as effective as in

the primary analysis. This is because death corresponds to a QALY value of zero, thereby attenuating the effect of the surgery.

Strengths and limitations

All treatments, in particular surgical treatment, are associated with placebo effects[33]. As our study did not include a sham surgery control group, we were not able to evaluate the proportion of the 24 months treatment effects attributable to contextual factors[34]. Neither did we include a group receiving TKR without the non-surgical treatment, leaving us without the possibility of evaluating the additional effect and cost of the non-surgical treatment. As 32% from the non-surgical group had TKR surgery during the 24 months, it is likely that the true additional effect and cost of TKR have been underestimated in the study. Furthermore, as one of the exclusion criteria was mean pain the previous week above 60 mm on a 100-mm visual analogue scale, our results might not be generalizable to patients with more severe pain at baseline. However, 42% of the patients reported pain higher than 60 mm when asked about worst pain during the previous 24 hours and the mean pain intensity in our trial of 49 on a 0-100 worst to best scale is comparable to a range of previous clinical studies evaluating pain severity prior to TKR[35-37]. Additionally, the effects from non-surgical treatments, such as exercise, does not seem to be associated with pain severity at baseline[38], suggesting that the non-surgical treatment might be as effective in patients with more severe pain. The short time horizon and the different findings in the analysis without adjustment for covariates and imputation of missing values and the sub-analysis including deaths emphasize the susceptibility of the results and highlight the need for further analyses in the field including follow-ups at 5-10 years. The study strengths include the highly comparable treatment groups as a result of the randomization and the use of data from the unique Danish registries, which comprise data deemed

to be of high quality. Linkage between these registries and the Danish Civil Registration system allowed for retrieving data on an individual level, which is a unique feature of this study.

CONCLUSIONS

From a 24 months perspective in secondary care in Denmark, TKR plus non-surgical treatment does not appear to be cost-effective compared to non-surgical treatment with the option of later TKR if needed in patients with moderate to severe osteoarthritis and moderate intensity pain, eligible for TKR. However, as TKR plus non-surgical treatment was just cost-effective when not adjusting for covariates and not imputing missing values, further confirmatory studies with longer follow-up are needed.

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Author contributions

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Final approval of the article. Skou, Kjellberg, Roos, Laursen, Arendt-Nielsen, Ibsen, Larsen, Rasmussen, Simonsen

All authors had full access to all the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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The funders played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript or decision to submit the manuscript for publication.

Conflict of interest

Dr. Roos is deputy editor of Osteoarthritis and Cartilage, the developer of the Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures and co-founder of Good Life with Osteoarthritis in Denmark (GLA:D), a not-for profit initiative hosted by the University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Dr. Skou is associate editor of Journal of Orthopaedic & Sports Physical Therapy, he has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all outside the submitted work. He is co-founder of GLA:D, a not-for profit initiative hosted by the University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Ms. Ibsen is partner in the company i2minds, who specialize in collecting, processing and analyzing data and information.

The authors report no other conflict of interest.

Data sharing

The data that support the findings of this study are available from Statistics Denmark but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors OS and ML upon reasonable request and with permission of Statistics Denmark.

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Figure legends

Fig 1. Flow of patients in the randomized controlled trial of patients eligible for total knee replacement. TKR=Total knee replacement; K-L score= Kellgren-Lawrence score; VAS=Visual Analogue Scale.

Fig 2. Cost-effectiveness acceptability curve illustrating the probability of TKR plus non-surgical treatment being cost-effective at different thresholds (excl. deaths).

