

Long-Term Outcomes and Costs of an Integrated Rehabilitation Program for Chronic Knee Pain: A Pragmatic, Cluster Randomized, Controlled Trial

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Objective. Chronic joint pain is a major cause of pain and disability. Exercise and self-management have short-term benefits, but few studies follow participants for more than 6 months. We investigated the long-term (up to 30 months) clinical and cost effectiveness of a rehabilitation program combining self-management and exercise: Enabling Self-Management and Coping of Arthritic Knee Pain Through Exercise (ESCAPE-knee pain).

Methods. In this pragmatic, cluster randomized, controlled trial, 418 people with chronic knee pain (recruited from 54 primary care surgeries) were randomized to usual care (pragmatic control) or the ESCAPE-knee pain program. The primary outcome was physical function (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] function), with a clinically meaningful improvement in physical function defined as a $\geq 15\%$ change from baseline. Secondary outcomes included pain, psychosocial and physiologic variables, costs, and cost effectiveness.

Results. Compared to usual care, ESCAPE-knee pain participants had large initial improvements in function (mean difference in WOMAC function -5.5 ; 95% confidence interval [95% CI] $-7.8, -3.2$). These improvements declined over time, but 30 months after completing the program, ESCAPE-knee pain participants still had better physical function (difference in WOMAC function -2.8 ; 95% CI $-5.3, -0.2$); lower community-based health care costs (£ -47 ; 95% CI £ $-94, £-7$), medication costs (£ -16 ; 95% CI £ $-29, £-3$), and total health and social care costs (£ $-1,118$; 95% CI £ $-2,566, £-221$); and a high probability (80–100%) of being cost effective.

Conclusion. Clinical and cost benefits of ESCAPE-knee pain were still evident 30 months after completing the program. ESCAPE-knee pain is a more effective and efficient model of care that could substantially improve the health, well-being, and independence of many people, while reducing health care costs.

INTRODUCTION

Chronic joint pain, the cardinal symptom of osteoarthritis (OA), is a major cause of distress, disability, dependency, psychosocial morbidity (anxiety, depression), reduced quality of life (1,2), and health care expenditure (3–5). These problems are set to increase as more people live longer.

In the leg, exercise (6,7), patient education, and self-

management advice (8,9) are core recommendations for management because they have short-term benefits for pain and physical and psychosocial functioning (10,11). Whether these benefits are sustained is unclear, as few studies follow participants for more than 6 months because evaluation of long-term benefit requires large, complex, expensive studies. The few studies with long-term followup have not found sustained clinical benefits and do not include an economic evaluation (12). Health care commissioners are reluctant to provide interventions without evidence of sustained benefits, so people may be deprived of potentially useful treatment.

We demonstrated a rehabilitation program integrating patient education, self-management strategies, and exercise, Enabling Self-Management and Coping of Arthritic Knee Pain Through Exercise (ESCAPE-knee pain), that had better short-term (up to 6 months) clinical and cost effectiveness than usual primary care (13,14). We hypothesized that these short-term clinical and cost benefits would be lost over time. Here we report the long-term (up to 30 months) clinical and cost effectiveness of ESCAPE-knee pain.

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Significance & Innovations

- Little is known about the long-term outcomes for exercise interventions for chronic knee pain/osteoarthritis (OA).
- A relatively brief, practicable, simple exercise-based rehabilitation program, Enabling Self-Management and Coping of Arthritic Knee Pain Through Exercise, had clinical and cost benefits that were sustained for up to 30 months after completing the program.
- It was more clinically effective, with less health care costs, and more cost effective than usual care.
- The program could be easily translated into clinical practice, providing more effective and efficient care for people with OA and chronic joint pain.

MATERIALS AND METHODS

Trial design. Detailed descriptions of the trial design, inclusion and exclusion criteria, randomization and clinical outcomes (13), and economic evaluation (14) have been published. Briefly, the study was a pragmatic, cluster randomized, controlled trial carried out and analyzed in accordance with the prespecified protocol. Participants ($n = 418$) were identified and recruited from 54 primary care surgeries in Southeast London. Broad inclusion criteria were used to ensure recruitment of a representative population of people with chronic knee pain from primary care: participants had to be age 50 years or over with mild, moderate, or severe knee pain of more than 6 months' duration. People were excluded if they had leg arthroplasty, physiotherapy for knee pain in the preceding 12 months, intraarticular injections in the preceding 6 months, unstable medical conditions, inability/unwillingness to exercise, severe lack of mobility, or inability to understand English. People were not excluded if they had stable comorbidities common in this age group (e.g., type 2 diabetes mellitus, cardiovascular or respiratory disorders), back, lower, or upper extremity pain. Management of all participants' knee and coexistent medical problems continued at the primary care physician's discretion, but was documented at all assessments.

A randomization list was generated and held at a central site away from the research center by personnel not involved in the trial. Primary care practices were the unit of randomization; therefore, because of the practice they attended, participants received usual care ($n = 178$), ESCAPE-knee pain program was delivered to individual participants ($n = 146$), or small groups of participants were collected ($n = 132$).

