Original article

Joint protection and hand exercises for hand osteoarthritis: an economic evaluation comparing methods for the analysis of factorial trials

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Abstract

Objectives. Evidence regarding the cost-effectiveness of joint protection and hand exercises for the management of hand OA is not well established. The primary aim of this study is to assess the cost-effectiveness (cost-utility) of these management options. In addition, given the absence of consensus regarding the conduct of economic evaluation alongside factorial trials, we compare different analytical methodologies.

Methods. A trial-based economic evaluation to assess the cost-utility of joint protection only, hand exercises only and joint protection plus hand exercises compared with leaflet and advice was undertaken over a 12 month period from a UK National Health Service perspective. Patient-level mean costs and mean quality-adjusted life years (QALYs) were calculated for each trial arm. Incremental cost-effectiveness ratios (ICERs) were estimated and cost-effectiveness acceptability curves were constructed. The base case analysis used a within-the-table analysis methodology. Two further methods were explored: the at-the-margins approach and a regression-based approach with or without an interaction term.

Results. Mean costs (QALYs) were £58.46 (S.D. 0.662) for leaflet and advice, £92.12 (S.D. 0.659) for joint protection, £64.51 (S.D. 0.681) for hand exercises and £112.38 (S.D. 0.658) for joint protection plus hand exercises. In the base case, hand exercises were the cost-effective option, with an ICER of £318 per QALY gained. Hand exercises remained the most cost-effective management strategy when adopting alternative methodological approaches.

Conclusion. This is the first trial evaluating the cost-effectiveness of occupational therapy-supported approaches to self-management for hand OA. Our findings showed that hand exercises were the most cost-effective option.

Key words: cost-effectiveness, cost-utility, hand osteoarthritis, factorial trial.

CLINICAL SCIENCE

Introduction

Hand OA is a common condition that affects a large proportion of the population aged 45 years and over [1–3].

OA places a strain on scarce resources; for example, in a recent study, the total annual direct cost of OA in the USA was estimated to be double that of similar patients who did not have OA [4]. In the UK, the total health care cost of OA is estimated at more than £1 billion (2010 prices) [5]. Symptoms of hand OA include pain, stiffness and limited hand function [6] and common management approaches include exercises, joint protection and topical agents for pain relief [2, 7]. European League Against Rheumatism (EULAR) guidelines recommend that joint protection and hand exercises should be offered in the management of hand OA [2]. However, until recently there has been limited evidence to support the clinical effectiveness and cost-effectiveness of these management options [8, 9].

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A 2×2 multicentre factorial trial was conducted to determine the effectiveness of joint protection and hand exercises for the management of hand OA. This trial design allowed for a simultaneous investigation of joint protection *vs* no joint protection and hand exercises *vs* no hand exercises [9]. In determining the cost-effectiveness of interventions, there is no consensus regarding how economic evaluations should be carried out alongside factorial trials. Recent research [10] has reported that economic evaluations alongside factorial trials have been carried out using a variety of methods, including within-the-table analysis, the at-the-margins approach and a regression-based approach [11].

This study evaluates the cost-utility of joint protection and hand exercises for the management of hand OA and compares alternative methodological approaches for conducting economic evaluation alongside factorial trials.

Methods

The health economic evaluation was carried out alongside a multicentre 2×2 factorial randomized trial in older adults with hand OA. Details of the trial methodology have been published elsewhere [8, 9]. Adults aged 50 years and over who consented and who met the eligibility criteria were randomly assigned to one of the four treatment groups: leaflet and advice, joint protection only, hand exercises only and joint protection plus hand exercises. The primary clinical outcome of the trial was response to treatment [Osteoarthritis Research Society International (OARSI)/OMERACT responder criteria] at 6 months [9]. The trial on which the present study is based was approved by the North West 7 Research Ethics Committee UK (rec reference: 07/H1008/235) and was monitored by an independent trial steering committee and a data monitoring committee (trial registration number ISRCTN 33870549).