Tables

Table 1. Baseline characteristics in the randomized controlled trial of patients eligible for total knee replacement (TKR)

Baseline characteristics	TKR-+non-surgical group (n=50)	Non-surgical group (n=50)
Women, n (%)	32 (64)	30 (60)
Age (years), mean (SD)	65.8 (8.7)	67.0 (8.7)
Body Mass Index, mean (SD)	32.3 (6.2)	32.0 (5.8)
Bilateral knee pain, n (%)	18 (36)	17 (34)
Radiographic knee OA severity (Kellgren-Lawrence), n (%)		
Grade 1	0 (0)	0 (0)
Grade 2	7 (14)	5 (10)
Grade 3	21 (42)	21 (42)
Grade 4	22 (44)	24 (48)
KOOS scores		
Pain	48.6 (17.5)	49.5 (13.1)
Symptoms	54.0 (15.0)	58.3 (15.2)
ADL	55.0 (17.0)	53.5 (14.2)
Sport/Rec	18.0 (14.7)	16.7 (15.1)
QOL	32.3 (15.3)	32.7 (13.3)
$KOOS_4$	47.4 (13.4)	48.5 (11.4)
Timed Up and Go test, seconds	9.4 (2.4)	8.6 (2.1)
20-meter walk test, seconds	13.4 (3.7)	12.2 (2.6)
Used pain medication in the last week, yes n (%)	33 (67)	29 (58)

Radiographic severity: Radiographic knee osteoarthritis severity on the Kellgren-Lawrence scale; $KOOS_4$: The mean score of four out of five of the Knee injury and Osteoarthritis Outcome Score subscales covering Pain, Symptoms, Function in daily living (ADL), Sport/Rec: Function in sport and recreation. and Quality of life (QOL), with scores ranging from 0 to 100 (worst to best scale).

Table 2. Average health costs and public transfer income (measured as weeks) for the TKR plus non-surgical treatment group and the non-surgical treatment group prior to the study, at 1 and 2 follow up.

Health costs	Pre-period			Year 1 (0-12 months)			Year 2 (12-24 months)		
	TKR+non-surgical (N=50)	Non-surgical (N=50)	*p* value	TKR+non-surgical (N=50)	Non-surgical (N=50)	p-value	TKR+non-surgical (N=50)	Non-surgical (N=50)	*p* value
	€	€		€	€		€	€	
Hospital sector									
Inpatient (incl. TKRs)	515	546	1.000	13,149	4,016	<0.001*	3,845	3,881	1.000
Inpatient (excl. TKRs)	515	546	1.000	3,412	1,515	0.980	3,436	2,278	1.000
Outpatient	1,132	1,234	1.000	2,035	2,188	1.000	1,887	2,772	1.000
Primary sector, all	448	421	1.000	454	351	0.550	382	361	1.000
General practitioner	270	238	1.000	325	193	0.010*	246	201	0.900
Medical specialist	126	122	1.000	84	91	1.000	91	90	1.000
Physiotherapy	37	42	1.000	24	45	0.980	25	44	1.000
Chiropractic	3	5	1.000	5	5	1.000	6	3	1.000
Lab work and other	12	14	1.000	17	18	1.000	15	24	1.000
Prescription medication, all	599	443	1.000	704	472	0.950	620	471	1.000
Other medication	534	377	1.000	607	382	0.920	572	403	1.000
Pain medication	65	66	1.000	97	91	1.000	48	69	1.000
NSAID (N02B + M01A)	51	50	1.000	53	66	1.000	33	52	0.980
Opioids (N02A)	13	13	1.000	45	21	0.250	14	14	1.000
All health costs (incl. TKRs)	2,695	2,644	1.000	16,343	7,028	<0.001*	6,733	7,486	1.000
All health costs (excl. TKRs)	2,695	2,644	1.000	6,606	4,527	1.000	6,325	5,882	1.000
Public transfer income	**Pre-period**			**Year 1 (0-12 months)**			**Year 2 (12-24 months)**		
	TKR+non-surgical	Non-surgical	*p* value	TKR+non-surgical	Non-surgical	*p* value	TKR+non-surgical	Non-surgical	*p* value
	Weeks	Weeks		Weeks	Weeks		Weeks	Weeks	
Observations (N)	19	15		19	15		19	15	
Total public transfer income	12.9	9.2	1.000	13.2	9.1	0.980	11.6	6.8	0.910
Unemployment	5.2	1.0	0.470	3.5	0.5	0.570	5.7	0.2	0.080
Sick pay	3.1	0.0	0.140	5.3	0.7	0.200	1.7	0.8	1.000
Disability pension	0.9	1.0	1.000	1.0	1.0	1.000	1.0	1.2	1.000
Early retirement	3.8	7.1	0.930	3.4	6.9	0.950	3.2	4.7	1.000

TKR=Total knee replacement. Significant differences ($p<0.05$) are indicated with an asterisk.