The study was approved by St. Thomas', Guys', Lewisham's, and Kings College Hospital's Ethics Committees.

Interventions. Participants randomized to usual care (the pragmatic control arm) received whatever services or interventions their physicians considered appropriate.

Participants randomized to ESCAPE-knee pain also continued to receive whatever services or interventions their physician considered appropriate, but in addition they participated in an exercise-based rehabilitation program designed to improve function by integrating exercise, education, and self-management strategies to dispel inappropriate health beliefs, alter behavior, and encourage regular physical activity. Participants were invited to attend 12 supervised sessions twice weekly for 6 weeks. For 15–20 minutes of each session, the supervising physiotherapist (NEW) facilitated a discussion on a specific topic, advising and suggesting simple coping strategies. Then, for 35–40 minutes each participant performed a simple individualized exercise regimen to address their disabilities and progressed this as they improved. The content of the program was similar whether delivered to individual participants or small groups of 8 participants. To ensure consistency in content and delivery, the same physiotherapist (who had 13 years of postgraduate clinical experience) devised, supervised, and progressed all sessions of all participants. After completion, participants were discharged with encouragement to perform home exercises and physical activity, especially walking, but did not receive any additional intervention as part of the program.

Clinical outcomes. The primary outcome was self-reported functioning assessed using the physical function subscore of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (15). High WOMAC scores signify poor functioning; therefore, a reduction in WOMAC score indicates improvement. A clinically meaningful improvement in physical functioning was defined as a reduction of at least 15% from a participant's baseline WOMAC function score (16).

Secondary outcomes were pain (WOMAC pain), objective functional performance measured by the aggregated time of 4 common activities of daily living (AFPT) (17), exercise-related health beliefs and self-efficacy questionnaire (ExBeliefs) (18), Hospital Anxiety and Depression Scale (HADS) (19), condition-specific health-related quality of life (McMaster Toronto Arthritis Questionnaire [MACTAR]) (20), quadriceps strength (17), and voluntary activation (17). Reductions in WOMAC pain, AFPT, and HADS scores and increases in other scores indicate improvement.

All outcomes were assessed at baseline, immediately after completion of the intervention or recruitment to the usual primary care arm (6-week assessment), and at 6 (the primary end point), 18, and 30 months following the 6-week postintervention assessment. The assessors were blinded to a participant's allocation.

This study focuses on the changes in the primary outcome, WOMAC function; secondary outcomes are reported to enable comparison with earlier results (13,14).

Sample size. Patients with knee OA have a mean \pm SD WOMAC function score of 41.3 ± 14.8 (15). A conservative estimate of a clinically meaningful improvement was considered to be 15% of the baseline value (16). Based on individual randomization, a sample size of 150 partici-

pants per arm was required for the trial to have 90% power to detect this target difference between 2 arms, with a 5% significance level (2-tailed) and allowing for 20% withdrawal by 6 months. Based on intracluster correlation coefficients observed in other studies of chronic conditions in primary care (21,22), this sample size was inflated by 33% (i.e., a design effect of 1.33, or 200 participants per arm) to take into account cluster randomization, and aimed to minimize the design effect by recruiting as many clusters as possible to decrease the average number of participants per cluster (21,22).

Statistical analysis. Statistical analysis followed a pre-specified protocol based on intent-to-treat with no interim analyses. As there were no differences in baseline values, treatment outcome, costs, or withdrawal data between the participants who received ESCAPE-knee pain individually ($n = 146$) and those who received ESCAPE-knee pain in small groups ($n = 132$), these data were combined ($n = 278$) and compared with usual care ($n = 178$). Since the primary care practice characteristics did not affect the results and the interventions are applied to individuals rather than primary care practices, the demographic and clinical outcome variables are described for individual participants. Cluster-weighted SDs and cluster-adjusted *t*-tests are reported for normally distributed variables to take into account within-cluster correlation (23).

Multilevel repeated-measures models were used to estimate the group means and differences in outcome effect of the rehabilitation programs over the 4 followup assessments (0, i.e., immediately after completing the intervention, 6, 18, and 30 months postintervention). There were 3 levels in the model: assessment occasions, participants, and primary care practices. This model allows the effect of treatment on function to be correlated (intracluster correlation) for each individual over the 4 followup assessments and for participants within the same clusters (primary care practices). Change in effect of treatment over time was modeled by fitting linear and quadratic time trends to each treatment group. All of the models were adjusted for baseline WOMAC function score. Multilevel modeling software for Windows, MLwiN version 2.01 (Bristol University), was used to analyze the data, using restricted iterative generalized least squares estimation to fit all of the models. Likelihood ratio tests were used to test random effects (the variance components) and Wald's tests were used to test fixed parameters.