The economic evaluation reported here took the form of a cost-utility analysis from a UK National Health Service (NHS) perspective, using quality-adjusted life years (QALYs) as the measure of health benefit. QALYs take into account the survival and quality of life of an individual—the focus here was on the potential for quality of life gains from a reduction in hand pain and improvement in hand functioning due to the intervention.

Data collection

Resource use and costs
Health care resource use data were obtained from participant responses to self-report questionnaires administered at 6 and 12 months. Resource use data concentrated on visits to health care professionals in primary and secondary care, medical investigations/interventions and prescribed medications. Resource use obtained from participant responses to the questionnaires were aggregated to generate overall resource use over the 12-month follow-up period. For the trial interventions, information was collected on the number and grades of staff involved

and the equipment used to deliver each intervention, as well as the number of sessions each participant attended.

In order to value health care resource use, unit costs were obtained from a number of sources, including the British National Formulary, Unit Costs of Health and Social Care and NHS reference costs [12–14] and were applied to resource use items. To estimate the cost of each intervention, unit costs associated with equipment used for each intervention were obtained. For the purpose of costing staff time associated with each intervention, we used the average time of a session: 60 min for joint protection only and hand exercises only and 90 min for joint protection plus hand exercises [8]. Since all participants in this study received leaflet and advice, this cost was not included in the analysis. Details of the unit costs applied to resource use are presented in Table 1. All unit costs were valued at 2010/2011 prices in UK pounds sterling.

Health outcomes
Quality of life was measured at baseline, 3, 6 and 12 months using the EuroQol five-dimensions questionnaire (EQ-5D), a generic questionnaire measuring health-related quality of life. The UK value set [15] was used to obtain EQ-5D index scores from participant responses to the EQ-5D questionnaire at each time point. These index scores were then used to calculate total QALYs over the 12-month period for every individual, using the analytical method described below.

TABLE 1 Unit cost of health care resource use data over 12 months

Health care resource	Unit cost, 2010/11 prices, £
Primary care contacts [13]	
Doctor at practice	28.00
Nurse at practice	10.00
Nurse at home	13.00
Secondary care contacts [14]	
Orthopaedic surgeon	70.00
Rheumatologist	81.00
Plastic surgeon	52.00
Physiotherapist	35.00
Occupational therapist	38.00
Intervention cost	
Leaflet and advice[a]	28.00
Joint protection plus hand exercises	64.17
Joint protection only	45.29
Hand exercises only	36.64
Prescribed medication [12]	Participant specific
Medical investigations/ interventions [14]	Participant specific
Other health care staff	Participant specific

[a]All participants received the leaflet and advice. For this reason, the costs associated with this intervention were assumed to be zero and were not included in the analysis.

Statistical analysis

The cost-utility analysis was carried out on an intention-to-treat basis, with the aim to estimate the difference in costs and QALYs between the four trial interventions; the exact nature of treatment comparisons is dependent on the methodological approach (discussed later in this section). Missing EQ-5D scores and costs at one or more of the time points were imputed using multiple imputation [16]. For each participant included in the study, a QALY score over the 12 month period was estimated using the area under the curve approach [17]. Total NHS costs over the 12 month period were calculated by multiplying the resource items used by the respective unit cost and summing over all items. Differences in mean costs and QALYs between trial arms were estimated, where appropriate (i.e. depending on the adopted methodology). Incremental QALY estimates were adjusted to control for imbalances in baseline utility between the interventions of interest [18].

Incremental cost-effectiveness ratios (ICERs) were estimated by dividing the difference in mean cost between two treatments by the difference in mean QALYs. Non-parametric bootstrapping was used to illustrate and quantify uncertainty. Five thousand paired estimates of mean differential costs and QALYs were estimated and presented graphically on a cost-effectiveness plane. To determine the probability of a treatment being deemed cost effective compared with an alternative treatment, a cost-effectiveness acceptability curve (CEAC) was constructed [19]. This shows the probability that an intervention is cost effective, relative to the chosen comparator, across a range of values that represent a decision maker's willingness to pay for an additional QALY. All the analyses were carried out in STATA version 12 (StataCorp, College Station, TX, USA) [20].