Table 3. Primary analysis excluding deaths. Health utilities for the TKR plus non-surgical treatment group and the non-surgical treatment group at baseline and at 3 months, 6 months, 12 months and 24 months follow-up.

	TKR+non-surgical group						Non-surgical group					
Utilities	Baseline	3 months	6 months	12 months	24 months	24 months (discounted)	Baseline	3 months	6 months	12 months	24 months	24 months (discounted)
Mean	0.658	0.848	0.866	0.858	0.878	0.853	0.680	0.780	0.755	0.795	0.758	0.736
SD	0.160	0.145	0.141	0.180	0.155	0.151	0.148	0.118	0.158	0.153	0.199	0.193
Median	0.723	0.824	0.824	0.919	1.000	0.971	0.723	0.776	0.776	0.776	0.776	0.753
25th	0.655	0.776	0.776	0.774	0.723	0.702	0.655	0.723	0.718	0.723	0.723	0.702
75th	0.723	1.000	1.000	1.000	1.000	0.971	0.771	0.824	0.824	1.000	0.838	0.814
N	47	39	41	41	43	43	49	45	48	48	47	47

TKR=Total knee replacement; QALY= quality-adjusted life-years; discounted= i.e. future **health utilities** value converted to present **health utilities** value.

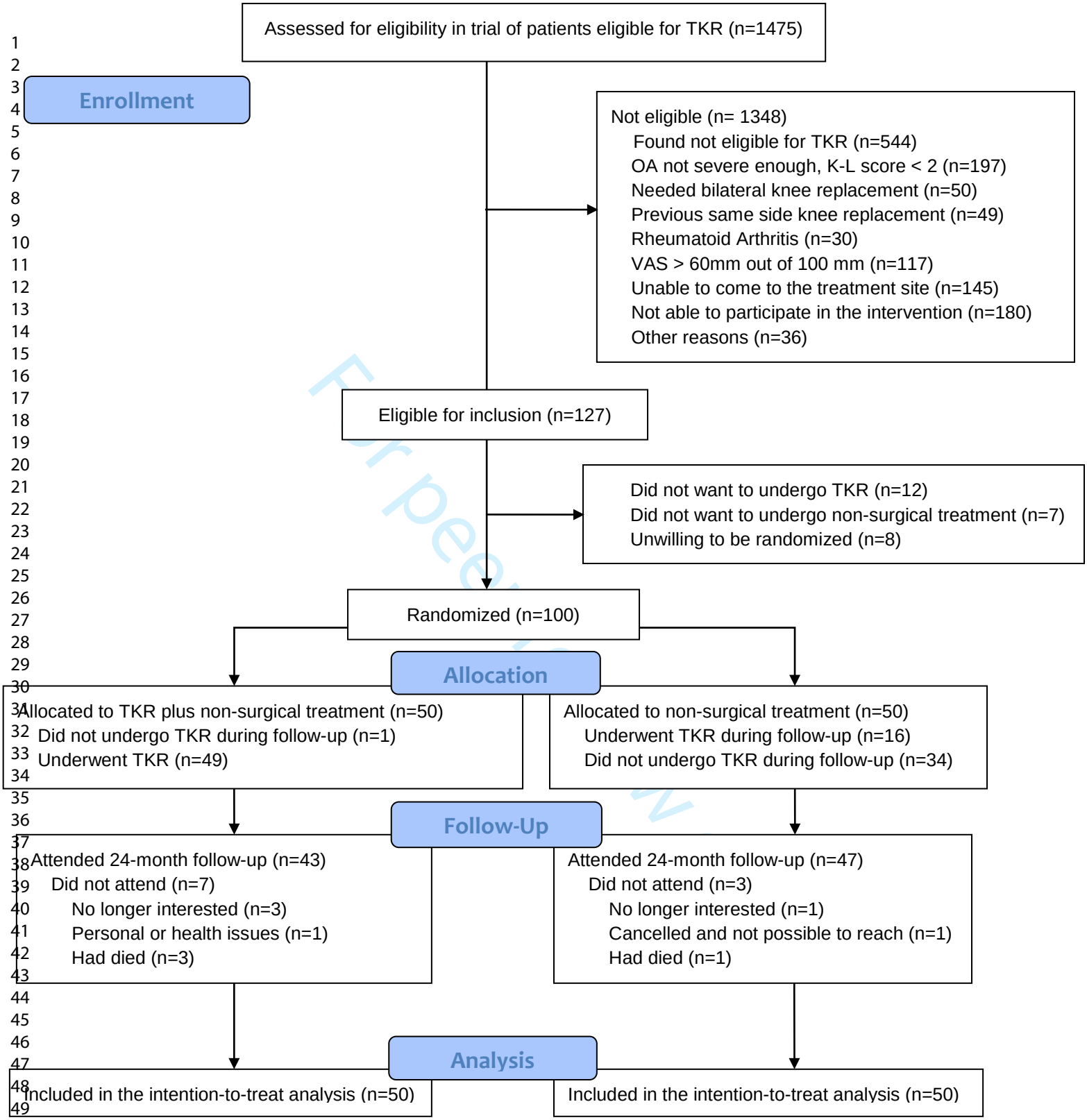
Table 4. Primary analysis excluding deaths. Incremental cost-effectiveness ratios (ICERs) and probability of cost-effectiveness of TKR plus non-surgical treatment vs non-surgical treatment alone for each scenario.

