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**Five-year follow-up of patients with knee osteoarthritis not eligible for total knee replacement: results from a randomized trial**

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Five-year follow-up of patients with knee osteoarthritis not eligible for total knee replacement: results from a randomized trial

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ABSTRACT

Objectives:

To investigate the 5-year outcomes in patients with radiographic and symptomatic knee osteoarthritis, randomized to one of two non-surgical treatments.

Setting:

Two study centers

Participants:

At baseline, 100 patients with radiographic and symptomatic knee osteoarthritis not found eligible for total knee replacement were included. Exclusion criteria were a score above 75 of the four Knee injury and Osteoarthritis Outcome Score subscales (pain, symptoms, function of daily living and quality of life; KOOS4) and 2) an average knee pain intensity in the previous week greater than 60 mm on a 100 mm visual analog scale.

Interventions

Patients were randomized to either supervised non-surgical treatment (MEDIC) or written advice. The MEDIC treatment included patient education, neuromuscular exercise, insoles, and a dietary weight loss program and/or pain medication if needed and written advice consisted of two leaflets.
Primary and secondary outcome measures:

Primary outcome was 5-year mean change of the KOOS₄. Secondary outcomes included KOOS subscales, self-reported general health, usage of pain medication and self-reported physical activity.

Results:

Thirty-nine (78%) and 36 (72%) from the MEDIC and written advice groups responded at 5-years. There were no between-group differences in KOOS₄ (mean improvement of 22.8 and 19.1, difference 5.3 (95% CI: -1.5 to 12.1), or any secondary outcomes. Seventy-six percent of the MEDIC group and 66% of the written advice group experienced clinically important improvements in KOOS₄.

Fifteen patients (30%) from the MEDIC group and 17 (34%) from the written advice group received knee replacement. Undergoing knee replacement did not result in a greater improvement in KOOS₄ (difference 6.1 (95% CI: -1.1 to 13.4)).

Conclusions:

No clinically relevant differences between supervised non-surgical treatment and written advice were demonstrated at 5-years. Most patients experienced clinically important improvements, irrespective of initial treatment strategy or knee replacement surgery.

Trial registration: ClinicalTrials.gov, NCT01535001.

Strengths and limitations of this study

- Long-term follow-up of patients with radiographic and symptomatic knee osteoarthritis.
Information on knee replacement (KR) surgery during follow-up was available from the hospital registry, ensuring high validity.

Outcomes of patients undergoing and not undergoing KR at different time points allows for an evaluation of different trajectories of patient outcomes over five years.

Outcomes are subjective and self-reported and no objective measures were included.

Given the long-term follow-up patients could have engaged in other treatments over time that could not be accounted for in the study.

BACKGROUND

Knee osteoarthritis (OA) is a leading contributor to pain and physical impairment and has substantial personal and societal impact, affecting hundreds of millions of people worldwide(1-3). Unicompartmental and total knee replacement (KR) are considered effective treatments of end-stage knee OA(4). As only 18-30% with OA undergo KR in a lifetime perspective(5,6), effective non-surgical treatments are needed for the vast majority of the population. First-line treatment for patients with knee OA includes multimodal non-surgical treatment consisting of exercise, patient education and weight management, while biomechanical interventions and pharmacological treatment can be initiated if needed(7-9).

Previously, our randomized controlled trial (RCT) with 12-month follow-up showed that non-surgical treatment, consisting of patient education, supervised exercise, weight loss, insoles, and pain medication (the MEDIC treatment) produced clinically significant improvements in patient-reported outcomes compared to written advice in patients with knee OA found not eligible for KR( 10). Prior research indicates that the effect of non-surgical treatment appears
to decrease over time (11,12). This could be due to a decrease in adherence over time.

However, the results from the 24-month follow-up of our RCT show that patients maintain improvements in patient-reported outcomes following both non-surgical treatments (13).

Therefore, improvements gained from non-surgical treatments could possibly be sustained for longer than 2 years, but long-term follow-up studies are required to investigate this.

Some patients found not eligible for KR by an orthopedic surgeon may experience a progression of OA and may later receive a KR (14). For patients diagnosed with knee OA, a lifetime risk of 30% for undergoing KR surgery has been reported (5). In general, patients receiving KR surgery will experience pain relief and functional improvements (4,15). This is important to take into consideration when evaluating long-term outcomes following non-surgical treatments.

Hence, the aim of this report was three-fold; 1) to investigate the 5-year outcomes following non-surgical treatments, 2) to determine the proportion undergoing KR in patients with knee OA initially receiving non-surgical treatment and 3) whether the 5-year outcomes differed in patients undergoing KR as compared to those not undergoing KR.

METHODS

Trial design

This is an exploratory analysis of the 5-year follow-up of a parallel group RCT (1:1 treatment allocation). The report follows the Consolidated standards of reporting trials (CONSORT) statement for reporting RCTs (16). The RCT was pre-registered at ClinicalTrials.gov (NCT01535001). Prior to the original RCT, a study protocol was published (17) in which details of the recruitment process, full eligibility criteria, and the process of randomization and allocation concealment were given. Written informed consent was obtained from patients prior to participation.
Patients and recruitment process

Patients were enrolled in the period between April 3, 2012 and July 12, 2013 from two outpatient clinics (Frederikshavn and Farsoe) at the Department of Orthopedics, Aalborg University Hospital, Denmark. Patients were referred to the outpatient clinics by their general practitioner. In total, 100 patients were recruited, all fulfilling the inclusion criteria of symptomatic and radiographically confirmed knee OA (Kellgren & Lawrence score ≥ 1 on the original scale(18)), but found not eligible for KR by the orthopedic surgeon (eligibility was based on factors such as pain, function and radiographic severity(19)). Main exclusion criteria were 1) a score above 75 on the Knee injury and Osteoarthritis Outcome Score (KOOS), defined as the average score for the subscales pain, symptoms, function of daily living and quality of life(20) and 2) an average knee pain intensity in the previous week greater than 60 mm on a 100 mm visual analog scale (VAS).

Patient and public involvement

Two patients with knee osteoarthritis participated in a feasibility study (unpublished). They underwent the non-surgical treatment (the MEDIC-treatment) and gave feedback on study procedures.

Randomization and allocation concealment

A priori, the randomization schedule was generated in permuted blocks of eight, stratified by clinic. The allocation numbers were concealed in opaque envelopes, which were organized by a staff member, who had no other part in the study. One research assistant at each clinic had access to the envelopes and these were opened following informed consent and baseline assessment.

Interventions
Patients were randomized either to receive the supervised MEDIC treatment program or to receive written advice. Both interventions have been thoroughly presented elsewhere\cite{10,13,17}. In brief, the MEDIC treatment included five components: patient education, neuromuscular exercise, insoles, and a dietary weight loss program (if a body mass index \(\geq 25\) at baseline) and/or pain medication prescribed if needed to participate in the exercise. Physiotherapists and dieticians supervised the treatments, which were delivered over a period of 12 weeks.

The written advice consisted of two standardized information leaflets containing information regarding etiology, symptoms, functional limitations, recommended treatments and general information on how to sustain a healthy lifestyle (the MEDIC group also received these leaflets).

**Outcomes**

Baseline and follow-up assessments at 3, 6, 12, 24 months were conducted at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital. At 5-year follow-up, the included patients were contacted by phone and urged to participate in the follow-up measurements. The same outcome assessor, who was specifically trained in all assessments, handled all measurements at 5 years. The outcome assessor was blinded towards treatment allocation and was not involved in other aspects of the study. At baseline and all follow-up time points, KOOS\textsubscript{4}, all KOOS subscales, self-reported general health and self-reported usage of pain medication were measured, whereas self-reported physical activity level was assessed only at the 5-year follow-up.

**Primary outcome measure**

The primary outcome for this 5-year follow-up was the between-group difference in change in KOOS\textsubscript{4}, with scores ranging from 0 (worst) to 100 (best). KOOS\textsubscript{4} was defined as the average
score for the subscales pain, symptoms, function of daily living (ADL) and quality of life(21,22). In order to evaluate whether clinically significant improvements from baseline had occurred, a minimal clinically important difference of 10 points in KOOS outcomes was applied(22). KOOS has been found to be a valid, reliable and responsive patient-reported outcome measure in studies of patients with knee OA and KR(20).

Secondary outcome measures

Patient-reported outcome measures

All five KOOS subscales, including sport/recreation, were assessed in order to support clinical interpretation of the primary outcome(23). Self-reported general health was measured using the descriptive index (EQ-5D Index) and the EQ VAS from the EQ-5D-3L to investigate changes in general health(24,25). Patients were asked to estimate their level of physical activity using the 10-point University of California Los Angeles (UCLA) activity-level rating in which the score that best described their physical activity level was chosen. Scores range from 1 to 10, with 1 representing “wholly inactive, dependent on others; cannot leave residence” and 10 representing ”regularly participate in impact sports such as jogging, tennis, skiing, acrobatics, ballet, heavy labor, or backpacking”(26). Self-reported usage of pain medication, defined as type, dosage and quantity taken within the last week, was assessed. Usage was dichotomized into yes/no due to non-uniformity of the distribution of pain medication intake.

Knee replacement

All patients undergoing KR were registered using the hospital’s medical records, which allowed for tracking of each individual patient. Joint replacement surgery was registered for both the index knee and the non-index knee.

Statistical analysis
Sample size

The sample size for this follow-up was determined by number of participants included in the RCT, based on the power calculation for the original 12-month endpoint. The sample size calculation for the 12-month endpoint was based on a 10-point difference between groups in the primary outcome KOOS4 (SD 14, power of 90% and P-value of 0.05 (two-sided))(21,22). Therefore, 41 patients in each group were required, but to account for missing data, a total of 100 patients were randomized. Thus, this 5-year follow-up included these 100 patients.

Primary and secondary analyses

The data analysis of the 5-year results was conducted using the same procedure as in the previous 12 and 24-month reports(10,13). Both the primary and secondary outcomes were analyzed using the intention-to-treat (ITT) method and the ITT population consisted of those randomized to the two treatment arms (n = 100). Between-group comparisons of treatment effect for all primary and secondary outcomes, except for pain medication and subjective physical activity, were performed using a linear mixed effects model with patient as a random factor and follow-up time (baseline, 3, 6, 12 and 24 months and 5 years), treatment arm (MEDIC treatment vs written advice), and site (Frederikshavn, Farsoe) as fixed factors. Interaction between follow-up and treatment arm was also included in the model. Since the linear mixed effects model includes all patients when at least the baseline value or a follow-up value is present, no imputation was required(27). Crude and adjusted (site) analyses were performed. The between-group differences in changes from baseline and 95% CI are presented. The relative risk of using pain medication was compared between groups using a modified Poisson regression model with a robust error estimator for the confidence intervals (CI) and accounting for clustering at patient level(28). To assess the difference between the groups for self-reported physical activity at 5-year follow up, Fisher’s exact test and the two-
sample $t$ test were applied to categorical and continuous data, respectively. The assumption of normally distributed data within groups was assessed and deemed reasonable from quantile plots.

