

Long term outcomes and costs of ESCAPE-knee pain: an integrated rehabilitation programme for chronic knee pain.

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Abstract

Objective. Chronic joint pain is a major cause of suffering 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 programme combining self-management and exercise – *Enabling Self-management and Coping of Arthritic knee Pain through Exercise, ESCAPE-knee pain*.

Methods. In this pragmatic, cluster randomised, controlled trial, 418 people with chronic knee pain (recruited from 54 primary care surgeries) were randomised to *Usual Care* (pragmatic control) or *ESCAPE-knee pain* programme. 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 $\geq 15\%$ change from baseline. Secondary outcomes included pain, psychosocial and physiological 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, CI-7.8 to -3.2). These improvements declined over time, but 30 months after completing the programme *ESCAPE-knee pain* participants still had better physical function (difference in WOMAC-function -2.8, CI-5.3 to -0.2), lower community-based healthcare costs (-£47, CI-£94 to -£7), medication costs (-£16, CI-£29 to -£3), total health and social care costs (-£1118, CI-£2566 to -£221) and high probability (80-100%) of being cost-effective.

Conclusions. Clinical and cost benefits of *ESCAPE-knee pain* were still evident 30 months after completing the programme. *ESCAPE-knee pain* is a more effective, efficient model of care, that could substantially improve many people's health, wellbeing and independence, while reducing healthcare costs.

Points of significance and innovation:

- little is known about the long-term outcomes for exercise interventions for chronic knee pain/OA
- a relatively brief, practicable, simple exercise-based rehabilitation programme, *ESCAPE-knee pain*, had clinical and cost benefits that were sustained for up to 30 months after completing the programme
- it was more clinically effective, with less healthcare costs and more cost-effective than usual care
- the programme could be easily translated into clinical practice providing more effective, efficient care people with OA and chronic joint pain

Introduction.

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

In the lower limb, exercise (6, 7), patient education and self-management advice (8, 9) are core recommendations for management because they have short-term benefits on pain, 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 follow-up have not found sustained clinical benefits and include no economic evaluation (12). Healthcare commissioners are reluctant to provide interventions without evidence of sustained benefits, so people may be deprived of potentially useful treatment.

We demonstrated a rehabilitation programme integrating patient education, self-management strategies and exercise – *Enabling Self-management and Coping of Arthritic knee Pain through Exercise, ESCAPE-knee pain* – had better short-term (up to 6 months) clinical and cost-effectiveness than usual primary care (13, 14). We hypothesised 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*.

METHODS

Trial Design. Detailed descriptions of the trial design, inclusion and exclusion criteria, randomisation and clinical outcomes (13) and economic evaluation (14) have been published. Briefly, the study was a pragmatic, cluster randomised, controlled trial carried out and analysed in accordance with the pre-specified protocol (Current Controlled Trials, ISRCTN 94658828). Participants (n=418) were identified and recruited from 54 primary care surgeries in South East 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 aged 50 years or over, with mild, moderate or severe knee pain of more than 6 months duration. People were excluded if they had: lower limb arthroplasty; physiotherapy for knee pain in preceding 12 months; intra-articular injections in 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 co-morbidities common in this age group (e.g. type II diabetes, cardiovascular or respiratory disorders), back, lower or upper limb pain. Management of all participants' knee and co-existent medical problems continued at the primary care physician's discretion, but was documented at all assessments.

A randomisation list was generated and held at a central site away from the research centre by personnel not involved in the trial. Primary care practices were the unit of randomisation so, by dint of the practice they attended, participants received *Usual Care* (n=178), *ESCAPE-knee pain* programme delivered to individual participants (n=146) or small groups of participants (n=132).

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

Interventions. Participants randomised to *Usual Care* (the pragmatic control arm), received whatever services or interventions their physicians considered appropriate.

Participants randomised 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 programme designed to improve function by integrating exercise, education and

self-management strategies to dispel inappropriate health beliefs, alter behaviour 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 facilitated a discussion on a specific topic, advising and suggesting simple coping strategies. Then for 35-40 minutes each participant performed a simple individualised exercise regimen to address their disabilities and progressed this as they improved. The content of the programme 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 postgraduate clinical experience) devised, supervised and progressed all the 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 programme.