Missing data can be efficiently handled using the multilevel repeated-measures model, since all data on all participants can be incorporated in the analysis, regardless of the number of followup assessments attended. The model assumes that information on outcome is "missing at random," so the value of the WOMAC function score that would have been observed on the missing assessment occasions depends only on: 1) the time since the start of followup, 2) a participant's treatment group, and 3) a participant's baseline WOMAC function score. To test the sensitivity of the model to this assumption, a further repeated-measures multilevel model was fitted with adjustment for baseline covariates that predicted missingness at

any time point (age, sex, MACTAR, HADS, AFPT, and ExBeliefs). This model allows the value of the WOMAC function score that would have been observed on the missing measurement occasions to depend on 1) the time since the start of followup, 2) a participant's treatment group, 3) a participant's baseline WOMAC function score, and 4) covariates that predict missingness.

The number needed to treat (NNT) estimates the number of people who would need to undertake ESCAPE-knee pain for 1 person to have a clinically meaningful improvement ($\geq 15\%$) from baseline WOMAC function. At each assessment point, the NNT was derived from the difference in the proportion of participants who attained this improvement in ESCAPE-knee pain versus usual care, with 95% confidence intervals (95% CIs) obtained from the reciprocal transformation of the CIs for the difference in proportions.

Statistical significance was set at *P* values less than 0.05. Data are shown as the mean score, with 95% CIs, where appropriate.

Economic evaluation. The economic evaluation was from a health and social care payer perspective for publicly-funded services accessible for free at the point of delivery. We included the cost of knee pain-related medications obtained by free prescription, knee pain-related health and social care service use in hospital and community settings (see Supplementary Appendix A, available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)), and ESCAPE-knee pain. These resource use data were measured retrospectively for 6 months prior to the baseline assessment and the periods between assessments (6 weeks to 6 months, 6–18 months, 18–30 months) by interview using an adapted Client Services Receipt Inventory (CSRI) (21).

Individual-level costs were calculated by multiplying these resource use data with unit costs standardized to 2003/2004 prices (see Supplementary Appendix A, available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)) (14). ESCAPE-knee pain unit costs included all of the resource inputs normally associated with running one session of each individual and group program (e.g., contact and non-contact time with the therapist, capital costs, overhead costs, exercise equipment, materials/photocopying), calculated as the total cost per person per session to apply to individuals' attendance rates.

Costs are shown in English pounds sterling (£), and can be converted to Euros or US dollars using the rates £1 = \$1.56 and £1 = €1.36 (based on 2003 purchasing power parities that equalize the purchasing power of the currencies [24]). We discounted data because the economic evaluation covered more than 1 year. An annual discount rate of 3.5% was used for both costs and outcomes (as per the National Institute for Health and Clinical Excellence reference case [25]).

Analyses were by intent-to-treat. Mean 30-month costs per group are participant-level costs unadjusted for clustering. Estimates of mean differences between the groups and 95% CIs were obtained using linear regression with

the cluster adjustment procedure in Stata, version 8.2, and 1,000 nonparametric bootstrap replications were used to allow for the non-normal distribution commonly associated with cost data. Comparisons of followup costs included a covariate for baseline costs.

To maximize the usefulness of the economic evaluation for health care commissioners, the cost-effectiveness analysis was based on the clinically meaningful version of the WOMAC function outcome rather than on point differences. Therefore, we linked between-group differences in total costs with the proportion of each group showing at least a 15% improvement in WOMAC function at 30-month followup using cost-effectiveness acceptability curves based on the net benefit approach (26,27). These show the probability that the ESCAPE-knee pain program is cost effective compared to usual care, for a range of values a health care commissioner may be prepared to pay for 1% increases in the proportion of people meaningfully improving in WOMAC function. Only those with relevant cost and outcome data were included.

Two sensitivity analyses were performed. First, we investigated any effects of outliers (which is common in cost data). Although nonparametric bootstrapping addresses such non-normal distributions, we separately examined the variable for total discounted health/social care costs for outliers (defined as those having a Z score of ± 3). One such outlier was identified in the usual care arm as a participant who developed postoperative complications following knee surgery, which necessitated prolonged intensive care, hospitalization, and postdischarge health care. The total discounted health and social care costs are presented with and without this participant. Second, loss of CSRI followup at various assessment points prevented the calculation of total 30-month costs for affected cases and thus reduced the sample size for the cost and cost-effectiveness analyses. We therefore imputed missing total discounted health/social care costs and explored the impact of this on group means and mean differences. We used the multiple imputation procedure in Stata, version 10.1, and imputed based on variables expected to predict followup costs: intervention, age, sex, baseline WOMAC function, and baseline health/social care costs.

RESULTS

Of the 418 participants recruited, 375 (90%) were assessed on at least 1 followup occasion. At 30 months, data were available from 283 participants (68%) (Figure 1). There was no difference between the participants' anthropometric characteristics at baseline in either trial arm (Table 1).

