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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

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4 1 **Cost-effectiveness of total knee replacement in addition to non-surgical treatment: 2-year**  
5 **outcome from a randomized trial**  
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## 25 Abstract

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

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

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

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

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4 47 **Trial registration:** ClinicalTrials.gov (NCT01410409).  
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7 48 **Keywords:** Osteoarthritis; Therapeutics; Randomized controlled trial; Knee Replacement; Medical  
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9 economics  
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## 11 12 13 50 **Strengths and limitations of this study** 14 15

- 16  
17 51 • This study is the first economic evaluation of total knee replacement that is based on a  
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19 52 randomized trial of surgical and non-surgical treatment thereby providing highly comparable  
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21 53 treatment groups.  
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- 24 54 • Cost data was retrieved from the Danish health registries which contain detailed, high-quality  
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26 55 information on health sector costs, social costs, and prescription medication on individual  
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28 56 patients, and effectiveness data was systematically and rigorously collected in the randomized  
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31 57 trial.  
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- 33 58 • The 24-month time horizon limits conclusions on the long-term cost-effectiveness of total knee  
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35 59 replacement  
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## 70 INTRODUCTION

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

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

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

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

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4 93 (QALYs) data from the randomized trial and the unique Danish health registries which contain  
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6 94 detailed information on health sector costs, social costs, and prescription medication on the trial  
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9 95 participants. We hypothesized that TKR plus non-surgical treatment would be a more cost-effective  
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11 96 procedure compared to non-surgical treatment alone due to greater improvements in quality of life  
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13 97 counterbalancing the expected additional cost related to the surgery.  
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## 1 2 3 4 5 112 **METHODS**

### 8 9 113 **Study design**

12 114 This was a pre-planned baseline to 24 months cost-utility analysis from a parallel group assessor-  
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15 115 blinded randomized trial (1:1 ratio) that conforms to the CHEERS statement for reporting health  
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17 116 economic evaluations<sup>15</sup>. Costs were collected from a limited societal perspective (i.e. health care  
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19 117 costs and public transfer payments), with QALYs used as the outcome measure. Individual-level  
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22 118 data were obtained from the clinical trial and linked with data from national registries for use in the  
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24 119 analyses.

27 120 A brief presentation of the trial methods is provided below. Full details about the process for  
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30 121 recruitment, criteria for eligibility, the randomization procedure, allocation concealment and  
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32 122 detailed description of the interventions have been published previously <sup>16</sup>.

### 35 36 123 **Ethics**

40 124 The study was designed to follow the principles of the Declaration of Helsinki and ethics approval  
41  
42 125 was obtained from the local Ethics Committee of The North Denmark Region (N-20110024) and the  
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44 126 study was registered at ClinicalTrials.gov (NCT01410409).

### 47 48 127 **Participants**

51 128 One hundred patients diagnosed with symptomatic and moderate to severe radiographic knee OA  
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54 129 considered eligible for TKR by the orthopedic surgeon were included in the study. The study had  
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56 130 three major exclusion criteria: 1) mean pain the previous week above 60 mm on a 100-mm visual  
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4 131 analogue scale, 2) previous knee replacement on the same side, and 3) need for bilateral  
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6 132 simultaneous TKR.  
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## 10 133 **Setting and time horizon**

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14 134 Patients were recruited between September 2011 and December 2013 from one of two specialized,  
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16 135 public outpatient clinics at Aalborg University Hospital, Denmark (Frederikshavn and Farsoe), and  
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18 136 all patients provided informed written consent before being enrolled. To have identical time periods  
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20 137 for the whole population, we compared resource use and costs 1 year before randomization (pre-  
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23 138 period) to resource use and costs 2 years after randomization for each individual patient.  
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## 26 139 **Randomization procedure and allocation concealment**

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30 140 The randomization schedule was generated a priori in permuted blocks of eight, stratified by site,  
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32 141 and the allocation numbers were concealed in sealed, opaque envelopes prepared by an independent  
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35 142 staff member. One research assistant at each of the two sites had access to the envelopes, opening  
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37 143 them only after informed consent and baseline outcomes had been obtained.  
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## 41 144 **Comparators**

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45 145 Patients were randomly assigned (1:1) to 1) undergo TKR plus 12 weeks of supervised non-surgical  
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47 146 treatment or 2) receive only the 12 weeks of supervised non-surgical treatment.  
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## 51 147 **Total knee replacement**

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54 148 A total cemented prosthesis with patellar resurfacing (NexGen, CR-Flex, fixed bearing or LPS-Flex,  
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56 149 fixed bearing, Zimmer, Warsaw, Indiana, USA) was inserted by high-volume orthopedic specialists  
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150 using the surgical methods recommended by the manufacturer<sup>17</sup>. Surgery was performed by the  
151 surgeon in charge of the assessment at the time of recruitment.

## 152 **Supervised non-surgical treatment**

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

### 156 **Exercise**

157 The NEuroMuscular EXercise training program (NEMEX), previously found feasible in patients  
158 with moderate to severe knee OA awaiting joint replacement<sup>18</sup>, was administered in 60-min group-  
159 based sessions twice weekly supervised by a physiotherapist. To increase long-term adherence, after  
160 12 weeks of exercise, the patients undertook a transition period of 8 weeks where the exercise  
161 program was increasingly performed at home.

### 162 **Patient education**

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

### 167 **Dietary advice**

168 Patients with a body mass index  $\geq 25$  at baseline had four individual 1-hour consultations with a  
169 dietician with the overall aim of reducing body weight by at least 5%<sup>19</sup>. The program was based on  
170 motivational interviewing<sup>20</sup>.

## 171 **Insoles**

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

## 176 **Pain medication**

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

## 181 **Booster sessions**

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

## 185 **Patient and public involvement**

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

## 188 **Measurement of resource use and costs**

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

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4 192 registration number), which allows for the linking of information between national registries at the  
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7 193 individual level. This enables identification of the patients in the trial and calculations of costs  
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9 194 associated with these individuals. Health care costs comprised expenses associated with inpatient  
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11 195 services, outpatient visits, primary care services and prescription medication. Inpatient services  
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13 196 were assessed as both including and excluding TKR surgeries during the study period. Inpatient and  
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16 197 outpatient costs are available from the National Patient Registry (NPR), which contains information  
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18 198 on all kinds of patient contacts including diagnoses and diagnostic and treatment procedures.  
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20 199 Linking the data with the Danish Case Mix System (Diagnosis-Related Groups) enabled estimation  
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23 200 of associated costs. Primary care included visits to the general practitioner, medical specialist,  
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25 201 physiotherapist, chiropractor, laboratory work and others. Resources related to utilization of the  
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27 202 primary care services were derived from the Danish National Health Insurance Service Register.  
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30 203 Costs were estimated for all prescription medication; pain medication (ATC-codes N02A, N02B  
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32 204 and M01A) and non-pain medication (i.e. anything else besides pain medication), respectively.  
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34 205 Medication costs were calculated by multiplying the retail price with the prescribed quantity,  
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36 206 available from the Danish Medicines Agency.  
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40 207 Non protocol-driven resources, e.g. costs of recruitment, were included. As both groups received  
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42 208 the same supervised non-surgical treatment (as described above), this cost was not included for  
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44 209 either group. The cost of the non-surgical treatment was estimated to be between 560 € (actual cost  
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46 210 of the non-surgical treatment in the trial) to 1646 € (estimated cost of the non-surgical treatment in  
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49 211 private practice in Denmark) per person.  
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52 212 To increase the international applicability of the study, costs were adjusted to 2015-equivalent price  
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54 213 levels using the consumer price index and converted to Euros (1 € = 7.45 DKK). 1 Euro  
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56 214 corresponded to 1.13 US dollars at the 2017 average exchange rate.  
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4 215 Public transfer income was calculated as the number of weeks a person was receiving sick leave  
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6 216 pay, disability pension, early retirement and unemployment benefits (including activated persons).  
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9 217 About half of the participants were older than 64 years (56%), and retired (age pension). This  
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11 218 information was available from national registries from Statistics Denmark.  
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## 14 219 **Measurement of effectiveness**