Alternative analytical approaches

Three methods were explored. Each method has been used for the analysis of clinical outcomes in factorial trials and recent evidence suggests that the methods can also be applied in economic evaluation [10].

Within-the-table analysis

A within-the-table analysis assumes that the interventions are mutually exclusive, i.e. the costs and effects of joint protection are influenced by the inclusion of hand exercises and vice versa, therefore each trial arm is treated separately with this approach. This approach formed the base case analysis and involved considering each treatment option individually. Interventions were ordered in terms of increasing cost, and cost and outcomes for each arm were compared incrementally. The most cost-effective option was selected based on the principles of dominance [where an intervention is less costly and more effective than the appropriate comparator(s)] and extended (weak) dominance (where an intervention is ruled out if the ICER is greater than that of a more effective intervention) [21].

At-the-margins approach

This approach assumes that interventions are independent, i.e. the cost and outcomes of joint protection are not affected by whether hand exercises are included or not and vice versa. The approach also assumes that the effects of the treatments when used together are additive, i.e. there is no interaction between treatments [11], and this approach considers the factorial trial as two separate two-arm trials [22]. For this analysis, cost and outcomes associated with participants who received hand exercises (alone or in combination with joint protection) were compared with those who did not receive hand exercises. Similarly cost and outcomes associated with participants who received joint protection (alone or in combination with hand exercises) were compared with those who did not receive joint protection.

Regression approach

Two separate analyses were carried out for the regression approach. First, it was assumed that there was no interaction between the treatments (joint protection and hand exercises), therefore an interaction term was not included in the regression model. The second analysis involved accounting for interactions between joint protection and hand exercises by including an interaction term in the regression model. In both cases the estimates of incremental cost and QALYs associated with hand exercises and joint protection were obtained from the regression output.

Results

Baseline characteristics

A total of 257 participants were randomized to one of the four treatment arms. The average age across all treatment groups was 66 years (S.D. 9.1) and 66% of participants were female. The difference in baseline EQ-5D scores between treatment arms was not statistically significant. Overall, the average baseline EQ-5D score across all groups was 0.643. Full details of other baseline characteristics can be found elsewhere [9].

Resource use and costs

Complete resource use data were available for 209 participants (81%). Table 2 gives a breakdown of resource use data by trial arm. Mean health care costs per participant by trial arm after imputation over the 12 month period are presented in Table 3. The total mean cost associated with leaflet and advice, joint protection only, hand exercises only and joint protection plus hand exercises over the 12 month period were £58.46, £92.12, £64.51and £112.38, respectively.

Health outcomes

Overall, 71% of participants provided complete EQ-5D responses at all time points, however, the majority of those with missing data were missing just one EQ-5D score. Table 4 reports imputed EQ-5D scores at each time point and QALY scores at 12 months. EQ-5D scores at 12 months were higher than the baseline

TABLE 2 Mean resource use over the 12 month follow-up

Resource use category	Leaflet and advice (n = 50), mean (s.d.)	Joint protection only (n = 47), mean (s.d.)	Hand exercises only (n = 48), mean (s.d.)	Joint protection plus hand exercises (n = 52), mean (s.d.)
Primary care				
General practitioner	0.16 (0.62)	0.30 (0.93)	0.25 (0.81)	0.60 (1.90)
Nurse	0.02 (0.14)	0.04 (0.20)	0.06 (0.43)	0.12 (0.70)
Secondary care				
Orthopaedic surgeon	0.04 (0.20)	0.02 (0.15)	0.00 (–)	0.04 (0.28)
Rheumatologist	0.02 (0.14)	0.00 (–)	0.02 (0.14)	0.04 (0.28)
Plastic surgeon	0.02 (0.14)	0.00 (–)	0.00 (–)	0.00 (–)
Physiotherapist	0.18 (1.27)	0.09 (0.58)	0.00 (–)	0.00 (–)
Occupational therapist	0.2 (1.28)	0.11 (0.52)	0.00 (-)	0.08 (0.55)
Other health care staff	0.36 (0.88)	0.55 (1.43)	0.17 (0.66)	0.31 (1.00)
Prescribed medication[a]	1.34 (2.81)	1.76 (4.10)	1.79 (4.16)	1.48 (3.39)

[a]Mean number of prescribed drugs per patient.