During the 30-month observational period, all of the participants in the trial, regardless of which arm they were in, received whatever interventions their primary care physicians considered appropriate. For the majority, this consisted of prolonged medication (analgesia and non-steroidal antiinflammatory drugs), very few received other interventions (i.e., physiotherapy, surgery), and there were no between-group differences in the interventions received (see Supplementary Appendix A, available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

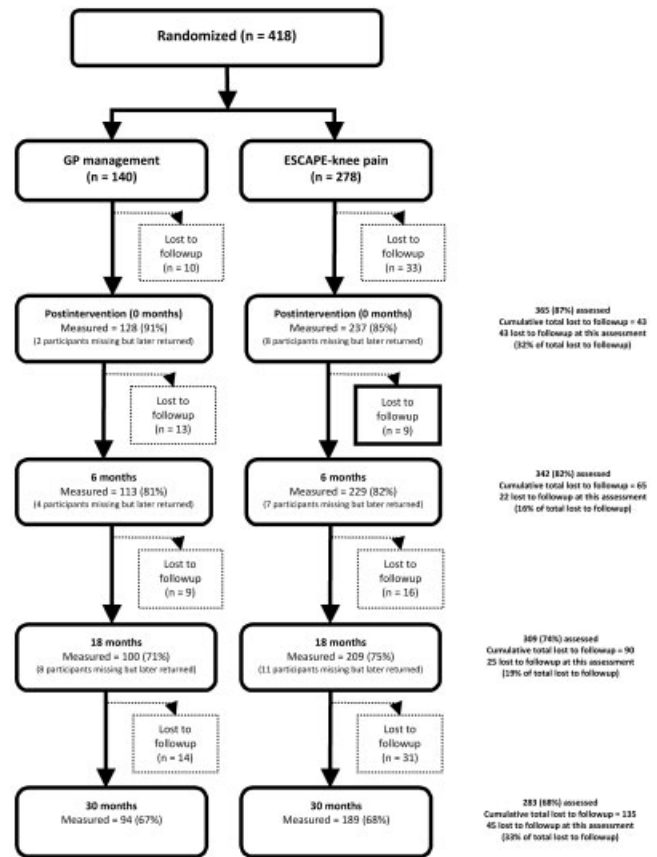


Figure 1. Participant flow through the trial. The total lost to followup is shown at each assessment point from individual arms. Values are shown as the number measured (percentage of number randomized). GP = general practitioner; ESCAPE-knee pain = Enabling Self-management and Coping of Arthritic Knee Pain Through Exercise.

Clinical outcomes. The mean baseline WOMAC function score was 27.2 for participants receiving usual care and 27.1 for participants randomized to receive ESCAPE-knee pain (Table 1). Immediately after the intervention, unadjusted WOMAC function score was lower in participants who had completed ESCAPE-knee pain in comparison to usual care participants (mean ESCAPE-knee pain 20.0 versus usual care 25.9; $P = 0.002$) (Table 1), and at all subsequent followup assessments there was no difference in unadjusted WOMAC function between ESCAPE-knee pain and usual care participants (Table 1). Most secondary outcomes showed a similar pattern of results with large initial improvements for ESCAPE-knee pain participants that declined over time, except for improvement in ESCAPE-knee pain participants' exercise health beliefs and self-efficacy, which were sustained for 18 months, and physiologic measures of sensorimotor muscle function, which showed no improvement at any assessment (Table 1).

A higher proportion of ESCAPE-knee pain participants had clinically meaningful improvements in WOMAC function at all assessment points compared to usual care (Table 1). The NNT for a between-group difference in clinically meaningful improvement in function was 3.7 (95% CI 2.7, 6.1; $P < 0.001$) (Table 1) immediately after the