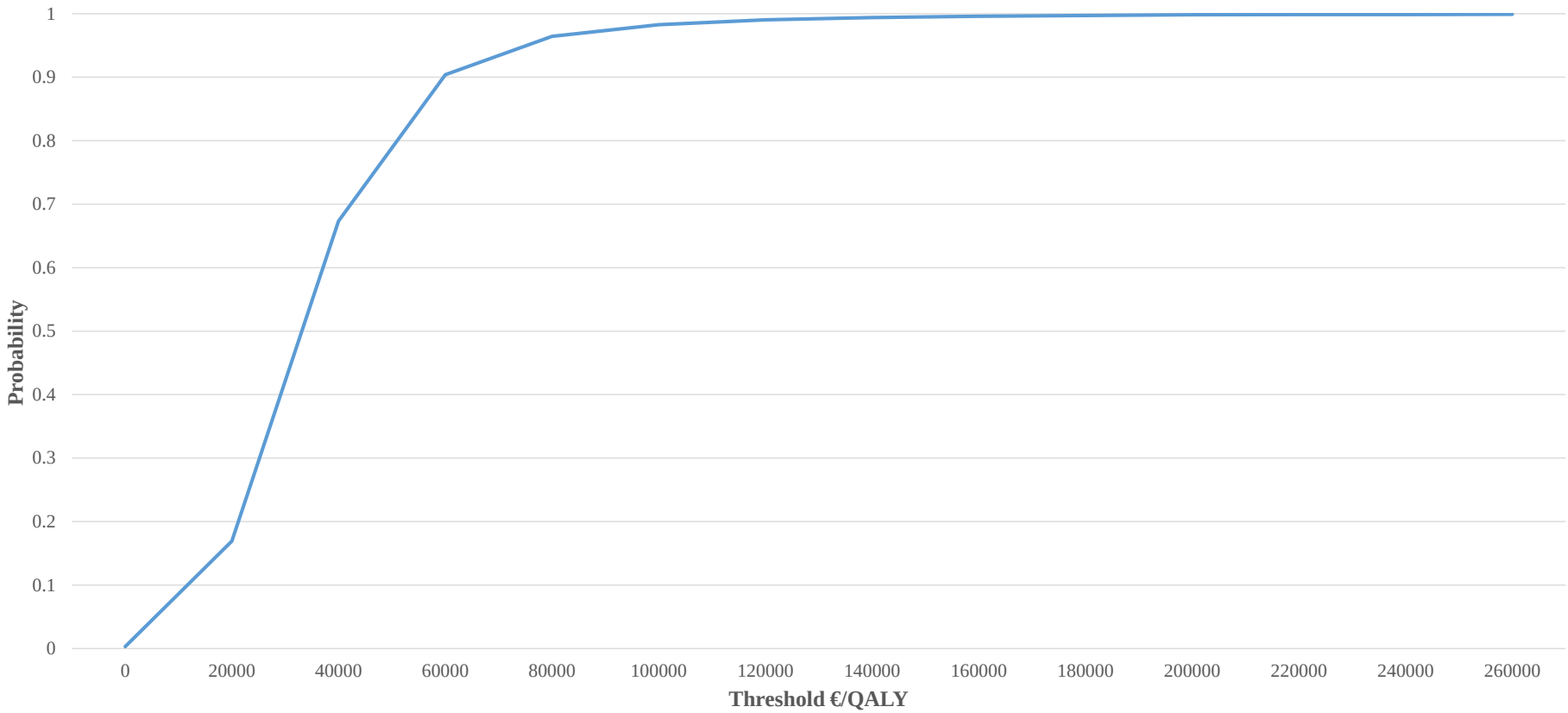
Analysis	Incremental cost	95% CI	Incremental effect	95% CI	ICER	Probability of cost-effectiveness at € 22,665
	€		QALY		€ / QALY	%
Base-case	6,070	1,857 to 10,283	0.186	0.078 to 0.294	32,611	23.2
Scenario 1	4,640	-200 to 9,480	0.233	0.088 to 0.378	19,917	58.3
Scenario 2	4,481	-668 to 9,629	0.242	0.095 to 0.390	18,497	61.9