A responder analysis, illustrating the proportion of patients in each group that experienced a minimal clinically important improvement for the KOOS$_4$ outcome, was conducted and results were analyzed using a Chi-squared test.

We conducted an analysis in which patients that had received KR were identified and compared to patients who had not received KR, using the same statistical model as for the primary and secondary outcomes. For the purpose of evaluating the influence of KR, the allocated treatment groups were combined and analyzed based on whether patients received KR or not.

Figures including data from all time points (baseline, 3, 6, 12, 24 months, and 5 years) are presented to visualize change over time in KOOS$_4$ for the patients allocated to the MEDIC group vs the written advice group and for the patients with and without KR. A similar figure illustrating the four groups ‘MEDIC with KR’, ‘MEDIC without KR’, ‘written advice with KR’ and ‘written advice without KR’ is displayed as supplementary material.

A confidence interval excluding 0 (1 for proportions) corresponding to a two-sided P value less than 0.05 was considered sufficient to reject the null hypothesis and conclude that there was a statistically significant difference between groups. All analyses were carried out in Stata 16.1 (StataCorp, College Station, TX, USA).

**RESULTS**

**Participant characteristics**
Patient flow can be seen in Figure 1 and baseline characteristics for the treatment groups can be observed in Table 1. Of the 100 patients randomized, respondents to the 5-year follow-up included 39/50 (78%) patients in the MEDIC treatment group and 36/50 (72%) patients in the written advice group (Figure 1). There were no significant differences in baseline characteristics for those attending 5-year follow-up and those that did not (supplementary file 1). The mean time from baseline to 5-year follow-up was 60.9 months (SD 2.5) in both groups.

Table 1: Baseline characteristics. Values are mean (SD) unless otherwise stated.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>MEDIC treatment (n= 50)</th>
<th>Written advice (n= 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>26 (52)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.8 (8.7)</td>
<td>67.1 (9.1)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>30.6 (5.6)</td>
<td>29.4 (5.2)</td>
</tr>
<tr>
<td>Bilateral knee pain, n (%)</td>
<td>18 (36)</td>
<td>21 (42)</td>
</tr>
<tr>
<td>Radiographic knee osteoarthritis severity (Kellgren–Lawrence), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>7 (14)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>13 (26)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>13 (26)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>17 (34)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>KOOS scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS₄</td>
<td>48.9 (11.8)</td>
<td>53.2 (12.1)</td>
</tr>
<tr>
<td>Pain</td>
<td>51.6 (14.3)</td>
<td>53.6 (13.7)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>54.6 (15.9)</td>
<td>59.5 (18.3)</td>
</tr>
<tr>
<td>ADL</td>
<td>55.5 (17.1)</td>
<td>60.4 (16.4)</td>
</tr>
<tr>
<td>Sport/Recreation</td>
<td>24.5 (18.2)</td>
<td>23.0 (16.5)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>34.0 (12.4)</td>
<td>39.5 (14.5)</td>
</tr>
<tr>
<td>EQ-5D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D index</td>
<td>0.660 (0.160)</td>
<td>0.689 (0.145)</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>64.9 (18.6)</td>
<td>68.2 (21.3)</td>
</tr>
<tr>
<td>Have used pain medication in the last week, n (%)</td>
<td>32 (64)</td>
<td>30 (60)</td>
</tr>
</tbody>
</table>

Radiographic osteoarthritis severity: Radiographic knee osteoarthritis severity on the Kellgren–Lawrence scale; KOOS₄: 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) and Quality of life, with scores ranging from 0 to 100 (worst to best scale).

**Primary outcome**

There was no difference in change in KOOS₄ between the MEDIC group and the written advice group (Table 2, Figure 2).

The responder analysis showed that 76% of the patients in the MEDIC group had experienced clinically important improvements and 66% in the written advice group at 5-year follow-up. No difference in the proportion of responders between groups was observed (relative risk 1.15 (95% CI 0.85 to 1.56).

**Table 2: Self-reported outcomes from baseline to 5-year follow up**

<table>
<thead>
<tr>
<th>Outcome (number of data pointsMEDIC, number of data pointswritten advice)*</th>
<th>Improvement in MEDIC group (95% CI)</th>
<th>Improvement in written advice group (95% CI)</th>
<th>Between-group (MEDIC vs. written advice) difference (crude) (95% CI)</th>
<th>Between-group (MEDIC vs. written advice) difference (adjusted)† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean change in KOOS₄ from baseline to 5-years</td>
<td>22.8 (16.9 to 28.8)</td>
<td>19.1 (10.8 to 27.3)</td>
<td>5.3 (-1.5 to 12.1)</td>
<td>5.3 (-1.5 to 12.1)</td>
</tr>
<tr>
<td>(267, 264)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
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</tr>
<tr>
<td>KOOS Pain</td>
<td>20.5 (13.1 to 27.8)</td>
<td>22.2 (13.1 to 31.2)</td>
<td>0.6 (-7.2 to 8.5)</td>
<td>0.6 (-7.2 to 8.4)</td>
</tr>
<tr>
<td>(270, 264)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS Symptoms</td>
<td>20.3 (13.7 to 27.0)</td>
<td>16.9 (8.4 to 25.4)</td>
<td>4.7 (-3.0 to 12.3)</td>
<td>4.7 (-3.0 to 12.4)</td>
</tr>
<tr>
<td>(270, 264)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>21.4 (14.8 to 27.9)</td>
<td>17.1 (8.3 to 25.8)</td>
<td>6.8 (-1.2 to 14.8)</td>
<td>6.8 (-1.2 to 14.8)</td>
</tr>
<tr>
<td>(270, 264)</td>
<td></td>
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</tr>
<tr>
<td>KOOS Sport/Recreation</td>
<td>16.5 (8.3 to 24.7)</td>
<td>22.8 (11.2 to 34.4)</td>
<td>-5.3 (-15.2 to 4.5)</td>
<td>-5.3 (-15.1 to 4.5)</td>
</tr>
<tr>
<td>(267, 257)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
KOOS Quality of life
(267, 264)
25.7
(18.2 to 33.2)
20.2
(11.1 to 29.2)
6.6
(-1.4 to 14.7)
6.6
(-1.4 to 14.7)

Mean change in EQ-5D
EQ-5D index (269, 264)
0.138
(0.074 to 0.203)
0.138
(0.060 to 0.215)
0.025
(-0.043 to 0.092)
0.025
(-0.043 to 0.092)
EQ VAS (267, 265)
6.0
(0.1 to 11.8)
10.2
(1.7 to 18.6)
-2.1
(-10.7 to 6.6)
-2.1
(-10.7 to 6.6)

* n refers to the number of data points out of 300 in each group (50 at baseline, 3, 6, 12, 24-months, and 5-years).
† The results were adjusted for follow-up (baseline, 3, 6, 12, 24 months, and 5 years), site (Frederikshavn, Farsoe), baseline values and interaction between follow-up and treatment arm. A positive between-group difference indicates a difference in favor of the MEDIC group and a negative between-group difference indicates a difference in favor of the written advice group. KOOS: Knee injury and Osteoarthritis Outcome Score.
KOOS4: 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) and Quality of life, with scores ranging from 0 to 100 (worst to best scale); Sport/Rec: Function in sport and recreation

Secondary outcomes
For all KOOS subscales, EQ-5D index and EQ VAS, no differences in improvement between groups were observed in the adjusted analysis (Table 2).
Change in use of pain medication did not differ between the groups (supplementary file 2).
There was no difference between groups (0.1 (95% CI -1.0 to 0.8)) for self-reported physical activity (UCLA) with the MEDIC group reporting a mean score of 6.1 (SD 2.0) and the written advice group reporting a mean score of 6.3 (SD 1.9).
A total of 15 patients (30%) from the MEDIC treatment group and 17 patients (34%) from the written advice group had KR in the index knee within the period from baseline to 5 years. No difference in risk for undergoing KR was observed with a relative risk of 1.13 (95% CI 0.64 to 2.01) for the written advice group compared to the MEDIC group.
Five patients received bilateral KR in the study period, two from the MEDIC group and three from the written advice group, and one patient from the written advice group received a KR in the non-index knee in the study period.

Secondary analysis

Table 3 and Figure 3 show the improvements from baseline to 5-year follow-up for patients divided into those receiving or not receiving KR.

No between-group difference in KOOS was observed (Table 3).

Table 3: Self-reported outcomes from baseline to 5-year follow up for patients receiving and not receiving knee replacement (KR).

<table>
<thead>
<tr>
<th>Outcome (number of data points)</th>
<th>Improvement in patients without KR (95% CI)</th>
<th>Improvement in patients with KR (95% CI)</th>
<th>Between-group (with KR vs. without KR) difference (crude) (95% CI)</th>
<th>Between-group (with KR vs. without KR) difference (adjusted)† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in KOOS from baseline to 5 years (351, 180)</td>
<td>18.7 (12.5 to 25.0)</td>
<td>25.3 (16.9 to 33.6)</td>
<td>6.1 (-1.1 to 13.4)</td>
<td>5.7 (-1.6 to 13.1)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS Pain (354, 180)</td>
<td>18.7 (11.7 to 25.6)</td>
<td>26.3 (16.3 to 36.4)</td>
<td>7.3 (-1.1 to 15.6)</td>
<td>6.6 (-1.7 to 14.9)</td>
</tr>
<tr>
<td>KOOS Symptoms (354, 180)</td>
<td>17.7 (11.2 to 24.1)</td>
<td>20.7 (11.3 to 30.1)</td>
<td>3.7 (-4.3 to 11.7)</td>
<td>3.3 (-4.7 to 14.1)</td>
</tr>
<tr>
<td>KOOS ADL (354, 180)</td>
<td>17.2 (10.3 to 24.1)</td>
<td>23.5 (15.1 to 31.8)</td>
<td>6.0 (-2.7 to 14.6)</td>
<td>5.6 (-3.2 to 14.3)</td>
</tr>
<tr>
<td>KOOS Sport/Recreation (349, 175)</td>
<td>19.1 (10.7 to 27.5)</td>
<td>19.8 (7.5 to 30.0)</td>
<td>-1.9 (-12.5 to 8.6)</td>
<td>-2.7 (-13.2 to 7.8)</td>
</tr>
<tr>
<td>KOOS Quality of life (351, 180)</td>
<td>19.0 (12.3 to 25.8)</td>
<td>30.5 (19.8 to 41.2)</td>
<td>9.2 (0.6 to 17.8)</td>
<td>9.0 (0.4 to 17.7)</td>
</tr>
<tr>
<td><strong>Mean change in EQ-5D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D index (352, 181)</td>
<td>0.118 (0.058 to 0.179)</td>
<td>0.174 (0.087 to 0.261)</td>
<td>0.037 (-0.034 to 0.109)</td>
<td>0.032 (-0.040 to 0.103)</td>
</tr>
<tr>
<td>EQ-5D VAS (352, 180)</td>
<td>7.8 (1.2 to 14.3)</td>
<td>8.5 (0.7 to 16.4)</td>
<td>-0.2 (-9.4 to 9.0)</td>
<td>0.0 (-9.2 to 9.2)</td>
</tr>
</tbody>
</table>
Treatment groups are merged into one population and compared based on those receiving knee replacement (KR) and those who did not. * n refers to the number of data points out of 50 in each group at 5 years. † The results were adjusted for follow-up (baseline, 3, 6, 12, 24 months, and 5 years), site (Frederikshavn, Farsoe), baseline values and interaction between follow-up and treatment arm. A positive between-group difference indicates a difference in favor of the KR group and a negative between-group difference indicates a difference in favor of the without KR group. KOOS: Knee injury and Osteoarthritis Outcome Score. KOOS4: 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) and Quality of life, with scores ranging from 0 to 100 (worst to best scale); Sport/Rec: Function in sport and recreation

For the KOOS subscales, there was a difference of 9.0 (95% CI 0.4 to 17.7) for the KOOS quality of life in favor of the KR group. No other differences were observed for the secondary outcomes (Table 3).