Table 1. Demographic variables at baseline*

	Baseline		Postintervention: 6-week followup		6-month followup		18-month followup		30-month followup	
	Usual care (n = 140)	ESCAPE-knee pain (n = 278)	Usual care (n = 128)	ESCAPE-knee pain (n = 237)	Usual care (n = 113)	ESCAPE-knee pain (n = 229)	Usual care (n = 100)	ESCAPE-knee pain (n = 209)	Usual care (n = 94)	ESCAPE-knee pain (n = 189)
Demographic variables										
Women:men, no.	96:44	198:80	85:43	173:64	74:39	172:57	68:32	156:53	63:31	143:46
Age, mean (range) years	67 (51-89)	67 (50-91)	66 (51-89)	67 (50-91)	66 (51-89)	67 (50-91)	67 (52-90)	68 (51-92)	68 (53-91)	69 (52-93)
Duration of symptoms, median (IQR) years	9.6 (3-15)	9.5 (3-12)	10.5 (4-15)	9.5 (3-12)	10.2 (3-15)	9.0 (3-12)	9.9 (4-15)	8.6 (2-12)	10.5 (4-15)	9.0 (2.5-12)
Height, mean (range) meters	1.65 (1.46-1.89)	1.64 (1.39-1.97)	1.65 (1.46-1.89)	1.63 (1.39-1.92)	1.66 (1.47-1.89)	1.63 (1.39-1.92)	1.65 (1.47-1.89)	1.63 (1.39-1.92)	1.65 (1.47-1.87)	1.63 (1.39-1.92)
Body mass, mean (range) kg	81.8 (48-135)	80.4 (47-139)	81.8 (50-130)	80.4 (45-130)	80.5 (49-131)	79.0 (46-130)	80.0 (51-132)	79.6 (45-139)	80.8 (47-130)	79.3 (45-125)
BMI, mean (range) kg/m ²	30.3 (20-51)	30.1 (18-50)	29.9 (20-50)	30.1 (18-47)	29.2 (21-46)	29.6 (18-47)	28.8 (20-45)	29.9 (18-50)	29.0 (18-43)	29.8 (17-45)
Primary outcome										
WOMAC function, mean ± SD	27.2 ± 7.0	27.1 ± 6.7	25.9 ± 6.3	20.0 ± 5.9	23.4 ± 7.5	21.7 ± 6.7	24.3 ± 6.6	21.9 ± 7.5	23.8 ± 6.3	22.3 ± 8.7
Proportion improved by ≥15%	-	-	0.34	0.61	< 0.001	0.54	0.40	0.52	0.35	0.50
NNT, no. (95% CI)										
Secondary clinical outcomes										
WOMAC pain, mean ± SD	7.7 ± 1.7	7.5 ± 1.7	7.1 ± 1.8	5.2 ± 1.7	6.5 ± 2.1	5.7 ± 1.9	6.4 ± 2.1	5.7 ± 2.0	6.4 ± 2.0	5.9 ± 2.6
APPT, median (IQR) seconds	52.8 (40.6-78.2)	51.3 (40.7-70.7)	48.9 (39.1-71.0)	44.1 (36.3-57.9)	46.4 (38.0-59.7)	46.2 (37.6-65.1)	48.6 (37.6-62.5)	46.2 (37.6-67.4)	49.3 (39.3-66.8)	48.8 (39-63.7)
ExBeliefs, mean ± SD	64.0 ± 3.1	64.4 ± 2.9	63.7 ± 3.2	69.2 ± 3.2	64.2 ± 3.5	67.8 ± 3.4	65.3 ± 3.6	68.0 ± 3.4	66.3 ± 4.1	67.6 ± 3.5
HADS anxiety subscore, median (IQR)	6.0 (3.0-9.0)	6.0 (3.0-9.0)	5.0 (3.0-9.0)	5.0 (2.0-7.0)	5.0 (2.0-9.0)	5.0 (2.0-7.0)	6.0 (2.0-8.0)	4.0 (2.0-7.0)	5.0 (2.0-7.0)	4.0 (2.0-7.0)
HADS depression subscore, median (IQR)	5.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	3.0 (1.0-6.0)	3.0 (2.0-6.0)	3.0 (1.0-6.0)	4.0 (2.0-6.0)	3.0 (1.0-5.0)	3.0 (1.0-6.0)	3.0 (1.0-5.0)
MACTAR score, mean ± SD	31.6 ± 2.5	31.6 ± 2.2	41.6 ± 2.8	47.6 ± 3.6	42.2 ± 2.7	44.2 ± 4.0	40.7 ± 4.3	41.5 ± 5.1	39.2 ± 3.9	39.2 ± 5.2
Physiologic variables										
Left quadriceps MVC, mean ± SD N	212.0 ± 46.9	199.3 ± 35.7	206.9 ± 50.1	212.5 ± 35.6	0.646					
Right quadriceps MVC, mean ± SD N	238.4 ± 51.4	222.9 ± 42.1	234.8 ± 50.8	245.2 ± 42.8	0.443	218.4 ± 55.0	203.8 ± 38.0	223.7 ± 51.7	208.8 ± 36.7	224.4 ± 70.6
Left quadriceps voluntary activation, median (IQR) %	80 (60-91)	77 (61-91)	79 (63.5-89)	81 (66-92)	0.622	245.6 (55.9)	231.1 (41.3)	262.6 (46.7)	252.2 (76.6)	240.7 (57.5)
Right quadriceps voluntary activation, median (IQR) %	79 (57-91.0)	78 (57-89)	74 (60-89)	79 (62-93)	0.279	75 (60-90)	81 (64.5-93)	84 (72-95)	84 (74-90)	86 (70-95)

* ESCAPE-knee pain = Enabling Self-Management and Coping of Arthritic Knee Pain Through Exercise; IQR = interquartile range; BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; NNT = number needed to treat; 95% CI = 95% confidence interval; APPT = aggregate function performance time; ExBeliefs = exercise-related health beliefs and self-efficacy questionnaire; HADS = Hospital Anxiety and Depression Scale; MACTAR = McMaster Toronto Arthritis questionnaire; MVC = maximum voluntary contraction.
 † Between-group difference.