TKR=Total knee replacement; QALY=quality-adjusted life-years; 95% CI=95% confidence interval
Base-case=Adjusted for age, sex and baseline value
Scenario 1=unadjusted; Scenario 2=unadjusted and without imputation of missing values

Supporting information captions

S1. Supplementary appendix including supp. table 1 and 2 and supp. figure 1.




Probability
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0.8
0.7
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100000
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260000
Threshold €/QALY

S1. Supplementary appendix

Supp. table 1. Sub-analysis including deaths. Health utilities for TKR plus non-surgical treatment vs non-surgical treatment alone at baseline and at 3 months, 6 months, 12 months and 24 months follow-up.

	TKR+non-surgical group						Non-surgical group					
Utilities	Baseline	3 months	6 months	12 months	24 months	24 months (discounted)	Baseline	3 months	6 months	12 months	24 months	24 months (discounted)
Mean	0.661	0.845	0.865	0.861	0.821	0.797	0.681	0.780	0.757	0.795	0.742	0.721
SD	0.156	0.145	0.139	0.177	0.266	0.258	0.147	0.117	0.157	0.151	0.225	0.219
Median	0.723	0.824	0.824	0.919	1.000	0.971	0.723	0.776	0.776	0.776	0.776	0.753
25th	0.655	0.750	0.776	0.776	0.723	0.702	0.655	0.723	0.723	0.723	0.723	0.701
75th	0.723	1.000	1.000	1.000	1.000	0.971	0.771	0.824	0.824	1.000	0.831	0.807
N	50	40	42	46	46	46	50	46	49	49	48	48