Clinical outcomes. The primary outcome was self-reported functioning assessed using the physical function sub score 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 - 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 (HAD) (19); condition specific health related quality of life (MACTAR) (20); quadriceps strength (17) and voluntary activation (17). Reductions in WOMAC-pain, AFPT and HAD 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 post intervention assessment. Assessors were blinded to a participant's allocation.

This paper 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 WOMAC-function of 41.3 (SD 14.8) (15). A conservative estimate of a clinically meaningful improvement was considered to be 15% of the baseline value (16). Based on individual randomisation, a sample size of 150 participants per arm was required for the trial to have 90% power to detect this target difference between two arms, with 5% significance level (two-tailed) and allowing for 20% withdrawal by 6-months. Based on intra-cluster correlation coefficients (ICC) 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; i.e. 200 participants per arm) to take into account cluster randomisation, and aimed to minimise the design effect by recruiting as many clusters as possible to decrease the average number of participants per cluster (21, 22).

Data 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 or withdrawal data between 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 standard deviations (SD) 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 four follow-up assessments (0- immediately after completing the intervention, 6-, 18- and 30-months post-intervention). There were three levels in the model, i) assessment occasions, ii) participants, iii) primary care practices. This model allows the effect of treatment on function to be correlated (intra-cluster correlation) for each individual over the four follow-up assessments and for participants within the same clusters (primary care practices). Change in

effect of treatment over time was modelled by fitting linear and quadratic time trends to each treatment group. All models adjusted for baseline WOMAC-function score. Multilevel Modelling for Windows, MLwiN v2.01, software was used analyse the data, using restricted iterative generalised least squares estimation to fit all models. Likelihood Ratio tests were used to test random effects (the variance components) and Wald tests 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 follow-up assessments attended. The model assumes that information on outcome is “missing at random”, so the value of WOMAC-function score that would have been observed on the missing assessment occasions depends only on: (a) the time since start of follow-up, (b) a participant’s treatment group and (c) 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 WOMAC-function score that would have been observed on the missing measurement occasions to depend on: (a) the time since start of follow-up, (b) a participant’s treatment group and (c) a participant’s baseline WOMAC-function score, (d) covariates that predict missingness.

The number needed-to-treat (NNT) estimates the number of people who would need undertake *ESCAPE-knee pain* for one person to have a clinically meaningful improvement ($\geq 15\%$) from baseline WOMAC-function. At each assessment point 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 obtained from the reciprocal transformation of the confidence intervals for the difference in proportions.

Statistical significance was set at $P < 0.05$. Data are presented as mean score, with 95% confidence interval where appropriate.

Economic evaluation. Data of the *ESCAPE-knee pain* programme is presented as one combined intervention because the two modes of delivery (individual and group) produced similar outcomes and

costs (Appendix). 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 Appendix), and *ESCAPE-knee pain*. These resource use data were measured retrospectively for six months prior to baseline assessment and the periods between assessments (6 weeks-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 standardised to 2003/2004 prices (see Hurley, 2007 #5756} and Appendix for details). *ESCAPE-knee pain* unit costs included all resource inputs normally associated with running one session of each individual and group programme (e.g. contact and non-contact time with the therapist, capital costs, overhead costs, exercise equipment, materials/photocopying) calculated as total cost per-person per session to apply to individuals' attendance rates.

Costs are presented in English pounds sterling (£), and can be converted to Euros or United States dollars (\$) using the rates £1 = \$1.56 and £1 = 1.36 (based on 2003 purchasing power parities which equalise the purchasing power of the currencies (24)). We discounted data because the economic evaluation covered more than one 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 intention-to-treat. Mean 30 month costs per group are participant-level costs unadjusted for clustering. Estimates of mean differences between groups and 95% confidence intervals were obtained using linear regression with the cluster adjustment procedure in Stata v8.2 and 1000 non-parametric bootstrap replications to allow for the non-normal distribution commonly associated with cost data. Comparisons of follow-up costs included a covariate for baseline costs.

To maximise the usefulness of the economic evaluation for healthcare commissioners, the cost-effectiveness analysis was based on the clinically meaningful version of the WOMAC-func outcome rather than on point differences. Thus 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

follow-up using cost-effectiveness acceptability curves (CEACs) based on the net benefit approach (26, 27). These show the probability that the *ESCAPE-knee pain* programme is cost-effective compared to *Usual Care*, for a range values that a healthcare 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. Firstly, we investigated any effects of outliers (which is common in cost data). While non-parametric 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 post-operative complications following knee surgery which necessitated prolonged intensive care, hospitalisation and post-discharge healthcare. The total discounted health and social care costs are presented with and without this participant. Secondly, loss of CSRI follow-up 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 10.1 and imputed based on variables expected to predict follow-up 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 one follow-up occasion, at 30-months data was available from 283 (68%) participants (Figure 1). There was no difference between the participant's anthropometric characteristics at baseline in either trial arm (Table 1).