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18 220 A generic measure of health in terms of QALYs gained was used as the effectiveness measure. This  
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20 221 is a composite measure that considers both the quantity and quality of life of an individual. The  
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23 222 maximum achievable QALY is 1, reflecting one year of full health, whereas a QALY value of 0  
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25 223 reflects death. Health-related quality of life (HRQoL) was measured using the three-level version of  
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27 224 the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), including the score on the  
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30 225 descriptive index (ranging from -0.59 to 1.00) and the score on the visual analogue scale (ranging  
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32 226 from 0 to 100)<sup>22</sup>, at baseline, at 3 months, 6 months, 12 months, and at the 24 months follow-up.  
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34 227 The baseline to 12 months EQ-5D data was previously published in the primary RCT report<sup>13</sup>, but  
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36 228 has not previously been used for cost-effectiveness analyses. The EQ-5D-3L has five digits  
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39 229 measuring mobility, self-care, usual activities, pain discomfort and anxiety/depression. The  
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41 230 descriptive index is based on a Danish “time trade-off” value set<sup>23</sup>, which is a method used to  
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43 231 evaluate the relative amount of time patients would be willing to sacrifice to avoid a certain poor  
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46 232 health state. The patients completed the EQ-5D at baseline and all follow-up visits at the  
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48 233 Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark.  
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## 239 **Analytical methods**

### 240 **Missing data**

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

### 246 **Costs in the pre-period, Year 1, and Year 2**

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

### 249 **Cost-effectiveness analyses**

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

258 QALY gains or losses were calculated as the difference in QALYs from baseline to 24 months  
259 taking into account changes in utility over time, i.e. from baseline to 3 months, 6 months, 12  
260 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)<sup>24</sup>.

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

## RESULTS



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## 281 Patient characteristics

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

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

286 Out of the 100 patients randomized, 24 months follow-up data were available for 47/50 (94%) in  
287 the non-surgical group and 43/50 (86%) in the TKR plus non-surgical group. Administrative data  
288 yielded that 16 out of 50 patients (32%) from the non-surgical group had a TKR before the 24  
289 months follow-up: 13 patients from baseline to 12 months and three patients between 12 and 24  
290 months. Mean duration (range) from initiating the non-surgical treatment to the TKR was 8.7 (2.6 to  
291 21.5) months. One of the 50 patients (2%) in the TKR plus non-surgical group decided not to  
292 undergo TKR anyway. One patient in the TKR plus non-surgical group had three revision surgeries  
293 ending up with the prosthesis being removed and the knee fused following a deep infection. Due to  
294 severe knee stiffness during the rehabilitation period after TKR, three patients in the TKR plus non-  
295 surgical group and one patient in the non-surgical group who had TKR later required manipulation  
296 of the knee under anesthesia. The mean follow-up time was 24.0 and 24.3 months in the TKR plus  
297 non-surgical group and the non-surgical group, respectively.

298  
299 Table 2 shows health care costs and public transfer income given as weeks in the pre-period, year 1  
300 (12 months) and year 2 (24 months), respectively. The groups had similar health care costs during  
301 the year prior to randomization (2,695 vs. 2,644 Euros). At 12 months after randomization, health  
302 care costs in the TKR plus non-surgical group were more than double those of the non-surgical

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4 303 group (16,343 vs. 7,028 Euros), mostly due to the surgical procedure. Although not statistically  
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6 304 significant, the costs in the TKR plus non-surgical group were lower at the 24 months follow-up  
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9 305 (6,733 vs. 7,486 €) because some patients in the non-surgical group underwent TKR. No significant  
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11 306 between-group differences were found in weeks of incurring public transfer income.  
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15 307 \*\*\*\*\* PLACE TABLE 2 AROUND HERE \*\*\*\*\*  
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20 309 The non-surgical group experienced a gain in QALYs of 0.056 from baseline to 24 months while  
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22 310 the TKR plus non-surgical group experienced a gain of 0.195, with the largest increases in QALYs  
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25 311 in both groups from baseline to 3 months (see Table 3 for QALY values at the different time  
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27 312 points).  
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30 313 \*\*\*\*\* PLACE TABLE 3 AROUND HERE \*\*\*\*\*  
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35 315 Incremental costs and QALYs for each scenario are presented in Table 4. In all scenarios, TKR plus  
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37 316 non-surgical treatment was more expensive, but also more effective in terms of QALY gain.  
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40 317 Incremental cost-effectiveness ratios (ICERs) and the probability of cost-effectiveness at the  
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42 318 willingness-to-pay threshold for each scenario are also presented in Table 4. In the Base-case  
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45 319 (adjusted) scenario, TKR plus non-surgical treatment costed 32,611 Euros per QALY gained, which  
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47 320 is above the threshold for willingness-to-pay defined by NICE (22,665 Euros/QALY). However, in  
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49 321 the unadjusted Scenario 1 and unadjusted and without imputation of missing values (scenario 2) the  
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51 322 ICERs were below the threshold (19,917 Euros/QALY and 18,497 Euros/QALY, respectively). The  
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54 323 probability of cost-effectiveness of TKR plus non-surgical treatment was only 23.2% in the  
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56 324 (adjusted) Base-case scenario but increased to 58.3% and 61.9% in Scenarios 1 and 2, respectively.  
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4 326 \*\*\*\*\* PLACE TABLE 4 AROUND HERE \*\*\*\*\*  
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## 10 **Sub-analysis including deaths**

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14 329 Three persons died in the TKR plus non-surgical treatment group and one person in the non-  
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16 330 surgical treatment only group. Including deaths in the analysis decreased the QALY gained in both  
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19 331 groups. The non-surgical group experienced a gain in QALYs of 0.040 from baseline to 24 months  
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21 332 while the TKR plus non-surgical group experienced a gain of 0.136, with the largest increases in  
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23 333 QALYs in both groups from baseline to 3 months (see Table 5 for QALY values at the different  
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26 334 time points).  
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29 335 \*\*\*\*\* PLACE TABLE 5 AROUND HERE \*\*\*\*\*  
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33 337 Including deaths in the regression analysis changed the estimates of incremental costs and QALYs  
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35 338 (Table 6). TKR plus non-surgical treatment was still more expensive and more effective for all  
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37 339 scenarios but in all three scenarios the ICER exceeded the NICE threshold. In the Base-case  
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40 340 scenario, the ICER was more than twice as high as the threshold for willingness-to-pay defined by  
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42 341 NICE (22,665 Euros/QALY), and the probability of cost-effectiveness was only 7.8%. In Scenario  
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44 342 1 and 2 the probability of cost-effectiveness was 12.4% and 13.8%, respectively.  
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51 344 \*\*\*\*\* PLACE TABLE 6 AROUND HERE \*\*\*\*\*  
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## 53 345 **DISCUSSION**