Table 2. Effect of ESCAPE-knee pain on WOMAC function score*

	Predicted WOMAC function for usual care (n = 140)	Predicted WOMAC function for ESCAPE-knee pain (n = 278)	Between-group difference in WOMAC function	Between-group difference, P
Adjusted for baseline WOMAC function				
Postintervention	25.9 (24.1, 27.8)	20.4 (19.0, 21.7)	-5.56 (-7.84, -3.27)	< 0.0001
6 months	25.9 (24.2, 27.6)	21.3 (20.0, 22.5)	-4.63 (-6.74, -2.52)	< 0.0001
18 months	26.0 (24.0, 27.9)	22.5 (21.1, 23.9)	-3.45 (-5.79, -1.11)	0.004
30 months	26.1 (24.0, 28.1)	22.9 (21.4, 24.4)	-3.17 (-5.70, -0.64)	0.014
Adjusted for baseline WOMAC function and predictors of missingness				
Postintervention	25.4 (23.2, 27.7)	19.9 (17.9, 22.0)	-5.49 (-7.78, -3.19)	< 0.0001
6 months	25.4 (23.3, 27.5)	21.0 (19.0, 22.9)	-4.44 (-6.54, -2.33)	< 0.0001
18 months	25.4 (23.1, 27.7)	22.3 (20.3, 24.3)	-3.10 (-5.44, -0.76)	0.010
30 months	25.4 (22.9, 27.8)	22.6 (20.5, 24.7)	-2.78 (-5.32, -0.23)	0.032

* Values are the mean (95% confidence interval). The missing data model predicted WOMAC function score for a participant with mean values of baseline variables. ESCAPE-knee pain = Enabling Self-Management and Coping of Arthritic Knee Pain Through Exercise; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

intervention, and the NNT increased over time and at 30 months was 6.7 (95% CI 3.8, 39.5; $P = 0.019$) (Table 1), i.e., 7 people would have to undertake ESCAPE-knee pain for 1 person to attain and retain clinically meaningful improvements in function for 30 months.

The decline in WOMAC function for usual care participants may, in part, be due to loss to followup rather than improvements in functioning for individual participants. Participants who were lost to followup had poorer functioning at baseline than those who were assessed on at least 1 followup occasion (WOMAC function score 29.0 versus 26.9; $P = 0.41$). In particular, participants who were lost to followup from the usual care arm had poorer baseline functioning than participants lost to followup from the ESCAPE-knee pain arm (mean WOMAC function score 32.2 versus 28.0; $P = 0.49$).

Results for 2 multilevel models are shown in Table 2 and Figure 2. The first model assumes the WOMAC function was missing at random, depending only on time of measurement, treatment group, and baseline WOMAC function (Table 2 and Figure 2A). However, examination of baseline variables found that participants who did not return for followup had worse physical functioning and exercise-related health beliefs and self-efficacy. Therefore, the second model allows the missing values of WOMAC function to additionally depend on these differences in baseline variables (Table 2 and Figure 2B), but adjusting for these baseline differences had little impact on the treatment effects. Overall, physical functioning of usual care participants did not change during the 30-month followup (Table 2 and Figure 2A). ESCAPE-knee pain participants had large improvements in WOMAC function (ESCAPE-knee pain 19.9 [95% CI 17.9, 22.0], usual care 25.4 [95% CI 23.2, 27.7], difference -5.49 [95% CI -7.78, -3.19]) (Table 2 and Figure 2), and these declined over time but were still evident at 30 months (WOMAC function ESCAPE-knee pain 22.6 [95% CI 20.5, 24.7], usual care 25.4 [95% CI 22.9, 27.8], difference -2.78 [95% CI

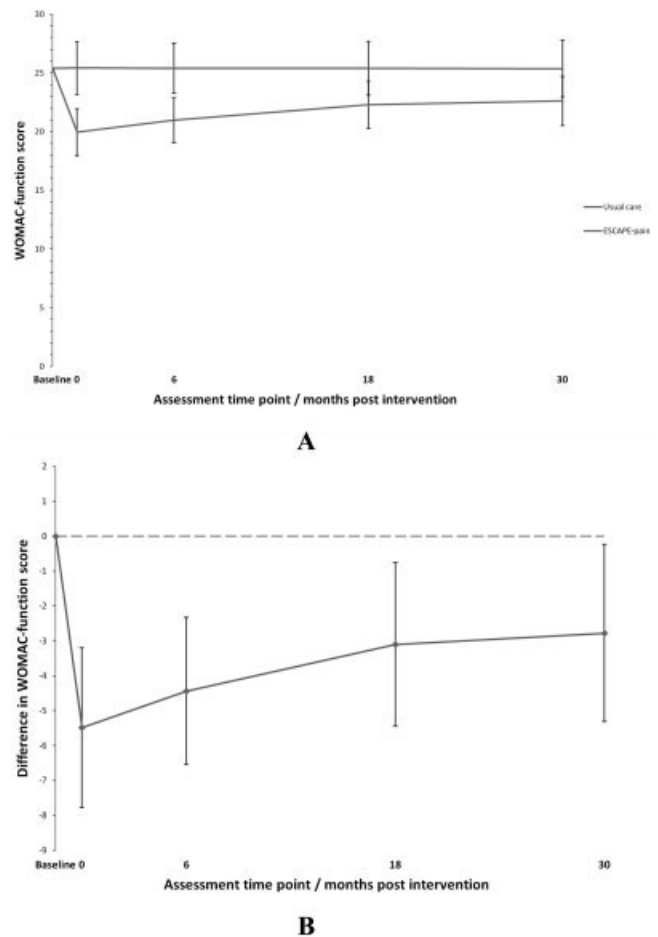


Figure 2. Effect of Enabling Self-Management and Coping of Arthritic Knee Pain Through Exercise (ESCAPE-knee pain) on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function score (adjusted for missing data). **A**, predicted WOMAC function score, **B**, difference in WOMAC function score between groups.