TABLE 3 Mean costs (in £) over the 12-month follow-up

Resource use category	Leaflet and advice (n = 65), mean (s.d.)	Joint protection only (n = 62), mean (s.d.)	Hand exercises only (n = 65), mean (s.d.)	Joint protection plus hand exercises (n = 65), mean (s.d.)
Primary care	5.98 (17.31)	8.53 (23.48)	8.31 (20.63)	16.17 (52.36)
Secondary care	16.75 (92.47)	15.70 (68.48)	3.00 (11.67)	10.36 (34.93)
Other health care	34.79 (175.07)	21.08 (60.84)	15.47 (67.89)	20.64 (56.69)
Prescribed medication	0.94 (1.82)	1.53 (3.76)	1.11 (3.62)	1.04 (2.31)
Intervention	0 (0)[a]	45.29 (0)	36.64 (0)	64.17 (0)
Total cost	58.46 (264.68)	92.12 (111.11)	64.51 (77.06)	112.38 (94.14)

[a]All participants received the leaflet and advice. For this reason, the costs associated with this intervention were assumed to be zero and were not included in the analysis.

TABLE 4 Mean EQ-5D scores and QALYs over 12 months for primary analysis

Health outcome	Leaflet and advice (n = 65), mean (s.d.)	Joint protection only (n = 62), mean (s.d.)	Hand exercises only (n = 65), mean (s.d.)	Joint protection plus hand exercises (n = 65), mean (s.d.)
EQ-5D (imputed)				
Baseline	0.623 (0.26)	0.646 (0.25)	0.645 (0.21)	0.659 (0.26)
3 months	0.665 (0.24)	0.682 (0.17)	0.660 (0.22)	0.676 (0.24)
6 months	0.658 (0.25)	0.635 (0.25)	0.692 (0.18)	0.672 (0.24)
12 months	0.634 (0.22)	0.684 (0.19)	0.708 (0.18)	0.659 (0.27)
QALYs (imputed)				
QALYs at 12 months	0.649 (0.21)	0.660 (0.19)	0.682 (0.16)	0.668 (0.23)
QALYs at 12 months, predicted mean[a]	0.662 (0.17)	0.659 (0.16)	0.681 (0.14)	0.658 (0.16)

[a]Values are predicted mean scores obtained from the multiple regression equation when controlling for baseline imbalances. None of the differences in EQ-5D or QALYs between the trial arms were statistically significant (Kruskal–Wallis test).

TABLE 5 Cost-utility analysis using within-the-table analysis

Intervention	Mean cost, £	Mean QALYs[a]	ICER
Leaflet and advice	58.46	0.662	—
Hand exercises only	64.51	0.681	£318/QALY gained[b]
Joint protection only	92.12	0.659	Dominated by hand exercises[c]
Joint protection plus hand exercises	112.38	0.658	Dominated by hand exercises[d]

[a]Values are predicted mean scores obtained from the multiple regression equation when controlling for baseline imbalances. [b]Hand exercises *vs* leaflet and advice. [c]Joint protection *vs* hand exercises. [d]Joint protection plus hand exercises *vs* hand exercises. ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

scores in all treatment arms. With regard to overall QALYs, the highest score over the 12-month period was recorded in the hand exercises group, while the lowest score was observed in the leaflet and advice group. When differences in overall QALYs were adjusted for baseline utility, hand exercises were still associated with the highest QALY gain over the 12-month period and joint protection plus hand exercises was associated with the lowest QALYs.