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56 346 TKR plus non-surgical treatment was more expensive, but also more effective than non-surgical  
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59 347 treatment alone. The cost-utility analysis demonstrated that TKR plus non-surgical treatment was  
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4 348 not cost-effective compared to non-surgical treatment alone from a 24-month limited societal  
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7 349 perspective when adjusting for covariates and imputing missing values. Results were sensitive to  
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9 350 changes, as the treatment was cost-effective in the unadjusted scenario.  
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12 351 Given the extensive burden of knee OA<sup>3,4</sup>, there is considerable societal demand for evidence on  
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14 352 cost-effective evidence-based treatments<sup>25</sup>. The current study provides the first direct comparison of  
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16 353 two different treatment strategies in terms of cost-effectiveness for patients with moderate to severe  
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18 354 symptomatic and radiographic knee OA. The cost-utility analysis was conducted alongside a  
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20 355 randomized trial, which demonstrated that TKR plus non-surgical treatment compared to non-  
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22 356 surgical treatment alone was twice as effective in terms of pain relief and functional  
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24 357 improvements<sup>13,26</sup>. Therefore, we hypothesized that TKR would be a cost-effective procedure due to  
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26 358 higher improvements in quality of life counterbalancing the expected additional cost related to the  
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28 359 procedure. However, in contrast to our hypothesis, TKR plus non-surgical treatment was not found  
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30 360 to be cost-effective compared to non-surgical treatment alone from a 24 months perspective. The  
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32 361 cost per QALY gained exceeded the threshold defined by NICE by approximately 10,000 Euros<sup>24</sup>.  
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34 362 However, without adjustment for covariates and imputation of missing values the cost per QALY  
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36 363 was just cost-effective according to the threshold (ICER of 18,497 Euros/QALY).  
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43 364 Our results from the Base-case scenario contrast with findings in a recent systematic review<sup>27</sup>. The  
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45 365 review included four studies examining the cost-effectiveness of TKR compared to non-surgical  
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47 366 procedures and all four concluded that TKR was a cost-effective option. However, as opposed to  
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49 367 our study, none of the previous studies were based on a randomized trial. Two of the previous  
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51 368 studies used a Markov model to assess the long-term and lifetime cost-effectiveness of TKR<sup>28,29</sup>.  
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53 369 The remaining two were cohort-based studies examining short-term cost-effectiveness of TKR<sup>30,31</sup>.  
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55 370 A recent cohort-based cost-effectiveness analysis, not included in the systematic review, concluded  
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57 371 that TKR was not cost-effective at a group level over 8 years, while it would be cost-effective if it  
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372 was restricted to patients with more severe symptoms<sup>14</sup>. In contrast, we did not find that TKR was  
373 cost-effective in addition to non-surgical treatment in patients with more severe symptoms. Our  
374 study provides the first cost-effectiveness analysis of TKR in addition to non-surgical treatment  
375 using two comparable treatment groups, thereby providing an important addition to the above  
376 mentioned non-randomized studies.

377 One could argue that extending the time horizon might have led to a different conclusion. If the  
378 positive effect of the surgery persists beyond the 24 months, TKR plus non-surgical treatment might  
379 eventually end up being a cost-effective option. However, as indicated by a previous report<sup>32</sup>,  
380 improvements in symptoms might decline from 1 to 5 years after TKR, questioning the assumptions  
381 underlining a potential long-term cost-effectiveness of TKR. This is supported by the observed  
382 change in QALY over time in this trial. Both patients undergoing TKR plus non-surgical treatment  
383 and patients undergoing non-surgical treatment only experienced the greatest gain in QALYs from  
384 baseline to 3 months. The QALY remained stable until the 24 months follow-up in the TKR plus  
385 non-surgical group, while the non-surgical treatment only had a small (0.044) decrease in QALY. If  
386 TKR plus non-surgical treatment was to become cost-effective in the longer term, the decrease in  
387 QALY in the non-surgical group would need to continue. In the TKR plus non-surgical group, three  
388 people died during the period, while only one person died in the non-surgical group. When  
389 including the deaths in the analysis, TKR plus non-surgical treatment was still more effective than  
390 non-surgical treatment alone, though not as effective as in the primary analysis. This is because  
391 death corresponds to a QALY value of zero, thereby attenuating the effect of the surgery. The short  
392 time horizon and the different findings in the analysis without adjustment for covariates and  
393 imputation of missing values and the sub-analysis including deaths emphasize the susceptibility of  
394 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<sup>33</sup>. 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<sup>34</sup>. 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<sup>35-37</sup>. 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

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

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## 436 **Author contributions**

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4 437 **Study conception and design.** Skou, Kjellberg, Roos, Laursen, Arendt-Nielsen, Rasmussen,

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7 438 Simonsen

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9 439 **Recruitment of patients:** Laursen, Simonsen.

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11 440 **Acquisition of data.** Skou, Kjellberg

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13 441 **Analysis and interpretation of data.** Skou, Kjellberg, Roos, Laursen, Arendt-Nielsen, Ibsen,

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20 444 Roos, Laursen, Arendt-Nielsen, Ibsen, Larsen, Rasmussen, Simonsen

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22 445 **Final approval of the article.** Skou, Kjellberg, Roos, Laursen, Arendt-Nielsen, Ibsen, Larsen,

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25 446 Rasmussen, Simonsen

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27 447 All authors had full access to all the data (including statistical reports and tables) in the study and

28  
29 448 take responsibility for the integrity of the data and the accuracy of the data analysis.

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## 56 57 459 **Role of the Funder/Sponsor**

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460 The funders played no role in the design and conduct of the study; collection, management,  
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462 decision to submit the manuscript for publication.

463

## 464 **Conflict of interest**

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

470 Dr. Skou is associate editor of Journal of Orthopaedic & Sports Physical Therapy, he has received  
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472 work. He is co-founder of GLA:D, a not-for profit initiative hosted by the University of Southern  
473 Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

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

476 The authors report no other conflict of interest.

477

## 478 **Data sharing**

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

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For peer review only

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## Figure legends

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

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60652 **Tables**653 **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 <sub>4</sub>	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)

654 Radiographic severity: Radiographic knee osteoarthritis severity on the Kellgren-Lawrence scale; KOOS<sub>4</sub>: The mean score of four out of five of the  
655 Knee injury and Osteoarthritis Outcome Score subscales covering Pain, Symptoms, Function in daily living (ADL), Sport/Rec: Function in sport and  
656 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									
General practitioner	448	421	1.000	454	351	0.550	382	361	1.000
Medical specialist	270	238	1.000	325	193	0.010*	246	201	0.900
Physiotherapy	126	122	1.000	84	91	1.000	91	90	1.000
Chiropractic	37	42	1.000	24	45	0.980	25	44	1.000
Lab work and other	3	5	1.000	5	5	1.000	6	3	1.000
Other	12	14	1.000	17	18	1.000	15	24	1.000
Prescription medication, all									
Pain medication	599	443	1.000	704	472	0.950	620	471	1.000
NSAID (N02B + M01A)	534	377	1.000	607	382	0.920	572	403	1.000
Opioids (N02A)	65	66	1.000	97	91	1.000	48	69	1.000
Other	51	50	1.000	53	66	1.000	33	52	0.980
Other	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.



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

QALY	TKR+non-surgical group						Non-surgical group					
	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

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

675 **Table 4. Primary analysis excluding deaths. Incremental cost-effectiveness ratios (ICERs) and probability of cost-effectiveness of TKR plus**  
 676 **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

677 TKR=Total knee replacement; QALY=quality-adjusted life-years; 95% CI=95% confidence interval

678 Base-case=Adjusted for age, sex and baseline value

679 Scenario 1=unadjusted; Scenario 2=unadjusted and without imputation of missing values

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

QALY	TKR+non-surgical group						Non-surgical group					
	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

682 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 0.346	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