There was no difference for change in usage of pain medication with an adjusted relative risk of 0.44 (0.25 to 0.76) in the group without KR and 0.38 (0.21 to 0.69) in the group with KR (between-group relative risk 1.11, 95% CI 0.48 to 2.54).

For self-reported physical activity (UCLA), the group without KR reported a mean score of 5.9 (SD 1.8) and the group with KR reported a mean score of 6.7 (SD 2.2), illustrating no between-group difference (0.7 (95% CI -1.7 to 0.2)).

**DISCUSSION**

At 5 years, 76% in the supervised non-surgical treatment group and 66% in the written advice group experienced clinically important improvements in KOOS4 relative to baseline. We observed no differences in self-reported pain, function, quality of life, usage of medication or self-reported physical activity between patients initially undergoing supervised non-surgical treatment and patients receiving written advice only. One third of patients underwent KR, and undergoing KR did not result in greater improvement in KOOS4 or any of the secondary
outcomes, except for the KOOS quality of life subscale which demonstrated greater improvement in the KR group. Interestingly, clinically important improvements were observed in both groups, irrespective of the initial non-surgical treatment strategy and whether they received a KR or not. While the group receiving supervised non-surgical treatment initially improved faster than the group receiving written advice, both groups showed improvements from baseline to the 5-year follow-up. This highlights that having symptomatic knee OA severe enough to warrant consultation with an orthopedic surgeon does not necessarily mean that symptoms will worsen over time. On the contrary, symptoms may improve, as reported in this study of patients initially having had non-surgical treatment. Trajectories of change in symptoms over time without standardized non-surgical treatment has been reported previously. In support of our findings, Nicholls et al. (14) were able to group a population of knee OA patients into five pain trajectories of “mild, non-progressive” (35%), “progressive” (28%), “moderate” (22%), “improving” (12%) and “severe, non-improving” (3%). The study concluded that knee OA in general should not be characterized as “slowly progressive” (14). Similarly, Rice et al. (29) suggested that long-term worsening of pain is not an unavoidable consequence in patients with knee OA. Despite this, knee OA is commonly perceived as a progressive and degenerative condition that eventually could require KR surgery (5,14). Studies have shown that radiological outcomes seem to progress with time, but also highlighted the lack of associations between radiologic changes and perceived pain and functional limitations (30).

In contrast to previous long-term follow-ups of non-surgical treatments including an exercise component, both groups of our study sustained the improvements experienced at 12 and 24 months after 5 years. Pisters et al. (31) found improvements in pain and physical function from baseline to 15-month follow-up. From 15 months to 60 months, the improvements started to decline, but remained higher than the baseline values (31). Hurley et al. (32) observed a
similar trajectory for their knee OA patients at 30 months of follow-up; initial improvements, followed by a decline, but remaining higher than baseline values(32). Similarly, Messier et al.(33) observed that a treatment of diet and/or exercise improved the clinical outcomes from baseline to 1.5 years follow-up. However, this was followed by a decline in improvements at 3.5 years follow-up, but outcomes did remain better than baseline values(33). While the reasons for this discrepancy in long-term improvements are unknown, it could be partially explained by a greater proportion undergoing KR during follow-up in our study. About 1/3 of our patients received a KR during follow-up, while only about 1/5 of the patients in the studies by Pisters et al.(31) and Messier et al.(33) received KR. A difference in populations does not seem to explain the long-term improvements in our study. Comparing baseline values for our population and the populations in the before-mentioned studies(14,31-33) revealed no differences regarding age, sex, BMI, duration of symptoms and Kellgren-Lawrence grades.

Contrary to the 12- and 24-month follow-ups(10,13), where the supervised non-surgical treatment group experienced significantly greater improvements, no differences were observed between the two groups at 5 years. Furthermore, we did not find differences in number of patients undergoing KR or in terms of self-reported physical activity with both groups regularly participating in moderate physical activities. Except for KR, no information is available regarding other treatments received during follow-up, which could potentially influence the long-term outcomes. Due to loss to follow-up at 5 years, the statistical power in the present report is lower compared to previous studies, which could also influence the lack of statistically significant between-group differences.

The study retrospectively registered the proportion of patients undergoing KR using administrative data, therefore no data on the reasons for undergoing KR were available. In general, worse symptomatic and radiographic severity as well as unacceptable physical
function guide the decision on KR surgery\(^{(15,34)}\). Although it is not uncommon that patients are referred to orthopedic surgery prior to undergoing non-surgical treatment\(^{(35)}\), clinical guidelines propose KR surgery as a treatment option if first-line treatments does not provide sufficient effect\(^{(7,36,37)}\). This is in line with Figure 3 and supplementary file 3, which indicate that patients undergoing KR seemed to be those initially not improving as much from non-surgical treatment.

**Clinical implications**

The majority of the patients with knee OA in our population experienced clinically important improvements from baseline to 5 years. A similar proportion of patients in both treatment groups (MEDIC: 76% vs written advice 66%) could be classified as responders, i.e. experienced an improvement in KOOS\(_4\) from baseline to 5 years of at least 10 points. This further underlines that clinically important improvements can be experienced from non-surgical treatment in the longer term and that knee OA is not necessarily associated with progression of symptoms over time. This is an important message to clinicians and patients with knee OA, since previous reports have shown that patients believe that knee OA will inevitably get worse\(^{(38,39)}\).

**Limitations**

The improvements from baseline to 5 years in both treatment groups could be influenced by *regression towards the mean*, i.e. patients originally sought medical care when their symptoms were most intolerable. Our study did not include a no-treatment control group and we did not take other treatments than KR during follow-up into account. Therefore, we were not able to conclude whether the long-term improvements were due to the actual treatments evaluated. Likewise, it was not possible to consider structural progression in the knee over time or psychosocial factors, possibly influencing the outcomes. There was a loss to follow-
up of 22% in the MEDIC group and 28% in the written advice group, possibly influencing the ability to detect differences between groups. Given that the 95% CI (-1.5 to 12.1) of the main outcome KOOS4 included the minimal clinically important difference (10 points), the true difference in change between groups could potentially be clinically relevant in favor of the non-surgical treatment group. Finally, no information was available on the reasons for undergoing KR surgery in the study period. Therefore, it is unknown whether KR surgery occurred because of progression of radiographic and symptomatic OA, functional limitations or perceived lack of effect from non-surgical treatments. Importantly, these sub-group analyses of patients with or without KR are based on a low number of patients in each group, highlighting the need for further studies in the area.

CONCLUSIONS

We found no differences between supervised non-surgical treatment and written advice at 5 years in terms of self-reported outcomes and rate of KR. The vast majority of patients experienced clinically important improvements at 5 years, irrespective of initial treatment strategy and whether they underwent KR or not. This highlights that having knee OA is not necessarily associated with progression of symptoms over time and that non-surgical treatments are relevant and effective as first-line interventions with long-term effect for patients with knee OA.

Research Ethics Approval

The study was approved by the local Ethics Committee of The North Denmark Region (N-20110085) and approval was extended for this long-term follow-up since the 5-year follow-up was not part of the initial registration. Written informed consent was obtained from patients prior to participation.
Funding

This trial is partially funded by The Danish Rheumatism Association and The Association of Danish Physiotherapists Research Fund. Dr. Skou is currently funded by a program grant from Region Zealand (Exercise First) and two grants from the European Union’s Horizon 2020 research and innovation program, one from the European Research Council (MOBILIZE, grant agreement No 801790) and the other under grant agreement No 945377 (ESCAPE). The funders did not have any role in this study other than to provide funding and all authors are independent from the funders.

Competing interests

ER is deputy editor of Osteoarthritis and Cartilage, the developer of the Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures and co-founder of Good Life with Osteoarthritis in Denmark (GLA:D®), a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice. STS is associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is co-founder of GLA:D®.

Author Contributions

Study conception and design: ER, ML, MSR, LAN, SR, STS. Acquisition of data: ER, ML, ST, STS. Analysis and interpretation of data: JBL, ER, ML, SH, MNJ, MSR, LAN, ST, STS. Drafting the article: JBL, STS. Revising the article critically for important intellectual content: JBL, ER, ML, SH, MNJ, MSR, LAN, ST, STS. Final approval of the article: JBL, ER, ML, SH, MNJ, MSR, LAN, ST, STS. All authors agree to be accountable for all aspects...
of the work in ensuring that questions related to the accuracy or integrity of any part of the
work are appropriately investigated and resolved.

**Patient consent for publication**

Not applicable

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the
corresponding author on reasonable request.