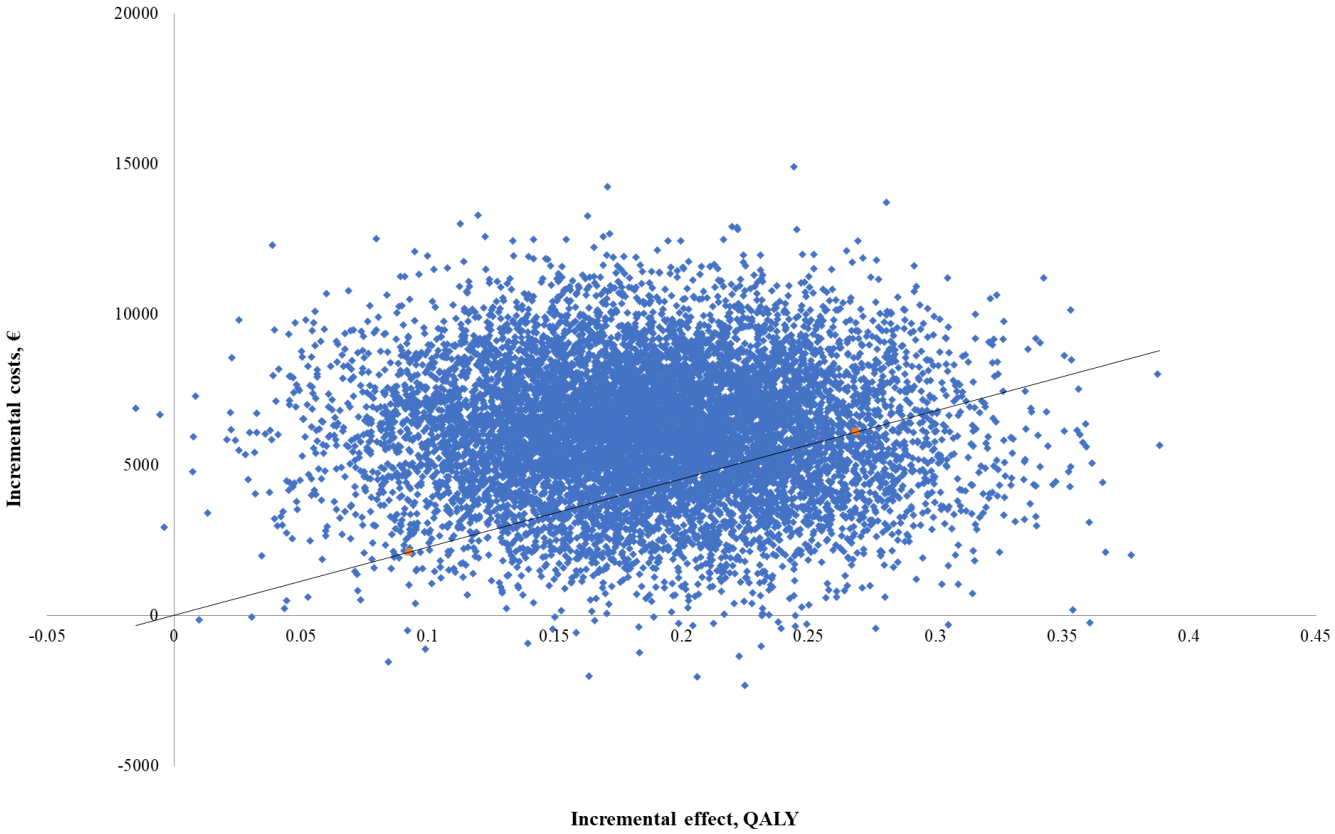
TKR=Total knee replacement; QALY=quality-adjusted life-years; discounted= i.e. future health utilities value converted to present health utilities value.

Supp. table 2. Sub-analysis including deaths. Incremental cost-effectiveness ratios (ICERs) and probability of cost-effectiveness of TKR plus non-surgical treatment vs non-surgical treatment alone for each scenario.

Analysis	Incremental cost	95% CI	Incremental effect	95% CI	ICER	Probability of cost-effectiveness at € 22,665
	€		QALY		€ / QALY	%
Base-case	7,880	2,894 to 12,867	0.123	-0.011 to 0.257	64,208	7.8
Scenario 1	8,585	2,442 to 14,728	0.178	0.011 to 0346	48,128	12.4
Scenario 2	8,805	2,201 to 15,409	0.190	0.023 to 0.357	46,277	13.8

TKR=Total knee replacement; QALY=quality-adjusted life-years; 95% CI=95% confidence interval
Base-case=QALY adjusted for age, sex and baseline value
Scenario 1=unadjusted; Scenario 2=unadjusted and without imputation of missing values

Supp. figure 1. Cost-effectiveness plane showing the uncertainty around the ICER (excl. deaths).



CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6-7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6-7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	7-9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	13
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	11
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	4+6

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9-11
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7+10
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	12-13
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	12-13
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	12-13
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	14-16
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	14-16
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	14-16
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	16
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	17-19
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	21-22
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	21-22

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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