Table 3. Mean and mean differences*

	Usual care		ESCAPE-knee pain		ESCAPE-knee pain vs. usual care†	
	Mean ± SD‡	N	Mean ± SD‡	N	Difference	95% CI
ESCAPE-knee pain intervention costs§	0 ± 0	140	224 ± 131	277	224	184, 262
Baseline total health and social care costs (for previous 6 months)	103 ± 185	140	98 ± 152	278	-5	-51, 30
Discounted total health and social care costs (including ESCAPE-knee pain costs) over 30 months						
Total health and social care costs	2,136 ± 10,318	77	1,018 ± 1,970	154	-1,177	-3,609, 313
Sensitivity analysis 1: 1 cost outlier removed	982 ± 2,000	76	1,018 ± 1,970	154	-24	-506, 413
Sensitivity analysis 2: missing cost data imputed	2,240 ± 7,651	140	1,109 ± 1,559	278	-1,118	-2,566, -221¶

* Costs are in English pounds sterling (2003/2004 prices). ESCAPE-knee pain = Enabling Self-Management and Coping of Arthritic Knee Pain Through Exercise.

† Cluster-adjusted mean differences and 95% confidence intervals (95% CIs), obtained from 1,000 bootstrap replications; 2.5-year cost comparisons included a covariate for baseline costs.

‡ Mean values per group are based on individual-level means, unadjusted for clusters.

§ Intervention costs are based on the full sample, regardless of followup status at 30 months.

¶ Costs associated with ESCAPE-knee pain are significantly lower than costs associated with usual care.

-5.32, -0.23]) (Table 2 and Figure 2). The effect of treatment from the missing data model was slightly smaller at all time points compared to the model without adjustment for predictors of missingness, suggesting participants who dropped out were expected to benefit slightly less from treatment than those who remained in the study.

Economic evaluation. Usual care incurred no rehabilitation costs, and participating in ESCAPE-knee pain cost £224 (95% CI £184, £262) (Table 3). At baseline there were no between-group differences in costs (£-5; 95% CI £-51, £30) (Table 3). Baseline costs of ESCAPE-knee pain participants who withdrew from the study (£103) were similar to those who remained in the trial (£95). However, usual care participants who withdrew had higher baseline costs than those who remained in the trial (£150 and £74, respectively; $P < 0.035$). This may have reduced the treatment effects.

Health care utilization was relatively low throughout the trial (see Supplementary Appendix A, available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)). In the 12 months prior to the 30-month assessment, costs were slightly lower for ESCAPE-knee pain than usual care participants, but this difference was only significant for some cost components (community-based care £-47; 95% CI £-94, £-7 and medication £-16; 95% CI £-29, £-3). There were no differences in total health and social care costs (£55; 95% CI £-221, £279). Over 30 months there were no differences in discounted total health and social costs (£-1,177; 95% CI £-3,609, £313) (Table 3) or removing a cost outlier (£-24; £-506, £413) (Table 3). Imputing missing data did suggest that ESCAPE-knee pain participants had lower costs (£-1,118; 95% CI £-2,566, £-221) (Table 3).

The cost-effectiveness acceptability curve suggests that ESCAPE-knee pain has a high probability (81–100%) of

being more cost effective than usual care across willingness-to-pay values ranging from £0 to £9,750 (Figure 3).

DISCUSSION

An exercise-based rehabilitation program for people with chronic knee pain/knee OA, ESCAPE-knee pain, produced large improvements in physical function that declined over time but were still evident 30 months after completing the program, and was more cost effective than usual care.

When interpreting this study's findings, its strengths and limitations need to be considered. It was a preplanned secondary analysis performed to address the sparse data available for long-term outcomes of exercise interventions

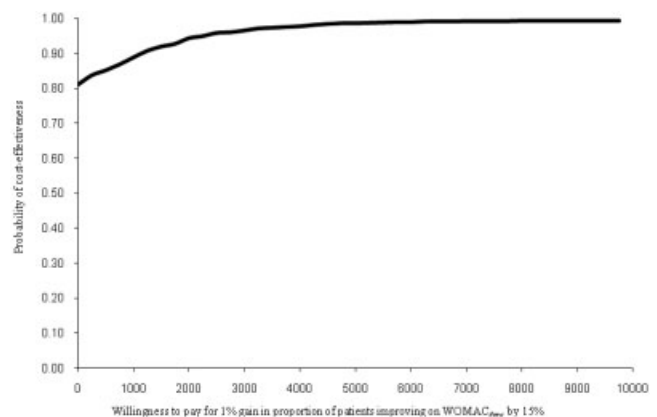


Figure 3. Cost-effectiveness acceptability curve comparing Enabling Self-Management and Coping of Arthritic Knee Pain Through Exercise (ESCAPE-knee pain) with usual care, based on a 1% increase in the proportion improving on the Western Ontario and McMaster Universities Osteoarthritis Index function subscale (WOMAC_{func}) by at least 15% and discounted health and social care costs and outcomes over the 2.5 years of the trial.

for chronic knee pain. It enrolled a representative patient population, so the intervention and findings are likely to be generalizable to the large number of people in primary care with chronic knee pain. In addition, the program does not require specialized training, sophisticated exercises, or equipment, so it could be replicated easily (28,29).