**Acknowledgments**

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treatment in the study. Finally, the study funders and patients participating should be
acknowledged, because without their participation, it would not have been possible to conduct
the trial.
References


Figure 1: Flow diagram of the patients in the randomized controlled trial from baseline to 5-year follow-up. K-L score: Kellgren-Lawrence grade. KOOS4: The average score for the Knee injury and Osteoarthritis Outcome Score subscales for pain, symptoms, function of daily living (ADL), and quality of life. KR: Knee replacement

- Assessed for eligibility in trial of patients not eligible for KR (n=654)
- Excluded (n=553)
  - Eligible for KR (n=192)
  - K-L grade < 1 (n=87)
  - Aged < 18 years (n=26)
  - KOOS4 > 75 (n=22)
  - Previous same side knee replacement (n=44)
  - Rheumatoid Arthritis (n=11)
  - VAS > 60mm out of 100 mm (n=12)
  - Unable to comply with study protocol (n=159)
- Eligible for inclusion (n=101)
- Unwilling to be randomised (n=1)
- Randomized (n=100)
- Allocated to non-surgical treatment (n=50)
  - Received the allocated treatment (n=48)
  - Did not want the treatment anyway (n=2)
- Allocated to written advice (n=50)
  - Received the allocated treatment (n=50)
- Follow-Up
  - Attended 5-year follow-up (n=39)
    - Did not attend (n=11)
      - No longer interested (n=2)
      - Cancelled and not possible to reach (n=5)
      - Had died (n=4)
    - Underwent joint replacement surgery during follow-up (n=15)
  - Attended 5-year follow-up (n=36)
    - Did not attend (n=14)
      - No longer interested (n=8)
      - Cancelled and not possible to reach (n=2)
      - Had died (n=4)
    - Underwent joint replacement surgery during follow-up (n=17)
- Analysis
  - Included in the intention-to-treat analysis (n=50)
  - Included in the sensitivity analysis (n=35)
Figure 2: Mean scores (95% CI) from the primary outcome of the Knee injury and Osteoarthritis Outcome Score4 covering pain, symptoms, function of daily living (ADL), and quality of life at baseline and at 3, 6, 12, 24, and 60-months follow-up for the MEDIC and written advice group. Error bars indicate 95% confidence intervals.
Figure 3: Mean scores (95% CI) from the primary outcome of the Knee injury and Osteoarthritis Outcome Score4 covering pain, symptoms, function of daily living (ADL), and quality of life at baseline and at 3, 6, 12, 24, and 60-months follow-up for patients receiving or not receiving knee replacement (KR). Error bars indicate 95% confidence intervals. Incidence of patients registered with KR in the index knee at 3 months: 1, at 6 months: 2, at 12 months: 5, at 24 months: 9 and at 60 months: 15. Prevalence of patients with KR in the index knee at 3 months: 1, at 6 months: 3, at 12 months: 8, at 24 months: 17 and at 60 months: 32.
### Supplementary file 1:

Baseline characteristics for patients attending 5-year follow-up and those that did not attend. Values are mean and SD unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Dropout (n= 25)</th>
<th>5-year follow-up (n= 75)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.6 (9.3)</td>
<td>65.1 (8.7)</td>
<td>0.086</td>
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<tr>
<td>Women, n (%)</td>
<td>13 (52%)</td>
<td>38 (51%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Body mass index</td>
<td>31.7 (4.7)</td>
<td>29.4 (5.6)</td>
<td>0.072</td>
</tr>
<tr>
<td>Kellgren-Lawrence grade, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1:</td>
<td>Grade 1: 4 (16%)</td>
<td>Grade 1: 14 (19%)</td>
<td>0.786</td>
</tr>
<tr>
<td>Grade 2:</td>
<td>Grade 2: 9 (36%)</td>
<td>Grade 2: 19 (25%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3:</td>
<td>Grade 3: 5 (20%)</td>
<td>Grade 3: 18 (24%)</td>
<td></td>
</tr>
<tr>
<td>Grade 4:</td>
<td>Grade 4: 7 (28%)</td>
<td>Grade 4: 24 (32%)</td>
<td></td>
</tr>
<tr>
<td>Intake of pain medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS&lt;sub&gt;4&lt;/sub&gt;</td>
<td>48.5 (12.0)</td>
<td>51.9 (12.1)</td>
<td>0.224</td>
</tr>
<tr>
<td>KOOS symptoms</td>
<td>52.1 (17.0)</td>
<td>58.7 (17.1)</td>
<td>0.099</td>
</tr>
<tr>
<td>KOOS pain</td>
<td>51.7 (14.2)</td>
<td>52.9 (14.0)</td>
<td>0.707</td>
</tr>
<tr>
<td>KOOS function of daily living</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS</td>
<td>55.3 (19.4)</td>
<td>58.8 (15.9)</td>
<td>0.370</td>
</tr>
<tr>
<td>KOOS sport/recreation</td>
<td>19.0 (14.1)</td>
<td>25.3 (18.1)</td>
<td>0.114</td>
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<tr>
<td>KOOS quality of life</td>
<td>35.0 (13.5)</td>
<td>37.3 (13.8)</td>
<td>0.463</td>
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</table>

KOOS: Knee injury and osteoarthritis outcome score.
**Supplementary file 2:**

Usage of pain medication at the 5-year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>MEDIC group (95% CI)</th>
<th>Written advice group (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of users of pain medication</strong>*(n: MEDIC, n: written advice)*</td>
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<td></td>
</tr>
<tr>
<td>Baseline (n: 50,50)</td>
<td>0.64 (0.50 to 0.76)</td>
<td>0.60 (0.46 to 0.73)</td>
</tr>
<tr>
<td>60-months (n: 39,35)</td>
<td>0.21 (0.11 to 0.36)</td>
<td>0.31 (0.18 to 0.48)</td>
</tr>
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</table>

**Risk ratio for usage of pain medication at 5 years vs. baseline**

<table>
<thead>
<tr>
<th></th>
<th>Crude estimate (95% CI)</th>
<th>Adjusted estimate† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n: 50,50)</td>
<td>0.32 (0.17 to 0.61)</td>
<td>0.32 (0.17 to 0.61)</td>
</tr>
<tr>
<td>60-months (n: 39,35)</td>
<td>0.32 (0.17 to 0.61)</td>
<td>0.32 (0.17 to 0.61)</td>
</tr>
</tbody>
</table>

**Risk ratio for taking pain medication at 5 years in the written advice group vs the MEDIC group**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted estimate† ‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n: 50,50)</td>
<td>1.53 (0.69 to 3.39)</td>
</tr>
</tbody>
</table>

* User of pain medication was defined as a patient using pain medication of any kind on a regular basis during the last week.

† The estimates were adjusted for site.

‡ The crude estimate was similar to the adjusted estimate (data not shown).
Supplementary file 3

Mean scores (95% CI) from the primary outcome of the Knee injury and Osteoarthritis Outcome Score covering pain, symptoms, function of daily living (ADL), and quality of life at baseline and at 3, 6, 12, 24, and 60-month follow-up for the MEDIC group receiving and not receiving knee replacement (KR) and the written advice group receiving and not receiving KR. Error bars indicate 95% confidence intervals.

Incidence of patients registered with KR in the index knee for the MEDIC KR group at 3 months: 1, at 6 months: 0, at 12 months: 2, at 24 months: 4 and at 60 months: 8 (in total, 15 patients). Incidence of patients registered with KR in the index knee for the written advice KR group at 3 months: 0, at 6 months: 2, at 12 months: 3, at 24 months: 5 and at 60 months: 7 (in total, 17 patients).
## Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

### Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORT reporting guidelines, and cite them as:


### Reporting Item | Page Number
--- | ---
**Title and Abstract**
Title | 
Abstract | 1
**Introduction**
Background and objectives | 4-5
Specific objectives or hypothesis | 5
**Methods**
Trial design | 5
Important changes to methods after trial commencement (such as eligibility criteria), with reasons | n/a

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Participants  
Eligibility criteria for participants  
Settings and locations where the data were collected  
Interventions  
The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered  
Outcomes  
Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed  
Outcomes  
Any changes to trial outcomes after the trial commenced, with reasons  
Sample size  
How sample size was determined.  
Sample size  
When applicable, explanation of any interim analyses and stopping guidelines  
Randomization - Sequence generation  
Method used to generate the random allocation sequence  
Randomization - Sequence generation  
Type of randomization; details of any restriction (such as blocking and block size)  
Randomization - Allocation concealment mechanism  
Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned  
Randomization - Implementation  
Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions  
Blinding  
If done, who was blinded after assignment to interventions (for example, participants, care
Blinding #11b If relevant, description of the similarity of interventions n/a

Statistical methods #12a Statistical methods used to compare groups for primary and secondary outcomes 9-10

Statistical methods #12b Methods for additional analyses, such as subgroup analyses and adjusted analyses 9-10

Results

Participant flow diagram (strongly recommended) #13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome Figure 1

Participant flow #13b For each group, losses and exclusions after randomization, together with reason Figure 1

Recruitment #14a Dates defining the periods of recruitment and follow-up 6-7

Recruitment #14b Why the trial ended or was stopped n/a

Baseline data #15 A table showing baseline demographic and clinical characteristics for each group 11

Numbers analysed #16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups Table 2 and 3

Outcomes and estimation #17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) Table 2 and 3

Outcomes and estimation #17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended Supplementary file 2

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Ancillary analyses #18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

Harms #19 All important harms or unintended effects in each group (For specific guidance see CONSORT for harms) Published in the manuscript with 12-months follow-up

Discussion

Limitations #20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses 18-19

Generalisability #21 Generalisability (external validity, applicability) of the trial findings 16-17

Interpretation #22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence 17

Registration #23 Registration number and name of trial registry 3

Other information

Interpretation #22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence 16-17

Registration #23 Registration number and name of trial registry 3

Protocol #24 Where the full trial protocol can be accessed, if available 5

Funding #25 Sources of funding and other support (such as supply of drugs), role of funders 20

None The CONSORT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai
Five-year follow-up of patients with knee osteoarthritis not eligible for total knee replacement: results from a randomized trial

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<tr>
<td>Complete List of Authors:</td>
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<td><strong>Primary Subject Heading</strong>:</td>
<td>Rehabilitation medicine</td>
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Five-year follow-up of patients with knee osteoarthritis not eligible for total knee replacement: results from a randomized trial

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ABSTRACT

Objectives:

The main objective was to investigate 5-year outcomes in patients with knee osteoarthritis, randomized to one of two non-surgical treatments.

Setting:

Two outpatient clinics.

Participants:

At baseline, 100 patients with radiographic and symptomatic knee osteoarthritis not found eligible for knee replacement (KR) were included. Main exclusion criteria were average score above 75 of the Knee injury and Osteoarthritis Outcome Score subscales pain, symptoms, function of daily living and quality of life; KOOS, and average knee pain the previous week greater than 60 mm on a 100 mm visual analog scale.

Interventions

Patients were randomized to supervised non-surgical treatment (MEDIC) or written advice. The 12-week MEDIC treatment included patient education, neuromuscular exercise, insoles, and a dietary weight loss program and/or pain medication if needed and written advice consisted of two leaflets.
Primary and secondary outcome measures:

Primary outcome was 5-year mean change for KOOS₄. Secondary outcomes included KOOS subscales, self-reported health, usage of pain medication and self-reported physical activity.

Results:

Thirty-nine (78%) and 36 (72%) from the MEDIC and written advice groups responded at 5-years. There were no between-group differences in KOOS₄ (difference 5.3 (95% CI; -1.5 to 12.1), or any secondary outcomes. However, the 95% CI included the minimal clinically important difference for the main outcome.

Seventy-six percent of the MEDIC group and 66% of the written advice group experienced clinically important improvements in KOOS₄.

Fifteen patients (30%) from the MEDIC group and 17 (34%) from the written advice group received KR in the index knee. Undergoing KR did not result in a statistically significant greater improvement in KOOS₄ (difference 6.1 (95% CI; -1.1 to 13.4)).