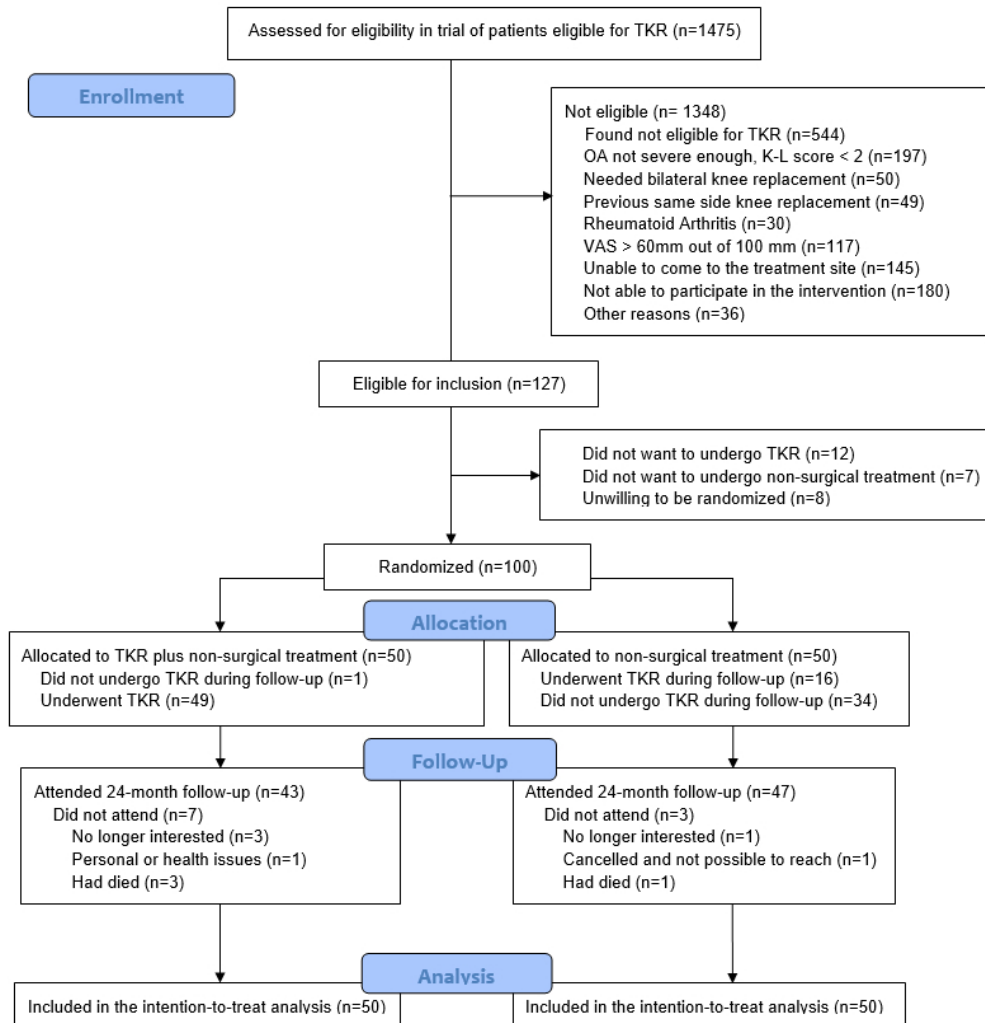


Fig 1. Flow of patients in the randomized controlled trial of patients eligible for total knee replacement. TKR=Total knee replacement; K-L score= Kellgren-Lawrence score; VAS=Visual Analogue Scale.

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
<b>Title and abstract</b>			
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
<b>Introduction</b>			
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
<b>Methods</b>			
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	<i>Single study-based estimates:</i> 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



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
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4	Measurement and	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
5	valuation of preference			
6	based outcomes			
7				
8	Estimating resources	13a	<i>Single study-based economic evaluation:</i> 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
9	and costs			
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15		13b	<i>Model-based economic evaluation:</i> 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
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22	Currency, price date,	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
23	and conversion			
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28	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
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31	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	12-13
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34	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
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42	<b>Results</b>			
43	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
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49	Incremental costs and	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
50	outcomes			
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53	Characterising	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	
54	uncertainty			
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		of methodological assumptions (such as discount rate, study perspective).	14-16
	20b	<i>Model-based economic evaluation</i> : 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
<b>Discussion</b>			
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
<b>Other</b>			
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>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. 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. *Value Health* 2013;16:231-50.



# 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-033495.R1
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<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Health economics
Keywords:	Osteoarthritis, THERAPEUTICS, Randomized controlled trial, Knee Replacement, Medical economics

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4 1 **Cost-effectiveness of total knee replacement in addition to non-surgical treatment: 2-year**  
5 **outcome from a randomized trial in secondary care in Denmark**  
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## 25 Abstract

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

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

37 **Results:** TKR plus non-surgical treatment was more expensive (mean of 23,076 vs. 14,514 Euros)  
38 but also more effective than non-surgical treatment. (mean 24-month improvement in QALY of  
39 0.195 vs. 0.056). While cost-effective in the unadjusted scenario (ICER of 18,497 Euros/QALY),  
40 TKR plus non-surgical treatment was not cost-effective compared to non-surgical treatment with  
41 the option of later TKR if needed in the adjusted (age, sex and baseline values), base-case scenario  
42 (ICER of 32,611 Euros/QALY) with a probability of cost-effectiveness of 23.2%. Including deaths,  
43 TKR plus non-surgical treatment was still not cost-effective (ICERs of 46,277 to 64,208  
44 Euros/QALY).

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

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4 47 patients with moderate to severe knee osteoarthritis and moderate intensity pain in secondary care in  
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6 48 Denmark. Results were sensitive to changes, highlighting the need for further confirmatory  
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9 49 research also assessing the long-term cost-effectiveness of TKR.  
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12 50 **Trial registration:** ClinicalTrials.gov (NCT01410409).  
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15 51 **Keywords:** Osteoarthritis; Therapeutics; Randomized controlled trial; Knee Replacement; Medical  
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17 52 economics  
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## 24 54 **Strengths and limitations of this study**

- 28 55 • This is the first economic evaluation of total knee replacement that is based on a randomized  
29 56 trial of surgical and non-surgical treatment thereby providing highly comparable treatment  
30 57 groups assessed and treated in a standardized and controlled setup.
- 35 58 • Cost data were retrieved from the Danish health registries which contain detailed, high-quality  
36 59 information on health sector costs, social costs, and prescription medication on individual  
37 60 patients, and effectiveness data were systematically and rigorously collected in the randomized  
38 61 trial.
- 45 62 • The 24-month time horizon and the selected population included limit conclusions on the long-  
46 63 term cost-effectiveness of total knee replacement and the generalizability to other populations
- 49 64 • Since nearly 1 out of 3 from the non-surgical group had TKR surgery during the 24 months, it is  
50 65 likely that the true additional effect and cost of TKR in addition to non-surgical treatment have  
51 66 been underestimated in the study.  
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## INTRODUCTION

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

In patients with end-stage knee OA, total knee replacement (TKR) is considered an effective<sup>6</sup> and cost-effective<sup>7</sup> treatment. However, approximately 20% continue to have chronic pain after otherwise successful surgery<sup>8</sup> and, in addition, the procedure is associated with a risk of serious adverse events<sup>9</sup>. 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<sup>10</sup>. As the number of TKR procedures performed each year has increased dramatically since the 1970s<sup>11</sup>, with around 600,000 annual procedures in the United States alone<sup>12</sup>, evidence of the effectiveness and cost-effectiveness of TKR in comparison to non-surgical treatments is warranted<sup>7</sup>.

In 2015, a randomized trial assessing the effectiveness of TKR plus non-surgical treatment as compared with non-surgical treatment alone was published<sup>13</sup>. 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<sup>7,14</sup>.

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

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4 91 using quality-adjusted life years (QALYs) data from the randomized trial and the unique Danish  
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6 92 health registries which contain detailed information on health sector costs, social costs, and  
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9 93 prescription medication on the trial participants. We hypothesized that TKR plus non-surgical  
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11 94 treatment would be a more cost-effective procedure compared to non-surgical treatment with the  
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13 95 option of later TKR if needed at 24 months due to greater improvements in quality of life  
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16 96 counterbalancing the expected additional cost related to the surgery.  
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For peer review only

## 1 2 3 4 5 110 **METHODS**

### 8 9 111 **Study design**

12 112 This was a pre-planned baseline to 24 months cost-utility analysis from a parallel group assessor-  
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15 113 blinded randomized trial (1:1 ratio) that conforms to the CHEERS statement for reporting health  
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17 114 economic evaluations<sup>15</sup>. Costs were collected from a health system perspective, with QALYs used  
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19 115 as the outcome measure. Individual-level data were obtained from the clinical trial and linked with  
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22 116 data from national registries for use in the analyses.

25 117 A brief presentation of the trial methods is provided below. Full details about the process for  
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27 118 recruitment, criteria for eligibility, the randomization procedure, allocation concealment and  
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30 119 detailed description of the interventions have been published previously <sup>16</sup>.

### 33 120 **Ethics**

37 121 The study was designed to follow the principles of the Declaration of Helsinki and ethics approval  
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40 122 was obtained from the local Ethics Committee of The North Denmark Region (N-20110024) and the  
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42 123 study was registered at ClinicalTrials.gov (NCT01410409).

### 45 124 **Participants**

49 125 One hundred patients diagnosed with symptomatic and moderate to severe radiographic knee OA  
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51 126 considered eligible for TKR by the orthopedic surgeon were included in the study. The study had  
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54 127 three major exclusion criteria: 1) mean pain the previous week above 60 mm on a 100-mm visual  
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56 128 analogue scale, 2) previous knee replacement on the same side, and 3) need for bilateral  
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58 129 simultaneous TKR.