During the 30-month observational period all participants in the trial, regardless of which arm they were in, received whatever interventions their primary care physicians considered appropriate. For the vast majority this consisted of prolonged medication (analgesia and NSAIDs), very few received other interventions (i.e. physiotherapy, surgery), and there were no between-group differences in the interventions received (Appendix, A4-A7).

Clinical outcomes. Baseline WOMAC-function was 27.2 for participants receiving *Usual Care* and 27.1 for participants randomised to receive *ESCAPE-knee pain* (Table 1). Immediately after the intervention, unadjusted WOMAC-function was lower in participants who had completed *ESCAPE-knee pain* in comparison to *Usual Care* participants (*ESCAPE-knee pain* 20.0 vs *Usual Care* 25.9; $p=0.002$; Table 1), at all subsequent follow-up 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 which declined over time, except for improvement in *ESCAPE-knee pain* participants' exercise health beliefs and self-efficacy, which were sustained for 18 months, and physiological 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 (2.7 to 6.1; $p<0.001$; Table 1) immediately after the intervention, the NNT increased over time and at 30 months was 6.7 (3.8 to 39.5; $p=0.019$; Table 1), i.e. 7 people would have to undertake *ESCAPE-knee pain* for one 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 follow-up rather than improvements in functioning for individual participants. Participants who were lost to follow-up had poorer functioning at baseline than those who were assessed on at least one follow-up occasion (WOMAC-function 29.0 versus 26.9 respectively; $p=0.41$). In particular, participants who were lost to follow-up from the *Usual Care* arm had poorer baseline functioning than participants lost to follow-up from the *ESCAPE-knee pain* arm (mean WOMAC-function 32.2 versus 28.0 respectively; $p=0.49$).

Results for two multilevel models are presented in Table 2 and Figure 2. The first model assumes WOMAC-function was missing at random, depending only on time of measurement, treatment group and baseline WOMAC-function (Table 2a; Figure 2a). However, examination of baseline variables found participants who did not return for follow-up 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 2b; 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 30-month follow-up (Table 2b; Figure 2a). *ESCAPE-knee pain* participants had large improvements in WOMAC-function (*ESCAPE-knee pain* 19.9, 17.9 to 22.0; *Usual Care* 25.4, 23.2 to 27.7; difference -5.49, -7.78 to -3.19; Table 2b; Figure 2), these declined over time but were still evident at 30 months (WOMAC-function *ESCAPE-knee pain* 22.6, 20.5 to 24.7; *Usual Care* 25.4, 22.9 to 27.8; difference -2.78, -5.32 to -0.23; Table 2b; 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, participating on *ESCAPE-knee pain* cost £224 (£184 to £262; Table 3a). At baseline there were no between-group differences in costs (-£5, -£51 to £30; Table 3b). Baseline costs of *ESCAPE-knee pain* participants who withdrew from the study (£103) were similar to those who remained on 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.

Healthcare utilisation was relatively low throughout the trial (Appendix A4-A7). In the twelve months prior to the 30 months 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, -£94 to -£7 and medication -£16, -£29 to -£3). There were no differences in total health and social care costs (£55, £-221 to £279). Over the 30 months there were no differences in discounted total health and social costs (-£1177, -£3609 to £313; Table 3c) or removing a cost outlier (-£24, -£506 to £413; Table 3c Sensitivity analysis 1). Imputing missing data did suggest *ESCAPE-knee pain* participants had lower costs (-£1118, -£2566 to -£221; Table 3c Sensitivity analysis 2).

The cost effectiveness acceptability curve suggests *ESCAPE-knee pain* has a high probability (81% to 100%) of being more cost-effective than *Usual Care* across willingness-to-pay values ranging from £0 to £9750 (Figure 3).

Discussion.