Conclusions:

No statistically significant differences between supervised non-surgical treatment and written advice were demonstrated at 5-years. Most patients experienced clinically important improvements, irrespective of initial treatment strategy or KR.

Trial registration: ClinicalTrials.gov, NCT01535001.

Strengths and limitations of this study

- Long-term follow-up of patients with radiographic and symptomatic knee osteoarthritis.
Information on knee replacement (KR) surgery during follow-up was available from the hospital registry, ensuring high validity.

Outcomes of patients undergoing and not undergoing KR at different time points allows for an evaluation of different trajectories of patient outcomes over five years.

Outcomes are subjective and self-reported and no objective measures were included.

Given the long-term follow-up patients could have engaged in other treatments over time that could not be accounted for in the study.

BACKGROUND

Knee osteoarthritis (OA) is a leading contributor to pain and physical impairment and has substantial personal and societal impact, affecting hundreds of millions of people worldwide (1–3). Unicompartmental and total knee replacement (KR) are considered effective treatments of end-stage knee OA (4). As only 18-30% with OA undergo KR in a lifetime perspective (5,6), effective non-surgical treatments are needed for the vast majority of the population. First-line treatment for patients with knee OA includes multimodal non-surgical treatment consisting of exercise, patient education and weight management, while biomechanical interventions and pharmacological treatment can be initiated if needed (7–9).

Previously, our randomized controlled trial (RCT) with 12-month follow-up showed that non-surgical treatment, consisting of patient education, supervised exercise, weight loss, insoles, and pain medication (the MEDIC treatment) produced clinically significant improvements in patient-reported outcomes compared to written advice in patients with knee OA found not eligible for KR (10). Prior research indicates that the effect of non-surgical treatment appears
to decrease over time (11,12). This could be due to a decrease in adherence over time.

However, the results from the 24-month follow-up of our RCT show that patients maintain improvements in patient-reported outcomes following the non-surgical MEDIC treatment (KOOS4 improvement of 18.5, 95% CI; 13.0 to 24.0) and written advice (KOOS4 improvement of 11.6, 95% CI; 5.6 to 17.2) with the MEDIC treatment exhibiting the highest improvement (KOOS4 between-group difference of 7.0 95% CI; 0.4 to 13.5 (13). Therefore, improvements gained from non-surgical treatments could possibly be sustained for longer than 2 years, but long-term follow-up studies are required to investigate this.

Some patients found not eligible for KR by an orthopedic surgeon may experience a progression of OA and may later receive a KR (14). For patients diagnosed with knee OA, a lifetime risk of 10-30% for undergoing KR surgery has been reported (5,6). In general, patients receiving KR surgery will experience pain relief and functional improvements (4,15).

This is important to take into consideration when evaluating long-term outcomes following non-surgical treatments.

Hence, the aim of this report was three-fold; 1) to investigate the 5-year outcomes following non-surgical treatments, 2) to determine the proportion undergoing KR in the index knee in patients with knee OA initially receiving non-surgical treatment and 3) whether the 5-year outcomes differed in patients undergoing KR as compared to those not undergoing KR in the index knee.

METHODS

Trial design

This is an exploratory analysis of the 5-year follow-up of a parallel group RCT (1:1 treatment allocation). The report follows the Consolidated standards of reporting trials (CONSORT) statement for reporting RCTs (16). The RCT was pre-registered at ClinicalTrials.gov.
(NCT01535001). Prior to the original RCT, a study protocol was published(17) in which
details of the recruitment process, full eligibility criteria, and the process of randomization
and allocation concealment were given. Written informed consent was obtained from patients
prior to participation.

**Patients and recruitment process**

Patients were enrolled in the period between April 3, 2012 and July 12, 2013 from two
outpatient clinics (Frederikshavn and Farsoe) at the Department of Orthopedics, Aalborg
University Hospital, Denmark. Patients were referred to the outpatient clinics by their general
practitioner. In total, 100 patients were recruited, all fulfilling the inclusion criteria of
symptomatic and radiographically confirmed knee OA (Kellgren & Lawrence score $\geq 1$ on the
original scale(18)), but found not eligible for KR by the orthopedic surgeon (eligibility was
based on factors such as pain, function and radiographic severity(19)). Main exclusion criteria
were 1) a score above 75 on the Knee injury and Osteoarthritis Outcome Score (KOOS)4,
defined as the average score for the subscales pain, symptoms, function of daily living and
quality of life(20) and 2) an average knee pain intensity in the previous week greater than 60
mm on a 100 mm visual analog scale (VAS).

**Patient and public involvement**

Two patients with knee osteoarthritis participated in a feasibility study (unpublished). They
underwent the non-surgical treatment (the MEDIC-treatment) and gave feedback on study
procedures.

**Randomization and allocation concealment**

A priori, the randomization schedule was generated in permuted blocks of eight, stratified by
clinic. The allocation numbers were concealed in opaque envelopes, which were organized by
a staff member, who had no other part in the study. One research assistant at each clinic had
access to the envelopes and these were opened following informed consent and baseline
assessment.

Interventions

Patients were randomized either to receive the supervised MEDIC treatment program or to receive written advice. Both interventions have been thoroughly presented elsewhere (10,13,17). In brief, the MEDIC treatment included five components: patient education, neuromuscular exercise, insoles, and a dietary weight loss program (if a body mass index $\geq 25$ at baseline) and/or pain medication prescribed if needed to participate in the exercise. Physiotherapists and dieticians supervised the treatments, which were delivered over a period of 12 weeks.

The written advice consisted of two standardized information leaflets containing information regarding etiology, symptoms, functional limitations, recommended treatments and general information on how to sustain a healthy lifestyle (the MEDIC group also received these leaflets).

Outcomes

Baseline and follow-up assessments at 3, 6, 12, 24 months were conducted at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital. At 5-year follow-up, the included patients were contacted by phone and urged to participate in the follow-up measurements. The same outcome assessor, who was specifically trained in all assessments, handled all measurements at 5 years. The outcome assessor was blinded towards treatment allocation and was not involved in other aspects of the study. At baseline and all follow-up time points, KOOS4, all KOOS subscales, self-reported general health and self-reported usage of pain medication were measured, whereas self-reported physical activity level was assessed only at the 5-year follow-up.
**Primary outcome measure**

The primary outcome for this 5-year follow-up was the between-group difference in change in KOOS, with scores ranging from 0 (worst) to 100 (best). KOOS was defined as the average score for the subscales pain, symptoms, function of daily living (ADL) and quality of life(21,22). In order to evaluate whether clinically significant improvements from baseline had occurred, a minimal clinically important difference of 10 points in KOOS outcomes was applied(22). KOOS has been found to be a valid, reliable and responsive patient-reported outcome measure in studies of patients with knee OA and KR(20).

**Secondary outcome measures**

*Patient-reported outcome measures*

All five KOOS subscales, including sport/recreation, were assessed in order to support clinical interpretation of the primary outcome(23). Self-reported general health was measured using the descriptive index (EQ-5D Index, ranging from -0.59 to 1.00) and the EQ VAS (ranging from 0 (worst health you can imagine) to 100 (best health you can imagine)) from the EQ-5D-3L to investigate changes in general health(24,25). Patients were asked to estimate their level of physical activity using the 10-point University of California Los Angeles (UCLA) activity-level rating in which the score that best described their physical activity level was chosen. Scores range from 1 to 10, with 1 representing “wholly inactive, dependent on others; cannot leave residence” and 10 representing ”regularly participate in impact sports such as jogging, tennis, skiing, acrobatics, ballet, heavy labor, or backpacking”(26).

Self-reported usage of pain medication, defined as type, dosage and quantity taken within the last week, was assessed. Usage was dichotomized into yes/no due to non-uniformity of the distribution of pain medication intake.

**Knee replacement**
All patients undergoing KR at one of the public hospitals in the North Denmark region were registered using the hospital’s medical records, which allowed for tracking of each individual patient. Joint replacement surgery was registered for both the index knee and the non-index knee.

Statistical analysis

Sample size

The sample size for this follow-up was determined by number of participants included in the RCT, based on the power calculation for the original 12-month endpoint. The sample size calculation for the 12-month endpoint was based on a 10-point difference between groups in the primary outcome KOOS4 (SD 14, power of 90% and P-value of 0.05 (two-sided))(21,22).

Therefore, 41 patients in each group were required, but to account for missing data, a total of 100 patients were randomized. Thus, this 5-year follow-up included these 100 patients.

Primary and secondary analyses

The data analysis of the 5-year results was conducted using the same procedure as in the previous 12 and 24-month reports(10,13). Both the primary and secondary outcomes were analyzed using the intention-to-treat (ITT) method and the ITT population consisted of those randomized to the two treatment arms (n = 100). Between-group comparisons of treatment effect for all primary and secondary outcomes, except for pain medication and subjective physical activity, were performed using linear mixed effects models. Model 1 included patient as a random factor and follow-up time (baseline, 3, 6, 12 and 24 months and 5 years), treatment arm (MEDIC treatment vs written advice) as fixed factors. Model 2 used the same factors as model 1 and further included site (Frederikshavn, Farsoe) as a fixed factor. Interaction between follow-up and treatment arm was also included in the models. Since the linear mixed effects models includes all patients when at least the baseline value or a follow-
up value is present, no imputation was required(27). The between-group differences in changes from baseline and 95% CI are presented. The relative risk of using pain medication was compared between groups using a modified Poisson regression model with a robust error estimator for the confidence intervals (CI) and accounting for clustering at patient level(28).

To assess the difference between the groups for self-reported physical activity at 5-year follow up, two-sample t test were applied to continuous data. The assumption of normally distributed data within groups was assessed and deemed reasonable from quantile plots.

A responder analysis, illustrating the proportion of patients in each group that experienced a minimal clinically important improvement for the KOOS4 outcome, was conducted and results were analyzed using a Chi-squared test.

We conducted an analysis in which patients that had received KR in the index knee were identified and compared to patients who had not received KR, using the same statistical model as for the primary and secondary outcomes. For the purpose of evaluating the influence of KR, the allocated treatment groups were combined and analyzed based on whether patients received KR or not in the index knee.

Figures including data from all time points (baseline, 3, 6, 12, 24 months, and 5 years) are presented to visualize change over time in KOOS4 for the patients allocated to the MEDIC group vs the written advice group and for the patients with and without KR in the index knee. A similar figure illustrating the four groups ‘MEDIC with KR’, ‘MEDIC without KR’, ‘written advice with KR’ and ‘written advice without KR’ is displayed as supplementary material.

A confidence interval excluding 0 (1 for proportions) corresponding to a two-sided P value less than 0.05 was considered sufficient to reject the null hypothesis and conclude that there
was a statistically significant difference between groups. All analyses were carried out in Stata 16.1 (StataCorp, College Station, TX, USA).