Unfortunately, as with most longitudinal studies, the main limitation is the large amount of missing data in the later assessments. Handling missing data incorrectly (for example, by ignoring missing data or performing “completers only” or “last observation carried forward” analysis) can give spurious results and conclusions (30). We used multilevel modeling and multiple imputation to generate robust predictions of the effect of missing data (30). The unadjusted data analysis, which ignores baseline values and missing data, suggests little or no between-group differences. However, this was greatly influenced by the differential withdrawal from usual care of participants with the highest health and social care costs and poorest function. This differential attrition reduced between-group treatment differences and masked the program’s greater and sustained clinical and cost benefits compared to usual primary care.

We anticipated short-term clinical benefits of exercise that have been found in most (31–34), but not all (35), recent studies of community-based self-management interventions for knee OA. However, we also thought that without additional input these benefits would decline over time (12) and would have disappeared by 2.5 years, so we were surprised to find sustained improvements. These sustained benefits may be due to the program’s design and content. ESCAPE-knee pain was designed on the premise that physiologic (muscle weakness, poor motor control), psychological (health beliefs, self-confidence), behavior (avoidance of movement, seeking medical attention), and socioeconomic variables are all important determinants of physical function, pain, behavior, and health care utilization (36,37). Combining formal and informal education and discussion of the safety and benefits of exercise with a challenging exercise regimen may prolong participants’ beliefs in the value of exercise in the management of joint pain and their ability to use exercise to control symptoms (38). Furthermore, the program is safe (there were no adverse side effects), effective (an **NNT of 7 is much lower than drug trials [39]**), and sustained over 30 months.

The findings of our economic evaluation corroborate other interventions of exercise/physical activity in primary care (34,40–42), and our earlier economic evaluation of **ESCAPE-knee pain (43) showed lower utilization of health care resources and cost effectiveness** for this patient population following this type of intervention. Our participants received typical primary care management that generally consisted of analgesia and nonsteroidal antiinflammatory drugs, and very few participants were referred for secondary care (13,14,44,45). **Although the only cost differences were for community-based services and medications, these resources are most frequently used by people with chronic knee pain, and extrapolation to the large number of people with knee pain could result in substantial cost savings in these areas of health care.**

The main difference between the program by Buszewicz

et al, which did not find clinical or cost improvements (35,46), and the more successful rehabilitation programs (12–14,40–42) was that Buszewicz et al did not include an active participatory exercise component. Therefore, inclusion of a participatory exercise component may be vital for effective self-management. Interviews of ESCAPE-knee pain participants describe how their beliefs about the importance of exercise in the management of knee pain is altered by their participation in the program (38). They highlight the importance they attach to the exercise component of the program and how first-hand direct experience of the exercise helped them appreciate the potential benefits of exercise (improvement in function, pain general health, and well-being), allayed their initial fears that exercise would exacerbate pain and joint damage, and increased their confidence in their ability to apply exercise as a self-management strategy that can reduce symptoms and control their knee condition, all of which resulted in them being less reliant on other people, with a consequent reduction in health care utilization and costs (38). Therefore, an active participatory exercise component is likely to be essential in any effective self-management regimen for knee OA/chronic pain.

The prevalence of chronic joint pain and OA is increasing faster than previously predicted (1,47) as more people live longer, obesity increases, pain-induced mobility limitations increase the risk of diabetes mellitus and cardiorespiratory comorbidity (48–50), and poor adherence to management guidelines (51) results in prolonged (mis)use of potentially harmful medication (52–55) and inappropriate surgical referral. Despite strong evidence of the benefit and safety of exercise and self-management programs, only a minority of people are referred to these interventions because they continue to be erroneously considered ineffective, expensive, and impractical. Consequently, few people benefit because of their poor provision and restricted access.

Evidence of sustained clinical and cost benefit achieved following a relatively brief, practicable, simple exercise-based rehabilitation program makes ESCAPE-knee pain an attractive treatment option for patients, clinicians, and health care commissioners. By design, the program has many of the attributes that facilitate translation to clinical practice (28,29), so ESCAPE-knee pain may provide more effective and efficient care for the large and growing number of people with OA and chronic joint pain.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Hurley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hurley, Walsh, Patel.

Acquisition of data. Hurley, Walsh, Mitchell.

Analysis and interpretation of data. Hurley, Nicholas, Patel.

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