Cost-utility analysis

Within-the-table analysis (base case)

Table 5 presents the costs and QALYs associated with each of the four interventions arranged in ascending order from the lowest to the highest cost. Joint protection plus hand exercises and joint protection only were eliminated from the analysis because they were strongly dominated. A direct comparison between hand exercises and leaflet and advice indicated that hand exercises were cost effective, with an ICER of £318/QALY gained. The cost-effectiveness plane is shown in Fig. 1A. Forty-nine per cent of the bootstrapped replicates indicate that hand exercises were more costly and more effective than leaflet and advice (north-east quadrant). Thirty-two per cent of the replicates indicate that hand exercises were less costly and more effective than leaflet and advice (south-east quadrant). The CEAC (Fig. 1b) shows that at a threshold of £20 000/QALY gained, hand exercises are associated with an 80% chance of being cost effective.

At-the-margins approach

With this approach, joint protection was more costly and less effective than no joint protection, and therefore strongly dominated. Hand exercises were slightly more expensive than no hand exercises (difference in cost of £13.55) but were more effective. The resulting ICER was £1506/QALY gained, indicating that hand exercises is a cost-effective intervention (see supplementary Table S1, available at *Rheumatology* Online). There was a 70% chance of hand exercises being cost effective at a £20 000 threshold (see supplementary Fig. S1, available at *Rheumatology* Online).

Regression approach

When interactions were ignored, hand exercises were cost effective, with an ICER of £1452/QALY gained, with a 70% chance of hand exercises being cost effective at a

threshold of £20 000/QALY gained (see supplementary Fig. S2, available at *Rheumatology* Online). Joint protection was strongly dominated by no joint protection. When an interaction term was included in the regression model, this resulted in an ICER of £318/QALY gained when hand exercises were compared with no hand exercises, with an 80% chance of hand exercises being cost effective at the £20 000/QALY threshold (see supplementary Fig. S2, available at *Rheumatology* Online). Joint protection was again more costly and less effective than no joint protection and therefore strongly dominated (see supplementary Table S2, available at *Rheumatology* Online).

Discussion

We evaluated the cost-utility of joint protection and hand exercises for the management of hand OA and compared alternative methodological approaches for conducting economic evaluation alongside factorial trials. The results showed that hand exercises appear to be the most cost-effective option for the management of hand OA and remain cost effective regardless of the approach adopted for the economic analysis. However, the strength of evidence in favour of hand exercises varied with the analysis method adopted. All analytical approaches showed hand exercises to be the most cost-effective option, with ICERs ranging from £318 to £1506/QALY gained. The identical results obtained from the within-the-table approach and regression with an interaction term were expected since the inclusion of an interaction term in the regression model allows the estimation of main effects of joint protection and hand exercises while controlling for the interactions between them. Comparable results obtained from the at-the-margins approach and the regression without an interaction term have also been shown in a previous study [10]

In the UK, the National Institute for Health and Care Excellence uses a cost-effectiveness threshold of between £20 000 and £30 000/QALY gained to determine whether an intervention is cost effective [23], which indicates that hand exercises are cost effective regardless of the analytical approach adopted.

This is the first study to provide evidence on the cost-effectiveness of these interventions for hand OA. In addition, the analysis considers a 12 month period, which allows for the identification of any longer-term impacts on quality of life and health care resource use, and although imputation was employed in the analysis, the

Cost-effectiveness plane and CEAC for the comparison of hand exercises *vs* leaflet and advice
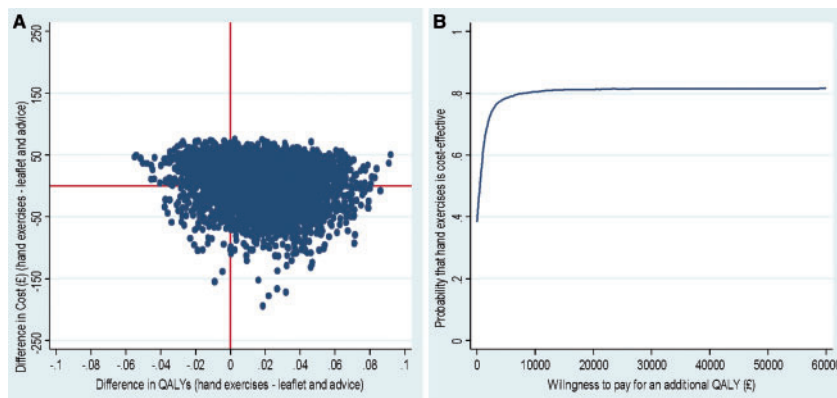
Based on within-the-table analysis: (**A**) cost-effectiveness plane for hand exercises *vs* leaflet and advice; (**B**) CEAC for hand exercises *vs* leaflet and advice. CEAC: cost-effectiveness acceptability curve.

rate of complete response to the health care resource use questions and EQ-5D questionnaire was reasonably high. Furthermore, the advantage of the factorial nature of the trial allowed us to compare four different management options within the same analysis. However, conducting an economic analysis alongside a factorial trial leads to a much reduced sample size for the base case health economic analysis, with four treatment options to compare. The majority of economic analyses alongside two-arm trials are underpowered due to the sample size being powered by differences in the primary clinical outcome rather than economic data. Therefore economic analyses alongside factorial trials are likely to have an even greater degree of uncertainty in the cost and outcome data.

To the best of our knowledge, no other study has assessed the cost-effectiveness of joint protection and hand exercises in hand OA. The clinical results of the trial on which the current analysis was based demonstrated that joint protection was the most clinically effective management strategy [9] at 6 months, although the between-group differences were not sustained at 12 months. It is important to note that the primary outcome measures differed between the clinical and cost-effectiveness studies, as did the time period assessed, i.e. incremental cost per QALY (with QALYs estimated using the EQ-5D) was the primary outcome measure for the economic analysis over 12 months, whereas the OARSI/OMERACT responder criterion over 6 months was the primary outcome measure for the clinical evaluation. Recent research has highlighted issues related to contradictory economic and clinical results [24].

Few studies have compared methods for the economic analysis of factorial trials, although results from recent work have shown that methods used for the economic analysis of factorial trials do matter and could change the results of a study [10]. The analyses reported in this article have demonstrated that the results were not altered by adopting different approaches, but it is important to point out that the results obtained in this study may not be generalizable to another disease area or context.

Although the results showed that there was very little difference in QALYs between the treatment arms, the agreed approach in health economics is to conduct a cost-effectiveness analysis, focussing on the joint estimation of costs and outcomes [25] rather than choosing the intervention of least cost. Therefore the results here favour hand exercises as the most cost-effective approach. This study raises the issue of the use of generic utility-based quality of life measures such as the EQ-5D. Even though generic measures are important in economic evaluation [26], they have also been shown to be insensitive in certain disease areas, such as patients with hearing impairment [27–30]. Previous studies have also shown that the EQ-5D is not very sensitive to subtle changes in OA in other joint sites [31]. The EuroQol group has now developed a five-level EQ-5D [32], which may be more sensitive to changes in this disease area.

As previously stated, there is still no consensus with regard to methods for conducting economic evaluation alongside factorial trials. In the clinical literature it has been suggested that the at-the-margins approach should only be used when interactions between treatments are not significant [33]. For this study, interactions between treatments were not significant, suggesting that the at-the-margins approach would be appropriate. However, it is possible that the study is not sufficiently powered to detect interactions between treatments. Problems associated with detecting interactions in factorial trials have been discussed elsewhere [22] and there is a need for further research into methods for the economic analysis of factorial trials.

Clinical guidelines, largely based on clinician expert consensus, recommend joint protection and hand exercises for people with hand OA [2]. The clinical results of the trial have demonstrated the clinical effectiveness of joint protection compared with no joint protection at 6 months [9]. The economic analysis further adds to the evidence base by demonstrating that hand exercises are a cost-effective option for the management of hand OA over a 12-month period. These findings therefore offer a

choice for the patient and health professional in deciding the best approach for the management of hand OA.

> ### Rheumatology key messages
>
> - European League Against Rheumatism guidelines recommend joint protection and hand exercises for the management of hand OA.
> - Hand exercises may offer a cost-effective option for the management of hand OA.
> - A different methodological approach to economic analysis of factorial trials may not lead to different conclusions.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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