RESULTS

Participant characteristics

Patient flow for the present analysis can be seen in Figure 1 and a flow diagram including drop-out reasons for all timepoints can be seen in supplementary file 1. Baseline characteristics for the treatment groups can be observed in Table 1. Of the 100 patients randomized, respondents to the 5-year follow-up included 39/50 (78%) patients in the MEDIC treatment group and 36/50 (72%) patients in the written advice group (Figure 1). There were no significant differences in baseline characteristics for those attending 5-year follow-up and those that did not (supplementary file 2). The mean time from baseline to 5-year follow-up was 60.9 months (SD 2.5) in both groups.

Table 1: Baseline characteristics. Values are mean (SD) unless otherwise stated.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>MEDIC treatment (n= 50)</th>
<th>Written advice (n= 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>26 (52)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.8 (8.7)</td>
<td>67.1 (9.1)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>30.6 (5.6)</td>
<td>29.4 (5.2)</td>
</tr>
<tr>
<td>Bilateral knee pain, n (%)</td>
<td>18 (36)</td>
<td>21 (42)</td>
</tr>
<tr>
<td>Radiographic knee osteoarthritis severity (Kellgren–Lawrence), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>7 (14)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>13 (26)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>13 (26)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>17 (34)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>KOOS scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS4</td>
<td>48.9 (11.8)</td>
<td>53.2 (12.1)</td>
</tr>
<tr>
<td>Pain</td>
<td>51.6 (14.3)</td>
<td>53.6 (13.7)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>54.6 (15.9)</td>
<td>59.5 (18.3)</td>
</tr>
<tr>
<td>ADL</td>
<td>55.5 (17.1)</td>
<td>60.4 (16.4)</td>
</tr>
</tbody>
</table>
Primary outcome

There was no difference in change in KOOS_4 between the MEDIC group and the written advice group (Table 2, Figure 2).

The responder analysis showed that 76% of the patients in the MEDIC group had experienced clinically important improvements and 66% in the written advice group at 5-year follow-up. No difference in the proportion of responders between groups was observed (relative risk 1.15 (95% CI 0.85 to 1.56).

Table 2: Self-reported outcomes from baseline to 5-year follow up

<table>
<thead>
<tr>
<th>Outcome (number of data points_{MEDIC, number of data points_{written advice}})</th>
<th>Improvement in MEDIC group (95% CI)</th>
<th>Improvement in written advice group (95% CI)</th>
<th>Between-group (MEDIC vs. written advice) difference (model 1)§ (95% CI)</th>
<th>Between-group (MEDIC vs. written advice) difference (model 2)† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in KOOS_4 from baseline to 5-years (267, 264)</td>
<td>22.8 (16.9 to 28.8)</td>
<td>19.1 (10.8 to 27.3)</td>
<td>5.3 (-1.5 to 12.1)</td>
<td>5.3 (-1.5 to 12.1)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS Pain (270, 264)</td>
<td>20.5 (13.1 to 27.8)</td>
<td>22.2 (13.1 to 31.2)</td>
<td>0.6 (-7.2 to 8.5)</td>
<td>0.6 (-7.2 to 8.4)</td>
</tr>
<tr>
<td>KOOS Symptoms</td>
<td>20.3</td>
<td>16.9</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>(270, 264)</td>
<td>(13.7 to 27.0)</td>
<td>(8.4 to 25.4)</td>
<td>(-3.0 to 12.3)</td>
</tr>
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<td>-------------------------</td>
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<tr>
<td><strong>KOOS ADL</strong></td>
<td>21.4</td>
<td>17.1</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>(270, 264)</td>
<td></td>
<td>(14.8 to 27.9)</td>
<td>(8.3 to 25.8)</td>
<td>(-1.2 to 14.8)</td>
</tr>
<tr>
<td><strong>KOOS Sport/Recreation</strong></td>
<td>16.5</td>
<td>22.8</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td>(267, 257)</td>
<td></td>
<td>(8.3 to 24.7)</td>
<td>(11.2 to 34.4)</td>
<td>(-15.2 to 4.5)</td>
</tr>
<tr>
<td><strong>KOOS Quality of life</strong></td>
<td>25.7</td>
<td>20.2</td>
<td>6.6</td>
<td>6.6</td>
</tr>
<tr>
<td>(267, 264)</td>
<td></td>
<td>(18.2 to 33.2)</td>
<td>(11.1 to 29.2)</td>
<td>(-1.4 to 14.7)</td>
</tr>
<tr>
<td><strong>Mean change in EQ-5D</strong></td>
<td>0.138</td>
<td>0.138</td>
<td>0.025</td>
<td>0.025</td>
</tr>
<tr>
<td>EQ-5D index (269, 264)</td>
<td>(0.074 to 0.203)</td>
<td>(0.060 to 0.215)</td>
<td>(-0.043 to 0.092)</td>
<td>(-0.043 to 0.092)</td>
</tr>
<tr>
<td>EQ VAS (267, 265)</td>
<td>6.0</td>
<td>10.2</td>
<td>-2.1</td>
<td>-2.1</td>
</tr>
<tr>
<td></td>
<td>(0.1 to 11.8)</td>
<td>(1.7 to 18.6)</td>
<td>(-10.7 to 6.6)</td>
<td>(-10.7 to 6.6)</td>
</tr>
</tbody>
</table>

* n refers to the number of data points out of 300 in each group (50 at baseline, 3, 6, 12, 24-months, and 5-years). § Estimates are from a linear mixed model adjusting for patient, follow-up, treatment arm and interaction between follow-up and treatment arm. † Estimates are from a linear mixed model adjusting for patient, follow-up, treatment, site and interaction between follow-up and treatment arm. A positive between-group difference indicates a difference in favor of the MEDIC group and a negative between-group difference indicates a difference in favor of the written advice group. KOOS: Knee injury and Osteoarthritis Outcome Score. KOOS4: 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) and Quality of life, with scores ranging from 0 to 100 (worst to best scale); Sport/Rec: Function in sport and recreation

**Secondary outcomes**

For all KOOS subscales, EQ-5D index and EQ VAS, no differences in improvement between groups were observed in the model 2 analysis (Table 2).

Change in use of pain medication did not differ between the groups (supplementary file 3).

There was no difference between groups (0.1 (95% CI -1.0 to 0.8)) for self-reported physical activity (UCLA) with the MEDIC group reporting a mean score of 6.1 (SD 2.0) and the written advice group reporting a mean score of 6.3 (SD 1.9).
A total of 15 patients (30%) from the MEDIC treatment group and 17 patients (34%) from the written advice group had KR in the index knee within the period from baseline to 5 years. No difference in risk for undergoing KR in the index knee was observed with a relative risk of 1.13 (95% CI 0.64 to 2.01) for the written advice group compared to the MEDIC group.

Five patients received bilateral KR in the study period, two from the MEDIC group and three from the written advice group, and one patient from the written advice group received a KR in the non-index knee in the study period.

Secondary analysis

Table 3 and Figure 3 show the improvements from baseline to 5-year follow-up for patients divided into those receiving or not receiving KR in the index knee.

No between-group difference in KOOS4 was observed (Table 3).

Table 3: Self-reported outcomes from baseline to 5-year follow up for patients receiving and not receiving knee replacement in the index knee (KR).

<table>
<thead>
<tr>
<th>Outcome (number of data points)</th>
<th>Improvement in patients without KR (95% CI)</th>
<th>Improvement in patients with KR (95% CI)</th>
<th>Between-group (with KR vs. without KR in the index knee) difference (model 1)§ (95% CI)</th>
<th>Between-group (with KR vs. without KR in the index knee) difference (model 2)† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in KOOS4 from baseline to 5 years (351, 180)</td>
<td>18.7 (12.5 to 25.0)</td>
<td>25.3 (16.9 to 33.6)</td>
<td>6.1 (-1.1 to 13.4)</td>
<td>5.7 (-1.6 to 13.1)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS Pain (354, 180)</td>
<td>18.7 (11.7 to 25.6)</td>
<td>26.3 (16.3 to 36.4)</td>
<td>7.3 (-1.1 to 15.6)</td>
<td>6.6 (-1.7 to 14.9)</td>
</tr>
<tr>
<td>KOOS Symptoms (354, 180)</td>
<td>17.7 (11.2 to 24.1)</td>
<td>20.7 (11.3 to 30.1)</td>
<td>3.7 (-4.3 to 11.7)</td>
<td>3.3 (-4.7 to 11.4)</td>
</tr>
<tr>
<td>KOOS ADL (354, 180)</td>
<td>17.2 (10.3 to 24.1)</td>
<td>23.5 (15.1 to 31.8)</td>
<td>6.0 (-2.7 to 14.6)</td>
<td>5.6 (-3.2 to 14.3)</td>
</tr>
</tbody>
</table>
Treatment groups are merged into one population and compared based on those receiving knee replacement (KR) and those who did not. ∗ n refers to the number of data points out of 50 in each group at 5 years. § Estimates are from a linear mixed model adjusting for patient, follow-up, treatment arm and interaction between follow-up and treatment arm. † Estimates are from a linear mixed model adjusting for patient, follow-up, treatment, site and interaction between follow-up and treatment arm. A positive between-group difference indicates a difference in favor of the KR group and a negative between-group difference indicates a difference in favor of the without KR group. KOOS: Knee injury and Osteoarthritis Outcome Score. KOOS: 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) and Quality of life, with scores ranging from 0 to 100 (worst to best scale); Sport/Rec: Function in sport and recreation.

For the KOOS subscales, there was a difference of 9.0 (95% CI 0.4 to 17.7) for the KOOS quality of life in favor of the KR group. No other differences were observed for the secondary outcomes (Table 3).

There was no difference for change in usage of pain medication with an adjusted relative risk of 0.44 (0.25 to 0.76) in the group without KR in the index knee and 0.38 (0.21 to 0.69) in the group with KR in the index knee (between-group relative risk 1.11, 95% CI 0.48 to 2.54).

For self-reported physical activity (UCLA), the group without KR in the index knee reported a mean score of 5.9 (SD 1.8) and the group with KR in the index knee reported a mean score of 6.7 (SD 2.2), illustrating no between-group difference (0.7 (95% CI -1.7 to 0.2)).