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

Strengths and limitations. When interpreting this study's findings its strengths and limitations need to be considered. It was a pre-planned secondary analysis performed to address the sparse data available of long-term outcomes for exercise interventions for chronic knee pain. It enrolled a representative patient population, so the intervention and findings are likely to generalise to the large number of people in primary care suffering chronic knee pain. In addition, the programme does not require specialised training, sophisticated exercises or equipment, so 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, performing "completers only" or "last observation carried forward" analysis) can give spurious results and conclusions (30). We used multilevel modelling and multiple imputation to generate robust predications of the effect of missing data (30). The unadjusted data analysis, which ignores baseline values and missing data, suggest 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 programme's greater and sustained clinical and cost benefits compared to usual primary care.

Findings in context. We anticipated short term clinical benefits of exercise that has 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 2½ years, so we were surprised to find sustained improvements. These sustained benefits may be due the programme's design and content. *ESCAPE-knee pain* was designed on the premise that physiological (muscle weakness, poor motor control), psychological (health beliefs,

self-confidence), behaviour (avoidance of movement, seeking medical attention) and socioeconomic variables are all important determinants of physical function, pain, behaviour and healthcare utilisation (36, 37). Combining formal and informal education and discussion of the safety and benefits of exercise with a challenging exercise regimen, may prolong participant's beliefs in the value of exercise in the management of joint pain and their ability to use exercise to control symptoms (38). Furthermore, the programme 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) that showed lower utilisation of healthcare resources and cost-effectiveness for this patient population following this type of intervention. Our participants received typical primary care management which generally consisted of analgesia and non-steroidal anti-inflammatory drugs, 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 Buszewicz et al's programme did not find clinical or cost improvements (35, 46), and the more successful rehabilitation programmes (13, 14 Pisters, 2007 #3719, 40-42) was that Buszewicz et al did not include an active, participatory exercise component. Thus inclusion of a participatory exercise component may be a vital for effective self-management. Interviews of *ESCAPE-knee pain* participants describes how their beliefs about the importance of exercise in the management of knee pain is altered by their participation on the programme (38). They highlight the importance they attach to the exercise component of the programme, 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, 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 healthcare utilisation and costs (38). Thus an active participatory exercise component is likely to be essential in any effective self-management regimen for knee OA/chronic pain.

Clinical Relevance. 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 risk of diabetes, cardio-respiratory co-morbidity (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 programmes, only a minority of people are referred to these interventions because they continue to be erroneously considered ineffectual, 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 programme, makes *ESCAPE-knee pain* an attractive treatment option for patients, clinicians and healthcare commissioners. By design the programme has many of the attributes that facilitate translation to clinical practice (28, 29), so *ESCAPE-knee pain* may provide more effective, efficient care for the large and growing number of people with OA and chronic joint pain.

Contributions to the study: 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 submitted for publication. In addition, MH was principal investigator, conceived and coordinated the trial, recruited primary care practices, assessed participants, led preparation of first draft manuscript and subsequent revisions. NW recruited participants, organised and supervised all rehabilitation sessions of all participants, contributed extensively to management of the trial. HM assessed participants, processed and entered data. AP adapted the CSRI for this patient population, conducted and interpreted the economic analyses. JN conducted and interpreted the statistical analyses. MH is guarantor for the paper, he 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.

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Conflict of interests: None of the authors have declared any conflict of interest

Figure 1. Participant flow through the trial. Showing total lost to follow-up at each assessment point, from individual arms. Presented as number measured (percentage of number randomised)

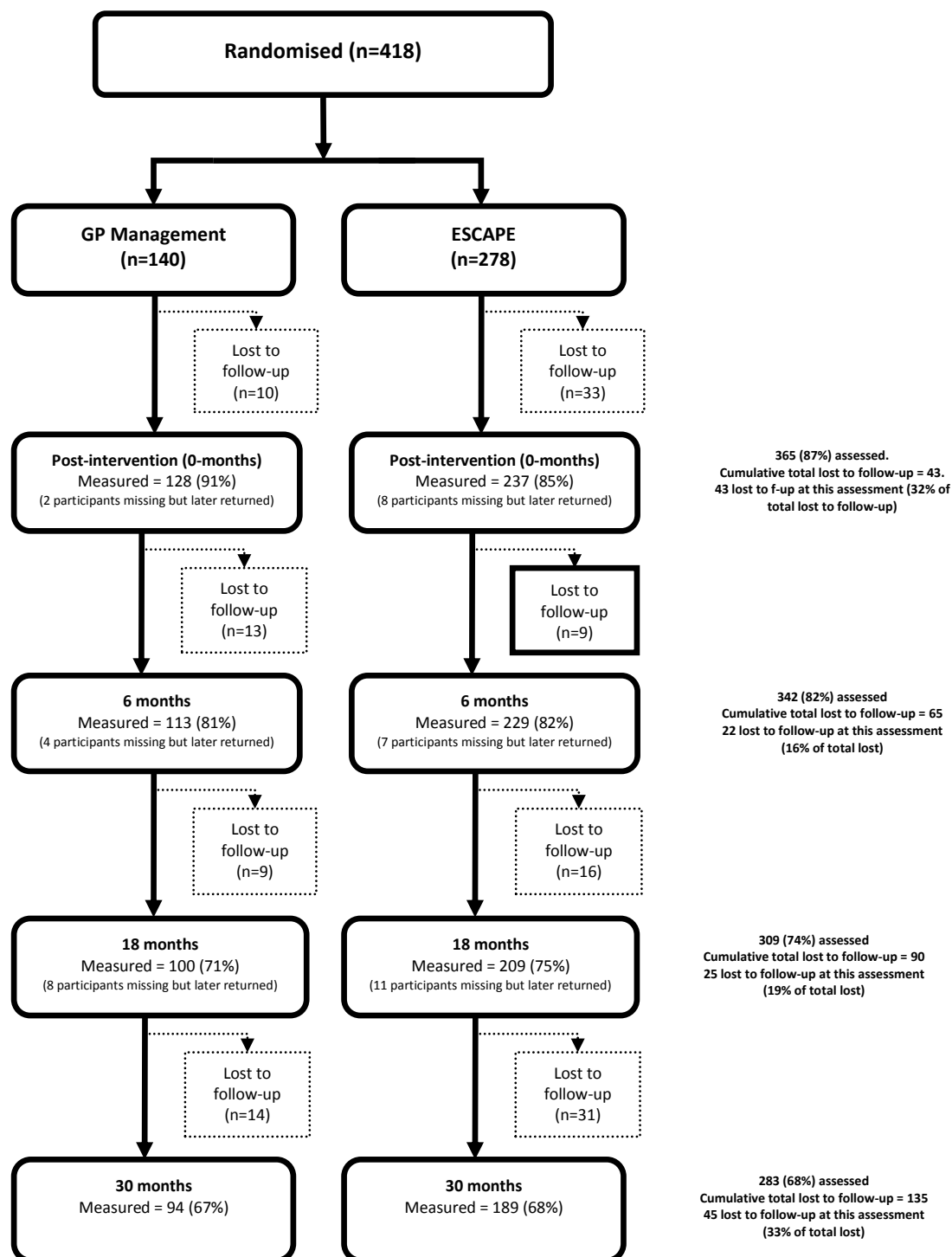
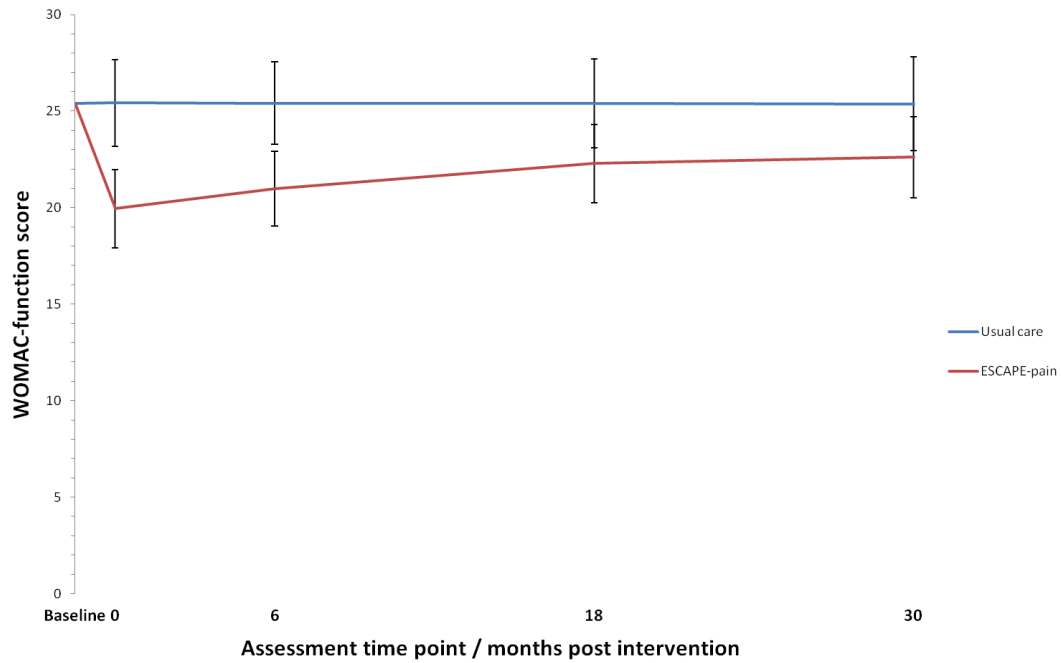


Figure 2. Effect of *ESCAPE-knee pain* on WOMAC-function score (adjusted for missing data)
a) predicted WOMAC-function score and b) difference in WOMAC-function score between groups

a)



b)

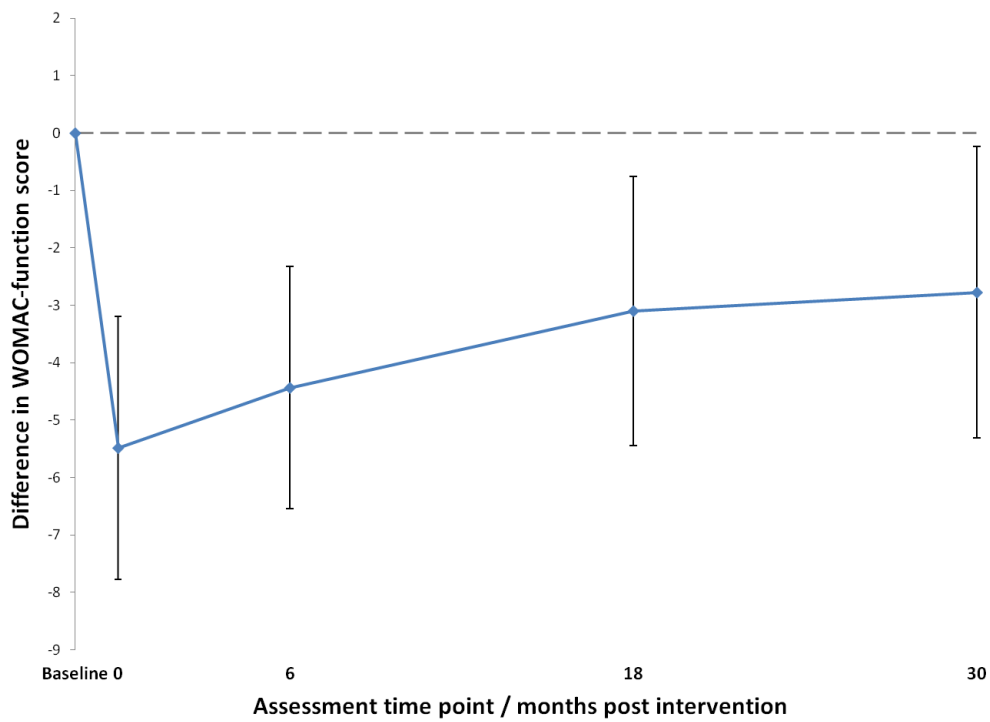


Table 1. Demographic variables at baseline [presented as means (range) except numbers of female:male and duration of symptoms are presented as median (interquartile range) due to skewness], clinical outcomes and physiological variables at baseline and subsequent follow-up assessments [presented as mean (standard deviation), *median (interquartile range) due to skewness, or **proportion of participants who had clinically meaningful amount improvement in function - equal to or more than 15% from baseline value WOMAC-function, number (95% confidence interval)].

	Baseline		Post-intervention - 6-week follow-up		Grp-diff p-value	6-month follow-up		Grp-diff p-value	18-month follow-up		Grp-diff p-value	30-month follow-up		Grp-diff p-value
	Usual care (n=140)	ESCAPE (n=278)	Usual care (n=128)	ESCAPE (n=237)		Usual care (n=113)	ESCAPE (n=229)		Usual care (n=100)	ESCAPE (n=209)		Usual care (n=94)	ESCAPE (n=189)	
Demographic variables:														
Number of female:male	96:44	198:80												
Age /yrs	67 (51-89)	67 (50-91)												
Duration of symptoms /yrs	6 (3-15)	5 (3-12)												
Height /m	1.65 (1.46-1.89)	1.64 (1.39-1.97)												
Body mass /kgs	81.8 (48-135)	80.4 (47-139)												
Body Mass Index	30.3 (20-51)	30.1 (18-50)												
Primary outcome:														
WOMAC-function	27.2 (7.0)	27.1 (6.7)	25.9 (6.3)	20.0 (5.9)	0.002	23.4 (7.5)	21.7 (6.7)	0.423	24.3 (6.6)	21.9 (7.5)	0.257	23.8 (6.3)	22.3 (8.7)	0.525
Proportion improved ≥ 15%**	-	-	0.34	0.61	<0.001	0.40	0.54	0.018	0.40	0.52	0.057	0.35	0.50	0.019
Number Needed to Treat***			3.7 (2.7-6.1)			7.3 (4.1-42.0)			8.5 (4.3-∞)			6.7 (3.8-39.5)		
Secondary clinical outcomes:														
WOMAC-pain	7.7 (1.7)	7.5 (1.7)	7.1 (1.8)	5.2 (1.7)	<0.001	6.5 (2.1)	5.7 (1.9)	0.178	6.4 (2.1)	5.7 (2.0)	0.263	6.4 (2.0)	5.9 (2.6)	0.459
AFPT /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)	0.048	46.4 (38.0-59.7)	46.2 (37.6-65.1)	0.975	48.6 (37.6-62.5)	46.2 (37.6-67.4)	0.705	49.3 (39.3-66.8)	48.8 (38.5-63.7)	0.803
ExBeliefs & self-efficacy	64.0 (3.1)	64.4 (2.9)	63.7 (3.2)	69.2 (3.2)	<0.001	64.2 (3.5)	67.8 (3.4)	0.001	65.3 (3.6)	68.0 (3.4)	0.012	66.3 (4.1)	67.6 (3.5)	0.238
HADS - anxiety*	6.0 (3.0-9.0)	6.0 (3.0-9.0)	5.0 (3.0-9.0)	5.0 (2.0-7.0)	0.310	5.0 (2.0-9.0)	5.0 (2.0-7.0)	0.456	6.0 (2.0-8.0)	4.0 (2.0-7.0)	0.237	5.0 (2.0-7.0)	4.0 (2.0-7.0)	0.466
HADS - depression*	5.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	3.0 (1.0-6.0)	0.056	3.0 (2.0-6.0)	3.0 (1.0-6.0)	0.341	4.0 (2.0-6.0)	3.0 (1.0-5.0)	0.199	3.0 (1.0-6.0)	3.0 (1.0-5.0)	0.766
Mactar Score	31.6 (2.5)	31.6 (2.2)	41.6 (2.8)	47.6 (3.6)	<0.001	42.2 (2.7)	44.2 (4.0)	0.081	40.7 (4.3)	41.5 (5.1)	0.621	39.2 (3.9)	39.2 (5.2)	0.973
Physiological variables:														
Left quads MVC/N	212.0 (46.9)	199.3 (35.7)	206.9 (50.1)	212.5 (35.6)	0.646									
Right quads MVC/ 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)	0.276	223.7 (51.7)	208.8 (36.7)	0.248	224.4 (70.6)	208.5 (44.0)	0.357
Left. quads vol act / %.*	80 (60-91)	77 (61-91)	79 (63.5-89)	81 (66-92)	0.622	245.6 (55.9)	231.1 (41.3)	0.299	262.6 (46.7)	242.1 (46.6)	0.151	252.2 (76.6)	240.7 (57.5)	0.577
Right quads vol act / %.*	79 (57-910)	78 (57-89)	74 (60-89)	79 (62-93)	0.279	75 (60-90)	81 (64.5-93)	0.041	84 (72-95)	85 (70-94)	0.583	84 (74-90)	86 (70-95)	0.794

n – number; Grp-diff – between-group difference; yrs – years; m – metres; kgs – kilograms; N-Newtons; %-percentage; WOMAC-function and WOMAC-pain - Western Ontario and McMaster's University Osteoarthritis Index function subscale and pain subscale scores; AFPT – Aggregate function performance time; ExBeliefs & self efficacy - exercise health beliefs and exercise self-efficacy; HADS-anxiety and HADS-depression – Hospital Anxiety and Depression Scale anxiety and depression subscores; MACTAR – McMaster's Toronto Arthritis questionnaire; quads MVC – quadriceps maximum voluntary contraction; quads vol. act. – quadriceps voluntary activation

Table 2 Effect of *ESCAPE-knee pain* on WOMAC-function score adjusted for (a) baseline WOMAC-function and (b) baseline WOMAC-function and predictors of missingness. Missing data model predicted WOMAC-function score for a participant with mean values of baseline variables. Data presented as mean (95% confidence interval).

	<i>Predicted WOMAC function for Usual Care (n=140)</i>	<i>Predicted WOMAC function for ESCAPE-knee pain (n=278)</i>	Between-group difference in WOMAC-function	Between group difference p-value
(a) adjusted for baseline WOMAC-function				
<i>Post-intervention</i>	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
(b) adjusted for baseline WOMAC-function and predictors of missingness				
Post-intervention	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

Table 3: Mean and mean differences in a) cost of *ESCAPE-knee pain*, b) baseline health and social care costs (for previous 6 months) and c) discounted health and social care costs (including *ESCAPE-knee pain* costs) over the whole 30 month follow-up period. Costs are in Pounds Sterling (2003/04 prices).

	Usual Care		ESCAPE-knee pain		ESCAPE-knee pain vs Usual Care**	
	Mean* (SD)	N	Mean* (SD)	N	Difference	95% CI
a) ESCAPE-knee pain intervention costs***	0 (0)	140	224 (131)	277	224	184 to 262
b) baseline total health & social care costs	103 (185)	140	98 (152)	278	-5	-51 to 30
c) discounted total health & social care costs over 30 months:						
Total health & social care costs	2136 (10318)	77	1018 (1970)	154	-1177	-3609 to 313
Sensitivity analysis 1: One cost outlier removed	982 (2000)	76	1018 (1970)	154	-24	-506 to 413
Sensitivity analysis 2: Missing cost data imputed	2240 (7651)	140	1109 (1559)	278	-1118	-2566 to -221#

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

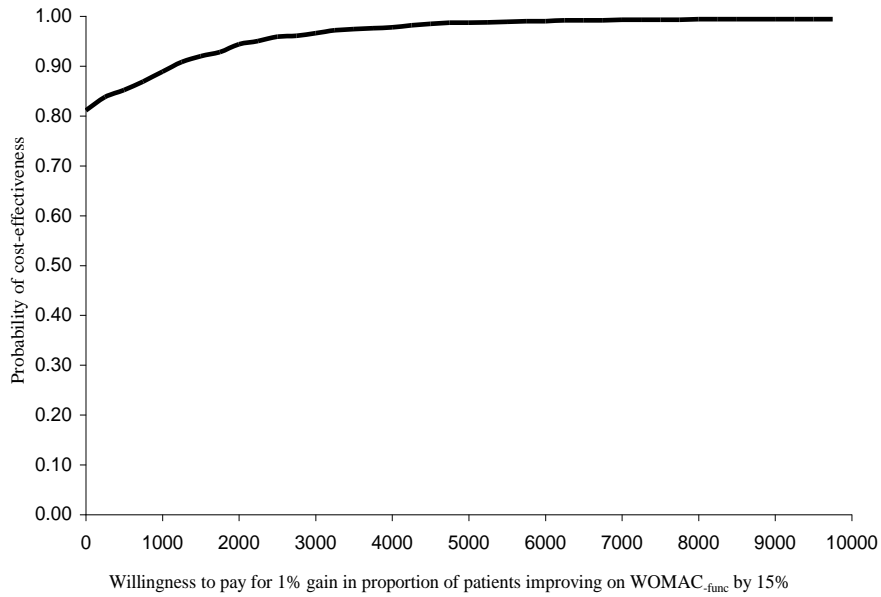
** Cluster-adjusted mean differences and confidence intervals, obtained from 1000 bootstrap replications. 2.5 year cost comparisons included a covariate for baseline costs.

*** Intervention costs are based on full sample regardless of follow-up status at 30 months.

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

SD – standard deviation; 95% CI - 95% confidence interval.

Figure 3: Cost-effectiveness acceptability curve comparing *ESCAPE-knee pain* with *Usual Care*. Based on a 1% increase in the proportion improving on WOMAC-function sub-scale by at least 15% and discounted health and social care costs and outcomes over the 2.5 years of the trial.



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