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## 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<sup>17</sup>. Surgery was performed by the surgeon in charge of the assessment at the time of recruitment.

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## 150 **Supervised non-surgical treatment**

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

### 154 **Exercise**

155 The NEuroMuscular EXercise training program (NEMEX), previously found feasible in patients  
156 with moderate to severe knee OA awaiting joint replacement<sup>18</sup>, was administered in 60-min group-  
157 based sessions twice weekly supervised by a physiotherapist. To increase long-term adherence, after  
158 12 weeks of exercise, the patients undertook a transition period of 8 weeks where the exercise  
159 program was increasingly performed at home.

### 160 **Patient education**

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

### 165 **Dietary advice**

166 Patients with a body mass index  $\geq 25$  at baseline had four individual 1-hour consultations with a  
167 dietician with the overall aim of reducing body weight by at least 5%<sup>19</sup>. The program was based on  
168 motivational interviewing<sup>20</sup>.

### 169 **Insoles**



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4 170 Patients received individually fitted full-length Formthotics Original Dual Medium (perforated)  
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6 171 insoles with medial arch support (Foot Science International, Christchurch, New Zealand). A 4°  
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9 172 lateral wedge was added to the insoles if patients had a knee-lateral-to-foot position (the knee  
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11 173 moves over, or lateral, to the 5th toe in three or more of five trials)<sup>21</sup>.

#### 14 174 **Pain medication**

16  
17 175 Paracetamol 1 g four times daily, ibuprofen 400 mg three times daily, and pantoprazole 20 mg daily  
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20 176 were prescribed by the orthopedic surgeon if indicated. Prescriptions were reassessed every 3 weeks  
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22 177 and the patients were instructed to contact the study team if they were uncertain about the need for  
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24 178 continued pain medication.

#### 27 179 **Booster sessions**

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31 180 After the 12-week non-surgical program and the 8-week transition period and until the 12-month  
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33 181 follow up, a physiotherapist phoned the patients monthly to support exercise adherence. Patients  
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35 182 consulting the dietician were telephoned twice by the dietician to encourage dietary adherence.

#### 38 183 **Patient and public involvement**

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41 184 While no patients were involved in this cost-effectiveness analysis, the specific content of the non-  
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43 185 surgical treatment was guided by feedback from patients to ensure feasibility and acceptance.

#### 47 186 **Measurement of resource use and costs**

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50 187 Information on resource use and costs, including health care costs and public transfer income for  
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52 188 each patient, was retrieved from Danish national registries up until the 24-month follow-up. In  
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54 189 Denmark, the Danish Civil Registration System assigns every citizen a personal identification  
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57 190 number (central personal registration number), which allows for the linking of information between  
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59 191 national registries at the individual level. This enables identification of the patients in the trial and  
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4 192 calculations of costs associated with these individuals. Health care costs comprised expenses  
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7 193 associated with inpatient services, outpatient visits, primary care services and prescription  
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9 194 medication. Inpatient services were assessed as both including and excluding TKR surgeries during  
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11 195 the study period. Data on inpatient and outpatient services are available from the National Patient  
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13 196 Registry (NPR), which contains information on all kinds of patient contacts including diagnoses  
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16 197 and diagnostic and treatment procedures. Linking data on resource use from NPR with the Danish  
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18 198 Case Mix System (Diagnosis-Related Groups) enabled estimation of associated costs. Primary care  
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20 199 included visits to the general practitioner, medical specialist, physiotherapist, chiropractor,  
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23 200 laboratory work and others. Resources related to utilization of the primary care services were  
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25 201 derived from the Danish National Health Insurance Service Register. Costs were estimated for all  
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27 202 prescription medication; pain medication (ATC-codes N02A, N02B and M01A) and non-pain  
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30 203 medication (i.e. anything else besides pain medication), respectively. Medication costs were  
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32 204 calculated by multiplying the retail price with the prescribed quantity, available from the Danish  
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34 205 Medicines Agency.

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37 206 Non protocol-driven resources, e.g. costs of recruitment, were not included. As both groups  
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40 207 received the same supervised non-surgical treatment (as described above), this cost was not  
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42 208 included for either group. The cost of the non-surgical treatment was estimated to be between 560 €  
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44 209 (actual cost of the non-surgical treatment in the trial) to 1646 € (estimated cost of the non-surgical  
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47 210 treatment in private practice in Denmark) per person.

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50 211 To increase the international applicability of the study, costs were adjusted to 2015-equivalent price  
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52 212 levels using the consumer price index and converted to Euros (1 € = 7.45 DKK). 1 Euro  
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54 213 corresponded to 1.13 US dollars at the 2017 average exchange rate.  
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4 214 Public transfer income was calculated as the number of weeks a person was receiving sick leave  
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6 215 pay, disability pension, early retirement and unemployment benefits (including activated persons).  
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9 216 About half of the participants were older than 64 years (56%), and retired (age pension). This  
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11 217 information was available from national registries from Statistics Denmark.  
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## 14 218 **Measurement of effectiveness**

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18 219 A generic measure of health in terms of QALYs gained was used as the effectiveness measure of  
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20 220 effects up until the 24-month follow-up. This is a composite measure that considers both the  
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23 221 quantity and quality of life of an individual. The maximum achievable health utility is 1 and hence,  
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25 222 a QALY value of 1 reflects one year of full health, whereas a QALY value of 0 reflects death.  
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27 223 Health-related quality of life (HRQoL; health utility) was measured using the three-level version of  
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30 224 the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), including the score on the  
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32 225 descriptive index (ranging from -0.59 to 1.00) and the score on the visual analogue scale (ranging  
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34 226 from 0 to 100)<sup>22</sup>, at baseline, at 3 months, 6 months, 12 months, and at the 24 months follow-up.  
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37 227 The baseline to 12 months EQ-5D data were previously published in the primary RCT report <sup>13</sup>, but  
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39 228 has not previously been used for cost-effectiveness analyses. The EQ-5D-3L has five digits  
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41 229 measuring mobility, self-care, usual activities, pain discomfort and anxiety/depression. The  
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43 230 descriptive index is based on a Danish “time trade-off” value set<sup>23</sup>, which is a method used to  
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46 231 evaluate the relative amount of time patients would be willing to sacrifice to avoid a certain poor  
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48 232 health state. The patients completed the EQ-5D at baseline and all follow-up visits at the  
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50 233 Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark.  
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## 237 **Analytical methods**

### 238 **Missing data**

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

### 246 **Costs in the pre-period, Year 1, and Year 2**

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

### 249 **Cost-effectiveness analyses**

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

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4 258 QALY gains or losses were calculated as the area under the curve, i.e. taking changes in utility over  
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6 259 time into account.

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10 260 Costs and effects were discounted by 3%.

### 11 12 13 261 **Sub-analysis**

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16 262 A sub-analysis, including deaths during the study period, was conducted for each scenario (Base-  
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18 case scenario, Scenario 1 and Scenario 2).  
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### 20 21 22 264 **Sensitivity analyses**

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25 265 A probabilistic sensitivity analysis was carried out for each scenario in the primary analysis and the  
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27 sub-analysis, respectively. The probabilistic sensitivity analysis takes into account all parameter  
28 266 uncertainty at once. Incremental costs and QALYs were used to simulate 10,000 random draws  
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30 267 resulting in a scatterplot reflecting the probability of cost-effectiveness. In Denmark, no officially  
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32 268 set willingness-to-pay threshold exists. Instead, we used a threshold of 22,665 Euros/QALY or  
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34 269 lower corresponding to the decision rule defined by the National Institute for Health and Care  
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36 270 Excellence (NICE) (£ 20,000)<sup>24</sup>.

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42 272 A cost-effectiveness acceptability curve illustrating the cost-effectiveness at different thresholds and  
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44 273 a cost-effectiveness plane showing the uncertainty around the ICER were produced (both excl.  
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46 274 deaths).

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50 275 All analyses were performed using SAS 9.1.3 (SAS Institute, North Carolina, USA) and the  
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52 276 significance level was set to 0.05.