**DISCUSSION**
We observed no statistically significant differences in self-reported pain, function, quality of life, usage of medication or self-reported physical activity between patients initially undergoing supervised non-surgical treatment and patients receiving written advice only. However, the 95% CI of the between group difference in the main outcome did include the minimal clinically important difference highlighting that the true difference could be clinically relevant. At 5 years, 76% in the supervised non-surgical treatment group and 66% in the written advice group experienced clinically important improvements in KOOS4 relative to baseline. One third of patients underwent KR in the index knee, and undergoing KR did not result in greater improvement in KOOS4 or any of the secondary outcomes, except for the KOOS quality of life subscale which demonstrated greater improvement in the KR group. Interestingly, clinically important improvements were observed in both groups, irrespective of the initial non-surgical treatment strategy and whether they received a KR or not in the index knee. While the group receiving supervised non-surgical treatment initially improved faster than the group receiving written advice, both groups showed improvements from baseline to the 5-year follow-up. This highlights that having symptomatic knee OA severe enough to warrant consultation with an orthopedic surgeon does not necessarily mean that symptoms will worsen over time. On the contrary, symptoms may improve, as reported in this study of patients initially having had non-surgical treatment. Trajectories of change in symptoms over time without standardized non-surgical treatment has been reported previously. In support of our findings, Nicholls et al.(14) were able to group a population of knee OA patients into five pain trajectories of “mild, non-progressive” (35%), “progressive” (28%), “moderate” (22%), “improving” (12%) and “severe, non-improving” (3%). The study concluded that knee OA in general should not be characterized as “slowly progressive”(14). Similarly, Rice et al.(29) suggested that long-term worsening of pain is not an unavoidable consequence in patients with knee OA. Despite this, knee OA is commonly perceived as a progressive and
335 degenerative condition that eventually could require KR surgery(5,14). Studies have shown
336 that radiological outcomes seem to progress with time, but also highlighted the lack of
337 associations between radiologic changes and perceived pain and functional limitations(30).
338 In contrast to previous long-term follow-ups of non-surgical treatments including an exercise
339 component, both groups of our study sustained the improvements experienced at 12 and 24
340 months after 5 years. Pisters et al.(31) found improvements in pain and physical function from
341 baseline to 15-month follow-up. From 15 months to 60 months, the improvements started to
342 decline, but remained higher than the baseline values(31). Hurley et al.(32) observed a similar
343 trajectory for their knee OA patients at 30 months of follow-up; initial improvements,
344 followed by a decline, but remaining higher than baseline values(32). Similarly, Messier et
345 al.(33) observed that a treatment of diet and/or exercise improved the clinical outcomes from
346 baseline to 1.5 years follow-up. However, this was followed by a decline in improvements at
347 3.5 years follow-up, but outcomes did remain better than baseline values(33). While the
348 reasons for this discrepancy in long-term improvements are unknown, it could be partially
349 explained by a greater proportion undergoing KR in the index knee during follow-up in our
350 study. About 1/3 of our patients received a KR in the index knee during follow-up, while only
351 about 1/5 of the patients in the studies by Pisters et al.(31) and Messier et al.(33) received KR.
352 A difference in populations does not seem to explain the long-term improvements in our
353 study. Comparing baseline values for our population and the populations in the before-
354 mentioned studies(14,31–33) revealed no differences regarding age, sex, BMI, duration of
355 symptoms and Kellgren-Lawrence grades.
356 Contrary to the 12- and 24-month follow-ups(10,13), where the supervised non-surgical
357 treatment group experienced significantly greater improvements, no differences were
358 observed between the two groups at 5 years. Furthermore, we did not find differences in
359 number of patients undergoing KR in the index knee or in terms of self-reported physical
activity with both groups regularly participating in moderate physical activities. Except for KR, no information is available regarding other treatments received during follow-up, which could potentially influence the long-term outcomes. Due to loss to follow-up at 5 years, the statistical power in the present report is lower compared to previous studies, which could also influence the lack of statistically significant between-group differences.

The study retrospectively registered the proportion of patients undergoing KR using administrative data, therefore no data on the reasons for undergoing KR were available. In general, worse symptomatic and radiographic severity as well as unacceptable physical function guide the decision on KR surgery\(^{15,34}\). Although it is not uncommon that patients are referred to orthopedic surgery prior to undergoing non-surgical treatment\(^{35}\), clinical guidelines propose KR surgery as a treatment option if first-line treatments do not provide sufficient effect\(^{7,36,37}\). This is in line with Figure 3 and supplementary file 4, which indicate that patients undergoing KR in the index knee seemed to be those initially not improving as much from non-surgical treatment.

**Clinical implications**

The majority of the patients with knee OA in our population experienced clinically important improvements from baseline to 5 years. A similar proportion of patients in both treatment groups (MEDIC: 76% vs written advice 66%) could be classified as responders, i.e. experienced an improvement in KOOS\(_4\) from baseline to 5 years of at least 10 points. This further underlines that clinically important improvements can be experienced from non-surgical treatment in the longer term and that knee OA is not necessarily associated with progression of symptoms over time. This is an important message to clinicians and patients with knee OA, since previous reports have shown that patients believe that knee OA will inevitably get worse\(^{38,39}\).
**Limitations**

Given that the 95% CI (-1.5 to 12.1) of the main outcome KOOS\textsubscript{4} and 3 out of 5 KOOS subscales included the minimal clinically important difference (10 points), the true difference in change between groups could potentially be clinically relevant in favor of the non-surgical treatment group. While a 2-year analyses of the study demonstrated that the MEDIC treatment was cost-effective as compared to written advice\cite{40}, the 5-year cost-effectiveness is unknown. The improvements from baseline to 5 years in both treatment groups could be influenced by *regression towards the mean*, i.e. patients originally sought medical care when their symptoms were most intolerable. Our study did not include a no-treatment control group and we did not take other treatments than KR during follow-up into account. Therefore, we were not able to conclude whether the long-term improvements were due to the actual treatments evaluated. Likewise, it was not possible to consider structural progression in the knee over time or psychosocial factors, possibly influencing the outcomes. There was a loss to follow-up of 22% in the MEDIC group and 28% in the written advice group, possibly influencing the ability to detect differences between groups. We were able to register patients undergoing KR in one of the hospitals in the North Denmark region. However, information on patients undergoing KR in a hospital outside the health care region or in a private hospital was not available. Finally, no information was available on the reasons for undergoing KR surgery in the study period. Therefore, it is unknown whether KR surgery occurred because of progression of radiographic and symptomatic OA, functional limitations or perceived lack of effect from non-surgical treatments. Importantly, these sub-group analyses of patients with or without KR in the index knee are based on a low number of patients in each group, highlighting the need for further studies in the area.

**CONCLUSIONS**
We found no differences between supervised non-surgical treatment and written advice at 5 years in terms of self-reported outcomes and rate of KR. However, the 95% CI of main outcome, i.e., KOOS\textsubscript{4}, did include the minimal clinically important difference. The vast majority of patients experienced clinically important improvements at 5 years, irrespective of initial treatment strategy and whether they underwent KR or not in the index knee. This highlights that having knee OA is not necessarily associated with progression of symptoms over time and that non-surgical treatments are relevant and effective as first-line interventions with long-term effect for patients with knee OA.

Research Ethics Approval

The study was approved by the local Ethics Committee of The North Denmark Region (N-20110085) and approval was extended for this long-term follow-up since the 5-year follow-up was not part of the initial registration. Written informed consent was obtained from patients prior to participation.

Funding

This trial is partially funded by The Danish Rheumatism Association and The Association of Danish Physiotherapists Research Fund. Dr. Skou is currently funded by a program grant from Region Zealand (Exercise First) and two grants from the European Union’s Horizon 2020 research and innovation program, one from the European Research Council (MOBILIZE, grant agreement No 801790) and the other under grant agreement No 945377 (ESCAPE). The funders did not have any role in this study other than to provide funding and all authors are independent from the funders.

Competing interests
ER is deputy editor of Osteoarthritis and Cartilage, the developer of the Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures and co-founder of Good Life with Osteoarthritis in Denmark (GLA:D®), a not-for-profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice. STS is associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is co-founder of GLA:D®.

**Author Contributions**

Study conception and design: ER, ML, MSR, LAN, SR, STS. Acquisition of data: ER, ML, SR, STS. Analysis and interpretation of data: JBL, ER, ML, SH, MNJ, MSR, LAN, SR, STS. Drafting the article: JBL, STS. Revising the article critically for important intellectual content: JBL, ER, ML, SH, MNJ, MSR, LAN, SR, STS. Final approval of the article: JBL, ER, ML, SH, MNJ, MSR, LAN, SR, STS. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Patient consent for publication**

Not applicable

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Acknowledgments**
The authors would like to thank professor of medical statistics, Jonas Ranstam, Lund University and Skåne University Hospital Lund, Sweden for statistical advice on the RCT design; the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark for allowing us to use their facilities for the treatment and outcome assessments; and the orthopedic surgeons and other health care personnel from the Department of Orthopaedic Surgery, Aalborg University Hospital involved in the recruitment of patients for the RCT. Furthermore, the authors would like to acknowledge project workers Anders Bundgaard Lind, Anders Nørre Jensen, Anna Emilie Livbjerg, Dorte Rasmussen, Helle Mohr Brøcher, Henriette Duve, Janus Duus Christiansen, Josephine Nielsen, Kate Mcgirr, Lasse Løgsgaard, Lonneke Hjermitslev, Malene Daugaard, Maria Helena Odefey, Mette Bøgedal, Mikkel Skinderholm, Niels Balslev, Rikke Elholm Jensen, Svend Lyhne and Tina Lyngholm Jensen for helping with the administration, data collection, data entry and treatment in the study. Finally, the study funders and patients participating should be acknowledged, because without their participation, it would not have been possible to conduct the trial.

**Figure legends:**

Figure 1: Flow diagram of the patients in the randomized controlled trial from baseline to 5-year follow-up. K-L score: Kellgren-Lawrence grade. KOOS₄: The average score for the Knee injury and Osteoarthritis Outcome Score subscales for pain, symptoms, function of daily living (ADL), and quality of life. KR: Knee replacement.

Figure 2: Mean scores (95% CI) from the primary outcome of the Knee injury and Osteoarthritis Outcome Score, covering pain, symptoms, function of daily living (ADL), and quality of life.
at baseline and at 3, 6, 12, 24, and 60-months follow-up for the MEDIC and written advice
group. Error bars indicate 95% confidence intervals. Data points are observed data. Data from
3, 6, 12 and 24 months are from the primary reports(10,13).