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## 279 RESULTS

### 280 Patient characteristics

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

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

285  
286 Out of the 100 patients randomized, 24 months follow-up data were available for 47/50 (94%) in  
287 the non-surgical group and 43/50 (86%) in the TKR plus non-surgical group. Administrative data  
288 yielded that 16 out of 50 patients (32%) from the non-surgical group had a TKR before the 24  
289 months follow-up: 13 patients from baseline to 12 months and three patients between 12 and 24  
290 months. Mean duration (range) from initiating the non-surgical treatment to the TKR was 8.7 (2.6 to  
291 21.5) months. One of the 50 patients (2%) in the TKR plus non-surgical group decided not to  
292 undergo TKR anyway. One patient in the TKR plus non-surgical group had three revision surgeries  
293 ending up with the prosthesis being removed and the knee fused following a deep infection. Due to  
294 severe knee stiffness during the rehabilitation period after TKR, three patients in the TKR plus non-  
295 surgical group and one patient in the non-surgical group who had TKR later required manipulation  
296 of the knee under anesthesia. The mean follow-up time was 24.0 and 24.3 months in the TKR plus  
297 non-surgical group and the non-surgical group, respectively.

298  
299 Table 2 shows health care costs and public transfer income given as weeks in the pre-period, year 1

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4 300 (12 months) and year 2 (24 months), respectively. The groups had similar health care costs during  
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7 301 the year prior to randomization (2,695 vs. 2,644 Euros). At 12 months after randomization, health  
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9 302 care costs in the TKR plus non-surgical group were more than double those of the non-surgical  
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11 303 group (16,343 vs. 7,028 Euros), mostly due to the surgical procedure. Although not statistically  
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13 304 significant, the costs in the TKR plus non-surgical group were lower at the 24 months follow-up  
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16 305 (6,733 vs. 7,486 €) because some patients in the non-surgical group underwent TKR. No significant  
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18 306 between-group differences were found in weeks of incurring public transfer income.  
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22 307 \*\*\*\*\* PLACE TABLE 2 AROUND HERE \*\*\*\*\*  
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27 309 The non-surgical group experienced a gain in health utilities of 0.056 from baseline to 24 months  
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29 310 while the TKR plus non-surgical group experienced a gain of 0.195, with the largest increases in  
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31 311 health utilities in both groups from baseline to 3 months (see Table 3 for utility values at the  
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33 312 different time points).  
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37 313 \*\*\*\*\* PLACE TABLE 3 AROUND HERE \*\*\*\*\*  
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42 315 Incremental costs and QALYs for each scenario are presented in Table 4. In all scenarios, TKR plus  
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44 316 non-surgical treatment was more expensive, but also more effective in terms of QALY gain.  
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47 317 Incremental cost-effectiveness ratios (ICERs) and the probability of cost-effectiveness at the  
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49 318 willingness-to-pay threshold for each scenario are also presented in Table 4. In the Base-case  
50  
51 319 (adjusted) scenario, TKR plus non-surgical treatment costed 32,611 Euros per QALY gained, which  
52  
53 320 is above the threshold for willingness-to-pay defined by NICE (22,665 Euros/QALY). However, in  
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56 321 the unadjusted Scenario 1 and unadjusted and without imputation of missing values (scenario 2) the  
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58 322 ICERs were below the threshold (19,917 Euros/QALY and 18,497 Euros/QALY, respectively). The  
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323 probability of cost-effectiveness of TKR plus non-surgical treatment was only 23.2% in the  
324 (adjusted) Base-case scenario but increased to 58.3% and 61.9% in Scenarios 1 and 2, respectively.

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

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

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

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

### 335 **Sub-analysis including deaths**

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

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



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4 346 the Base-case scenario, the ICER was more than twice as high as the threshold for willingness-to-  
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7 347 pay defined by NICE (22,665 Euros/QALY), and the probability of cost-effectiveness was only  
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9 348 7.8%. In Scenario 1 and 2 the probability of cost-effectiveness was 12.4% and 13.8%, respectively.  
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## 58 361 **DISCUSSION**

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4 362 TKR plus non-surgical treatment appear to be more expensive, but also more effective than non-  
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7 363 surgical treatment after 24 months in patients with knee OA eligible for TKR and moderate  
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9 364 intensity pain. The cost-utility analysis suggested that TKR plus non-surgical treatment was not  
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11 365 cost-effective compared to non-surgical treatment with the option of later TKR if needed from a 24-  
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13 366 month health system perspective in secondary care in Denmark when adjusting for covariates and  
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16 367 imputing missing values. Results were sensitive to changes, as the treatment was cost-effective in  
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18 368 the unadjusted scenario, highlighting the need for further research with 5 to 10-year time horizons.  
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21 369 Given the extensive burden of knee OA<sup>3,4</sup>, there is considerable societal demand for evidence on  
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23 370 cost-effective evidence-based treatments<sup>25</sup>. The current study provides the first direct comparison of  
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26 371 two different treatment strategies in terms of cost-effectiveness after 24 months for patients with  
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28 372 moderate to severe symptomatic and radiographic knee OA. The cost-utility analysis was conducted  
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30 373 alongside a randomized trial, which demonstrated that TKR plus non-surgical treatment compared  
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32 374 to non-surgical treatment was twice as effective in terms of pain relief and functional improvements  
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35 375 after 12 and 24 months<sup>13,26</sup>. Therefore, we hypothesized that TKR would be a cost-effective  
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37 376 procedure after 24 months due to higher improvements in quality of life counterbalancing the  
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40 377 expected additional cost related to the procedure. However, in contrast to our hypothesis, TKR plus  
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42 378 non-surgical treatment was not found to be cost-effective compared to non-surgical treatment with  
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44 379 the option of later TKR if needed from a 24 months perspective in secondary care in Denmark. The  
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46 380 cost per QALY gained exceeded the threshold defined by NICE by approximately 10,000 Euros<sup>24</sup>.  
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49 381 However, without adjustment for covariates and imputation of missing values the cost per QALY  
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51 382 was just cost-effective according to the threshold (ICER of 18,497 Euros/QALY).  
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54 383 Our results from the Base-case scenario contrast with findings in a recent systematic review<sup>27</sup>. The  
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56 384 review included four studies examining the cost-effectiveness of TKR compared to non-surgical  
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59 385 procedures and all four concluded that TKR was a cost-effective option. However, as opposed to  
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4 386 our study, none of the previous studies were based on a randomized trial and the content of the non-  
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7 387 surgical treatment was neither as comprehensive nor aligned with evidence-based recommendations  
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9 388 as the non-surgical treatment in our study. Two of the previous studies used a Markov model to  
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11 389 assess the long-term and lifetime cost-effectiveness of TKR<sup>28,29</sup>. The remaining two were cohort-  
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13 390 based studies examining short-term cost-effectiveness of TKR<sup>30,31</sup>. A recent cohort-based cost-  
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16 391 effectiveness analysis, not included in the systematic review, concluded that TKR was not cost-  
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18 392 effective at a group level over 8 years, while it would be cost-effective if it was restricted to patients  
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20 393 with more severe symptoms<sup>14</sup>. In contrast, we did not find that TKR was cost-effective in addition  
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23 394 to non-surgical treatment after 24 months in patients with moderate intensity pain. Our study  
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25 395 provides the first cost-effectiveness analysis of TKR in addition to recommended non-surgical  
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27 396 treatment using two comparable treatment groups, thereby providing an important addition to the  
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30 397 above mentioned non-randomized studies.

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33 398 One could argue that extending the time horizon might have led to a different conclusion. If the  
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35 399 positive effect of the surgery persists beyond the 24 months, TKR plus non-surgical treatment might  
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37 400 eventually end up being a cost-effective option. Though the mean utility fluctuates slightly over  
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40 401 time in both groups, there seems to be an overall improvement in the TKR plus non-surgical group  
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42 402 as compared to non-surgical treatment only. Assuming that this between-group difference is at least  
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44 403 maintained and a potential increased cost in the non-surgical group due to future TKR surgery, this  
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46 404 could improve the cost-effectiveness ratios in favor of TKR plus non-surgical treatment. However,  
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49 405 as indicated by a previous report<sup>32</sup>, improvements in symptoms might decline from 1 to 5 years  
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51 406 after TKR, questioning the assumptions underlining a potential long-term cost-effectiveness of  
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53 407 TKR. In the TKR plus non-surgical group, three people died during the period, while only one  
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56 408 person died in the non-surgical group. When including the deaths in the analysis, TKR plus non-  
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58 409 surgical treatment was still more effective than non-surgical treatment, though not as effective as in  
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410 the primary analysis. This is because death corresponds to a QALY value of zero, thereby  
411 attenuating the effect of the surgery.

## 412 **Strengths and limitations**

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

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4 432 to be of high quality. Linkage between these registries and the Danish Civil Registration system  
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6 433 allowed for retrieving data on an individual level, which is a unique feature of this study.  
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## 11 12 13 435 **CONCLUSIONS**

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17 436 From a 24 months perspective in secondary care in Denmark, TKR plus non-surgical treatment does  
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19 437 not appear to be cost-effective compared to non-surgical treatment with the option of later TKR if  
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21 438 needed in patients with moderate to severe osteoarthritis and moderate intensity pain, eligible for  
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24 439 TKR. However, as TKR plus non-surgical treatment was just cost-effective when not adjusting for  
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26 440 covariates and not imputing missing values, further confirmatory studies with longer follow-up are  
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28 441 needed.  
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457

## 458 **Author contributions**

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

461 **Recruitment of patients:** Laursen, Simonsen.

462 **Acquisition of data.** Skou, Kjellberg

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

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

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

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

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23  
24 485 decision to submit the manuscript for publication.  
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## 30 487 **Conflict of interest**

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32  
33 488 Dr. Roos is deputy editor of Osteoarthritis and Cartilage, the developer of the Knee injury and  
34  
35 489 Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome  
36  
37 490 measures and co-founder of Good Life with Osteoarthritis in Denmark (GLA:D), a not-for profit  
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40 491 initiative hosted by the University of Southern Denmark aimed at implementing clinical guidelines  
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42 492 for osteoarthritis in clinical practice.  
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49 495 work. He is co-founder of GLA:D, a not-for profit initiative hosted by the University of Southern  
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51 496 Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.  
52

53 497 Ms. Ibsen is partner in the company i2minds, who specialize in collecting, processing and analyzing  
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56 498 data and information.  
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58 499 The authors report no other conflict of interest.  
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## 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

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

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

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## 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 <sub>4</sub>	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<sub>4</sub>: 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).

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689**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									
General practitioner	448	421	1.000	454	351	0.550	382	361	1.000
Medical specialist	270	238	1.000	325	193	0.010*	246	201	0.900
Physiotherapy	126	122	1.000	84	91	1.000	91	90	1.000
Chiropractic	37	42	1.000	24	45	0.980	25	44	1.000
Lab work and other	3	5	1.000	5	5	1.000	6	3	1.000
Other	12	14	1.000	17	18	1.000	15	24	1.000
Prescription medication, all									
Other medication	599	443	1.000	704	472	0.950	620	471	1.000
Pain medication	534	377	1.000	607	382	0.920	572	403	1.000
NSAID (N02B + M01A)	65	66	1.000	97	91	1.000	48	69	1.000
Opioids (N02A)	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.

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

Utilities	TKR+non-surgical group						Non-surgical group					
	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.

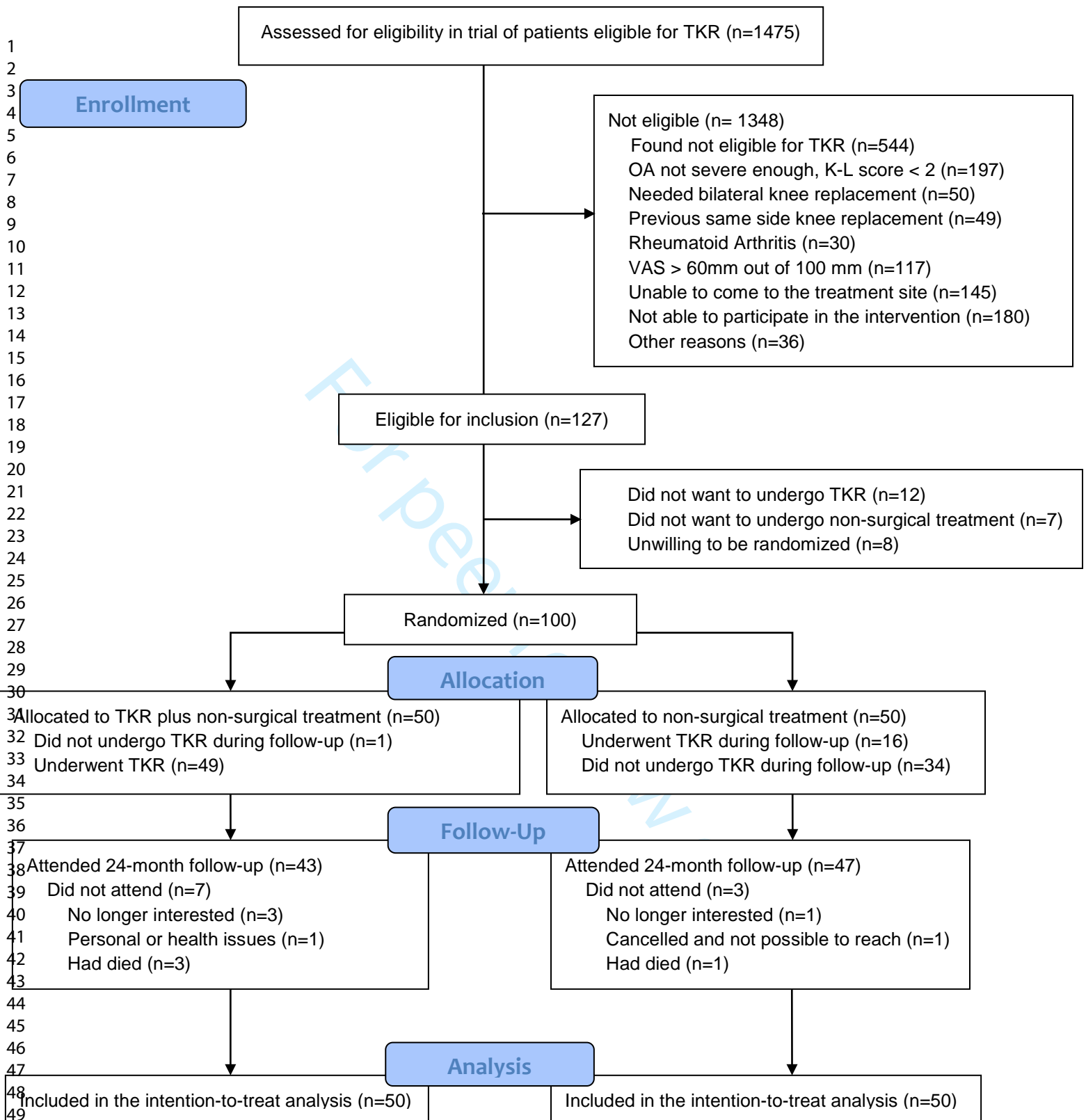
695 **Table 4. Primary analysis excluding deaths. Incremental cost-effectiveness ratios (ICERs) and probability of cost-effectiveness of TKR plus**  
 696 **non-surgical treatment vs non-surgical treatment alone for each scenario.**

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

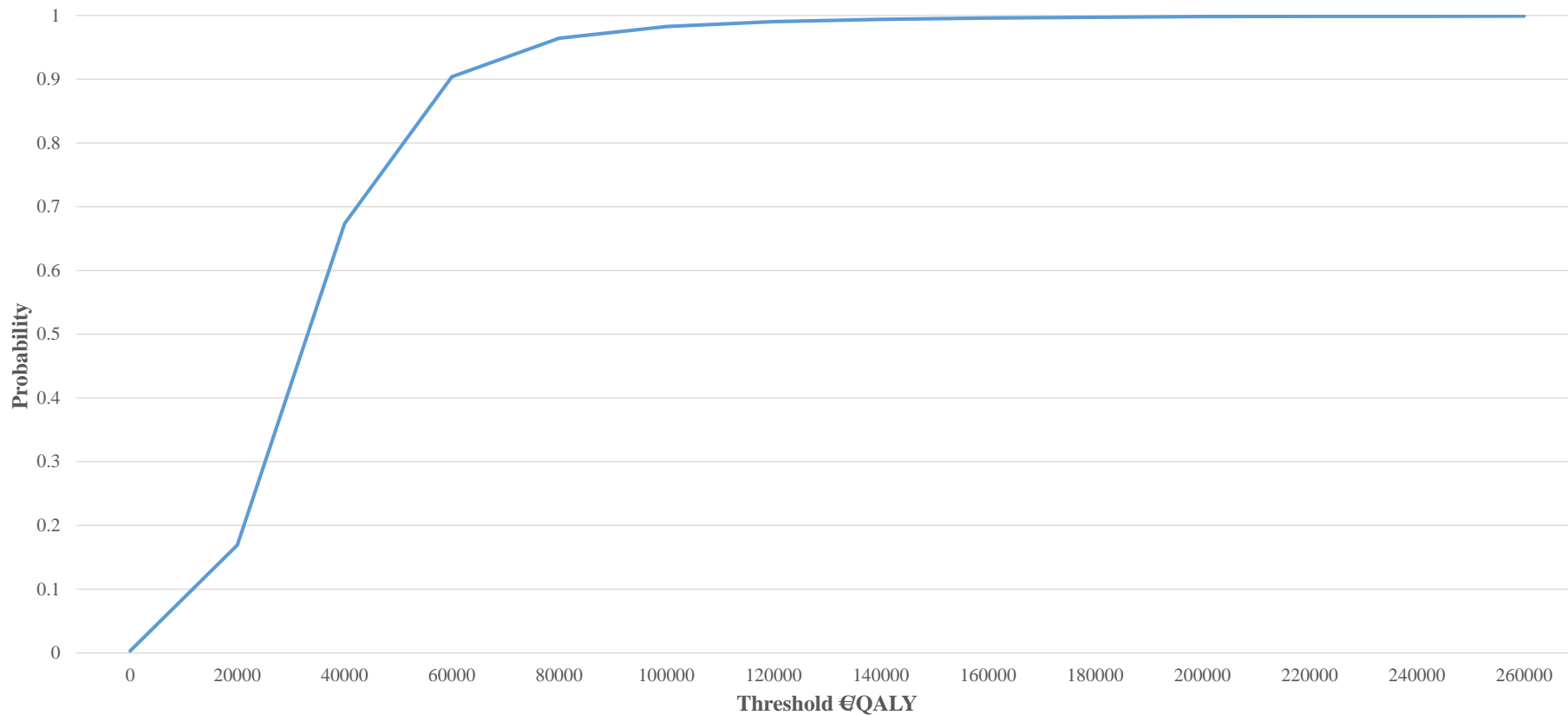
TKR=Total knee replacement; QALY=quality-adjusted life-years; 95% CI=95% confidence interval  
 Base-case=Adjusted for age, sex and baseline value  
 Scenario 1=unadjusted; Scenario 2=unadjusted and without imputation of missing values

## Supporting information captions

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







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## 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.**

Utilities	TKR+non-surgical group						Non-surgical group					
	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.**

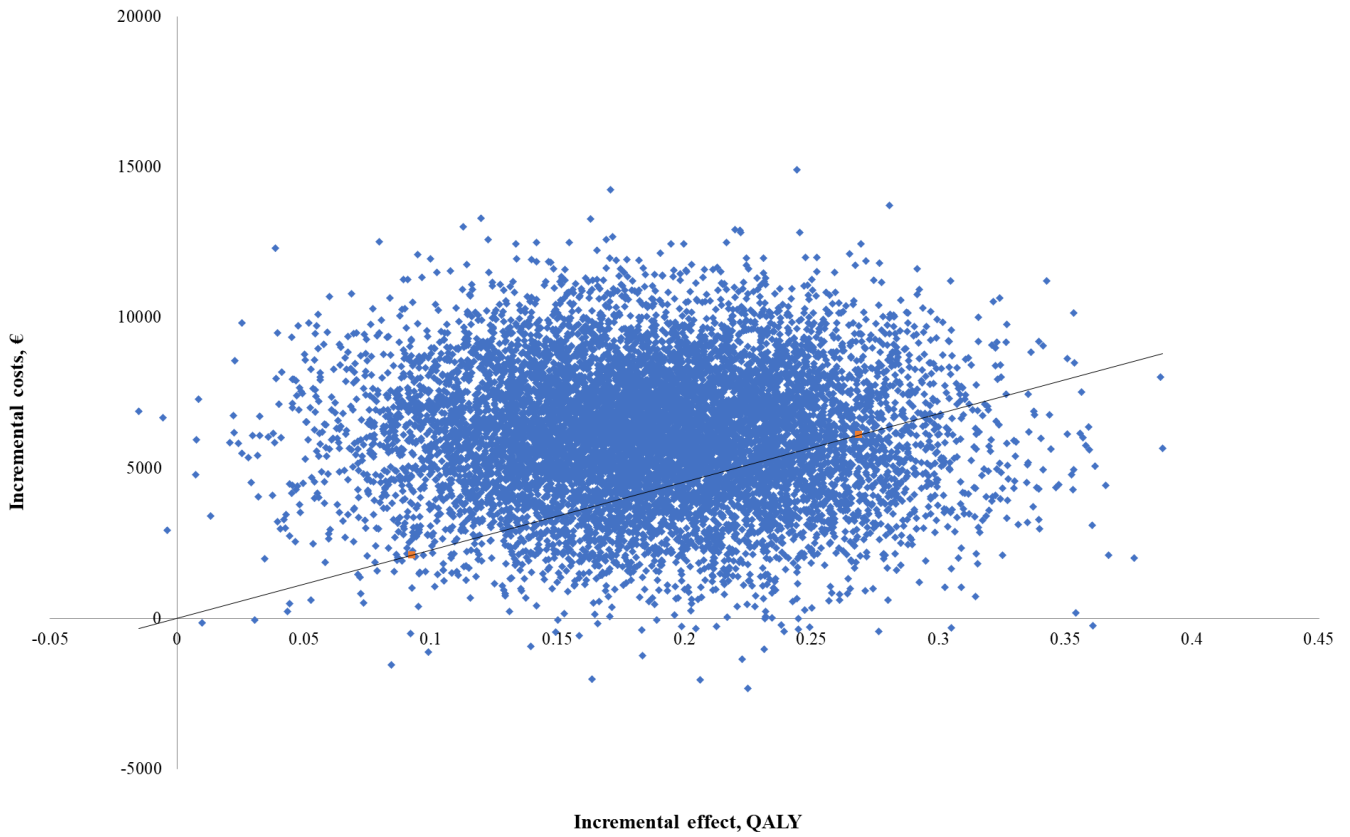
Analysis	Incremental cost	95% CI	Incremental effect	95% CI	ICER	Probability of cost-effectiveness at € 22,665
	€		QALY		€/QALY	%
Base-case	7,880	2,894 to 12,867	0.123	-0.011 to 0.257	64,208	7.8
Scenario 1	8,585	2,442 to 14,728	0.178	0.011 to 0.346	48,128	12.4
Scenario 2	8,805	2,201 to 15,409	0.190	0.023 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).



view only

## 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
<b>Title and abstract</b>			
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
<b>Introduction</b>			
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
<b>Methods</b>			
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	<i>Single study-based estimates:</i> 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



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
2				
3				
4	Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
5				
6	Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> 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
7				
8		13b	<i>Model-based economic evaluation:</i> 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
9				
10	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
11				
12	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
13				
14	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	12-13
15				
16	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
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19	<b>Results</b>			
20	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
21				
22	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
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24	Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	
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1		of methodological assumptions (such as discount rate, study perspective).	14-16
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4	20b	<i>Model-based economic evaluation</i> : 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
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7	Characterising heterogeneity	21	
8		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
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13	<b>Discussion</b>		
14	Study findings, limitations, generalisability, and current knowledge	22	
15		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
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19	<b>Other</b>		
20	Source of funding	23	
21		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
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24	Conflicts of interest	24	
25		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
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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>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. 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. *Value Health* 2013;16:231-50.