Figure 3:

Mean scores (95% CI) from the primary outcome of the Knee injury and Osteoarthritis
Outcome Score covering pain, symptoms, function of daily living (ADL), and quality of life
at baseline and at 3, 6, 12, 24, and 60-months follow-up for patients receiving or not receiving
knee replacement (KR). Error bars indicate 95% confidence intervals. Incidence of patients
registered with KR in the index knee at 3 months: 1, at 6 months: 2, at 12 months: 5, at 24
months: 9 and at 60 months: 15. Prevalence of patients with KR in the index knee at 3
months: 1, at 6 months: 3, at 12 months: 8, at 24 months: 17 and at 60 months: 32. Data points
are observed data. Data from 3, 6, 12 and 24 months are from the primary reports(10,13).
References


27. Ranstam J, Turkiewicz A, Boonen S, van Meirhaeghe J, Bastian L, Wardlaw D. Alternative analyses for handling incomplete follow-up in the intention-to-treat analysis: the randomized
Figure 1:

Excluded (n=553)
- Eligible for KR (n=192)
  - K-L grade < 1 (n=87)
  - Aged < 18 years (n=26)
  - KOOS > 75 (n=22)
  - Previous same side knee replacement (n=44)
  - Rheumatoid Arthritis (n=11)
  - VAS > 60mm out of 100 mm (n=12)
  - Unable to comply with study protocol (n=159)

Eligible for inclusion (n=101)
- Unwilling to be randomised (n=1)

Randomized (n=100)

Allocated to non-surgical treatment (n=50)
  - Received the allocated treatment (n=48)
  - Did not want the treatment anyway (n=2)

Allocated to written advice (n=50)
  - Received the allocated treatment (n=50)

Follow-Up

Attended 1-year follow-up (n=47)

Attended 2-year follow-up (n=46)

Attended 5-year follow-up (n=39)
  - Did not attend (n=11)
    - No longer interested (n=2)
    - Cancelled and not possible to reach (n=5)
    - Had died (n=4)
  - Underwent joint replacement surgery during follow-up (n=15)

Attended 1-year follow-up (n=44)

Attended 2-year follow-up (n=42)

Attended 5-year follow-up (n=36)
  - Did not attend (n=14)
    - No longer interested (n=8)
    - Cancelled and not possible to reach (n=2)
    - Had died (n=4)
  - Underwent joint replacement surgery during follow-up (n=17)

Analysis

Included in the intention-to-treat analysis (n=50)

Included in the intention-to-treat analysis (n=50)
Figure 2:

[Graph showing KOOS scores over time for MEDIC group and Written advice group.]

- MEDIC group
- Written advice group
Figure 3:
Supplementary file 1:

Flow diagram of the patients in the randomized controlled trial from baseline to 5-year follow-up including reasons for drop-outs at all timepoints. K-L score: Kellgren-Lawrence grade. KOOS4: The average score for the Knee injury and Osteoarthritis Outcome Score subscales for pain, symptoms, function of daily living (ADL), and quality of life. KR: Knee replacement
Attended 2-year follow-up (n=46)
  Did not attend (n=4)
    No longer interested (n=1)
    Cancelled and not possible to reach (n=2)
    Had died (n=1)

Attended 2-year follow-up (n=42)
  Did not attend (n=8)
    No longer interested (n=5)
    Cancelled and not possible to reach (n=1)
    Had died (n=1)
    Had moved to another country (n=1)

Attended 5-year follow-up (n=39)
  Did not attend (n=11)
    No longer interested (n=2)
    Cancelled and not possible to reach (n=5)
    Had died (n=4)
    Underwent joint replacement surgery during follow-up (n=15)

Attended 5-year follow-up (n=36)
  Did not attend (n=14)
    No longer interested (n=8)
    Cancelled and not possible to reach (n=2)
    Had died (n=4)
    Underwent joint replacement surgery during follow-up (n=17)

Included in the intention-to-treat analysis (n=50)

Included in the intention-to-treat analysis (n=50)
### Supplementary file 2:

Baseline characteristics for patients attending 5-year follow-up and those that did not attend. Values are mean and SD unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Dropout (n= 25)</th>
<th>5-year follow-up (n= 75)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.6 (9.3)</td>
<td>65.1 (8.7)</td>
<td>0.086</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>13 (52%)</td>
<td>38 (51%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Body mass index</td>
<td>31.7 (4.7)</td>
<td>29.4 (5.6)</td>
<td>0.072</td>
</tr>
<tr>
<td>Kellgren-Lawrence grade, n (%)</td>
<td>Grade 1: 4 (16%)</td>
<td>Grade 1: 14 (19%)</td>
<td>0.786</td>
</tr>
<tr>
<td></td>
<td>Grade 2: 9 (36%)</td>
<td>Grade 2: 19 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3: 5 (20%)</td>
<td>Grade 3: 18 (24%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 4: 7 (28%)</td>
<td>Grade 4: 24 (32%)</td>
<td></td>
</tr>
<tr>
<td>Intake of pain medication, n (%)</td>
<td>17 (68%)</td>
<td>45 (60%)</td>
<td>0.635</td>
</tr>
<tr>
<td>KOOS&lt;sub&gt;4&lt;/sub&gt;</td>
<td>48.5 (12.0)</td>
<td>51.9 (12.1)</td>
<td>0.224</td>
</tr>
<tr>
<td>KOOS symptoms</td>
<td>52.1 (17.0)</td>
<td>58.7 (17.1)</td>
<td>0.099</td>
</tr>
<tr>
<td>KOOS pain</td>
<td>51.7 (14.2)</td>
<td>52.9 (14.0)</td>
<td>0.707</td>
</tr>
<tr>
<td>KOOS function of daily living</td>
<td>55.3 (19.4)</td>
<td>58.8 (15.9)</td>
<td>0.370</td>
</tr>
<tr>
<td>KOOS sport/recreation</td>
<td>19.0 (14.1)</td>
<td>25.3 (18.1)</td>
<td>0.114</td>
</tr>
<tr>
<td>KOOS quality of life</td>
<td>35.0 (13.5)</td>
<td>37.3 (13.8)</td>
<td>0.463</td>
</tr>
</tbody>
</table>

KOOS: Knee injury and osteoarthritis outcome score.
**Supplementary file 3:**

Usage of pain medication at the 5-year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>MEDIC group (95% CI)</th>
<th>Written advice group (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of users of pain medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (n: 50,50)</td>
<td>0.64 (0.50 to 0.76)</td>
<td>0.60 (0.46 to 0.73)</td>
</tr>
<tr>
<td>60-months (n: 39,35)</td>
<td>0.21 (0.11 to 0.36)</td>
<td>0.31 (0.18 to 0.48)</td>
</tr>
<tr>
<td><strong>Risk ratio for usage of pain medication at 5 years vs. baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude estimate</td>
<td>0.32 (0.17 to 0.61)</td>
<td>0.52 (0.31 to 0.90)</td>
</tr>
<tr>
<td>Adjusted estimate †</td>
<td>0.32 (0.17 to 0.61)</td>
<td>0.53 (0.31 to 0.90)</td>
</tr>
<tr>
<td><strong>Risk ratio for taking pain medication at 5 years in the written advice group vs the MEDIC group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted estimate ‡</td>
<td>1.53 (0.69 to 3.39)</td>
<td>-</td>
</tr>
</tbody>
</table>

* User of pain medication was defined as a patient using pain medication of any kind on a regular basis during the last week.
† The estimates were adjusted for site.
‡ The crude estimate was similar to the adjusted estimate (data not shown).
**Supplementary file 4**

Mean scores (95% CI) from the primary outcome of the Knee injury and Osteoarthritis Outcome Score covering pain, symptoms, function of daily living (ADL), and quality of life at baseline and at 3, 6, 12, 24, and 60-month follow-up for the MEDIC group receiving and not receiving knee replacement (KR) at the index knee and the written advice group receiving and not receiving KR at the index knee. Error bars indicate 95% confidence intervals.

Incidences of patients registered with KR in the index joint for the MEDIC KR group at 3 months: 1, at 6 months: 0, at 12 months: 2, at 24 months: 4 and at 60 months: 8 (in total, 15 patients). Incidence of patients registered with KR in the index joint for the written advice KR group at 3 months: 0, at 6 months: 2, at 12 months: 3, at 24 months: 5 and at 60 months: 7 (in total, 17 patients).
# Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

**Instructions to authors**

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORT reporting guidelines, and cite them as:


<table>
<thead>
<tr>
<th>Reporting Item</th>
<th>Page Number</th>
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<tbody>
<tr>
<td><strong>Title and Abstract</strong></td>
<td></td>
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<tr>
<td>Title</td>
<td>#1a</td>
</tr>
<tr>
<td>Identification as a randomized trial in the title.</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>#1b</td>
</tr>
<tr>
<td>Structured summary of trial design, methods, results, and conclusions</td>
<td>2-3</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
</tr>
<tr>
<td>Background and objectives</td>
<td>#2a</td>
</tr>
<tr>
<td>Scientific background and explanation of rationale</td>
<td>4-5</td>
</tr>
<tr>
<td>Background and objectives</td>
<td>#2b</td>
</tr>
<tr>
<td>Specific objectives or hypothesis</td>
<td>5</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Trial design</td>
<td>#3a</td>
</tr>
<tr>
<td>Description of trial design (such as parallel, factorial) including allocation ratio.</td>
<td>5</td>
</tr>
<tr>
<td>Trial design</td>
<td>#3b</td>
</tr>
<tr>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td>n/a</td>
</tr>
</tbody>
</table>

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Participants

#4a Eligibility criteria for participants 6

Participants

#4b Settings and locations where the data were collected 6

Interventions

#5 The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered 6-7 and reference to previous studies

Outcomes

#6a Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed 7-8

Outcomes

#6b Any changes to trial outcomes after the trial commenced, with reasons n/a

Sample size

#7a How sample size was determined. 8-9

Sample size

#7b When applicable, explanation of any interim analyses and stopping guidelines n/a

Randomization - Sequence generation

#8a Method used to generate the random allocation sequence. 6

Randomization - Sequence generation

#8b Type of randomization; details of any restriction (such as blocking and block size) 6

Randomization - Allocation concealment mechanism

#9 Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned 6

Randomization - Implementation

#10 Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions 6

Blinding

#11a If done, who was blinded after assignment to interventions (for example, participants, care
providers, those assessing outcomes) and how.

Blinding #11b If relevant, description of the similarity of interventions n/a

Statistical methods #12a Statistical methods used to compare groups for primary and secondary outcomes 9-10

Statistical methods #12b Methods for additional analyses, such as subgroup analyses and adjusted analyses 9-10

Results

Participant flow #13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome Figure 1

Participant flow #13b For each group, losses and exclusions after randomization, together with reason Figure 1

Recruitment #14a Dates defining the periods of recruitment and follow-up 6-7

Recruitment #14b Why the trial ended or was stopped n/a

Baseline data #15 A table showing baseline demographic and clinical characteristics for each group 11

Numbers analysed #16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups Table 2 and 3

Outcomes and estimation #17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) Table 2 and 3

Outcomes and estimation #17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended Supplementary file 2
Ancillary analyses  #18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory  13-14

Harms  #19 All important harms or unintended effects in each group (For specific guidance see CONSORT for harms) Published in the manuscript with 12-months follow-up

Discussion

Limitations  #20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses  18-19

Generalisability  #21 Generalisability (external validity, applicability) of the trial findings  16-17

Interpretation  #22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence  17

Registration  #23 Registration number and name of trial registry  3

Other information

Interpretation  #22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence  16-17

Registration  #23 Registration number and name of trial registry  3

Protocol  #24 Where the full trial protocol can be accessed, if available  5

Funding  #25 Sources of funding and other support (such as supply of drugs), role of funders  20

None The CONSORT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai