The cost-effectiveness of different approaches to exercise and corticosteroid injection for Subacromial pain (impingement) syndrome

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Abstract:

Objectives: To determine whether physiotherapist-led exercise intervention and ultrasound-guided subacromial corticosteroid injection is cost-effective when compared to standard advice and exercise leaflet and unguided injection in patients with subacromial pain (impingement) syndrome.

Methods: An incremental cost–utility analysis using patient responses to the five-level EuroQoL-5D (EQ-5D-5L) questionnaire was undertaken from a health care perspective alongside a 2x2 factorial randomised trial with 256 participants over a 12-month follow-up period. Uncertainty was explored through the use of cost-effectiveness acceptability curves.

Results: The cost–utility analysis indicated that physiotherapist-led exercise was associated with an incremental cost of £155.99 (95% CI: 69.02 to 241.93) and 0.031 (95% CI: −0.01 to 0.07) additional quality-adjusted life-years (QALYs), an incremental cost-effectiveness ratio (ICER) of £5,031 per QALY gained and an 85% chance of being cost-effective at a threshold of £20,000 per QALY gained compared to the advice and exercise leaflet. Ultrasound-guided injection was associated with an incremental cost of £15.89 (95% CI: −59.36 to 109.86) and 0.024 (95% CI: −0.02 to 0.07) additional QALYs, an ICER of £662 per QALY gained and a 83% chance of being cost-effective at a threshold of £20,000 per QALY gained compared to unguided injection.

Conclusion: Physiotherapist-led exercise was cost-effective compared to the advice and exercise leaflet, and ultrasound-guided injection was cost-effective when compared to unguided injection.

Clinical trial registration number: ISRCTN (42399123)

Keywords: Cost-effectiveness, Subacromial pain (impingement) syndrome , Exercise, Corticosteroid injection, EQ-5D

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Rheumatology key messages:

- Guidelines recommend non-surgical options for the management of Subacromial pain (impingement) syndrome-.
- Physiotherapist-led exercise and ultrasound-guided corticosteroid injection appear to increase costs but lead to improved quality of life compared to unguided injection and advice and exercise leaflet.
- Physiotherapist-led exercise and ultrasound-guided injection are likely to be cost-effective.

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Introduction

Subacromial pain (impingement) syndrome (SAPS) is the most common cause of shoulder pain. The prevalence of SAPS increases with age and places a substantial burden on health systems, with estimates from GP consultations suggesting that approximately 16% of adults reporting musculoskeletal pain had shoulder pain [1-2]. Shoulder pain poses a considerable burden to society, accounting for a substantial number of days off work and associated productivity costs [3-4]. Treatment guidelines recommend initial non-surgical management including education/self-management advice, exercise, corticosteroid injection, and analgesia [5-6].

In order to explore how to optimise outcomes from exercise and subacromial corticosteroid injection, a randomised controlled trial was conducted to assess whether better improvements in pain and function were obtained with (1) a physiotherapist-led, individualised, supervised and progressed exercise programme versus a standardised advice and exercise leaflet, and (2) ultrasound-guided subacromial corticosteroid injection versus unguided injection. The clinical results of the trial showed that physiotherapist-led exercise was more effective than an exercise leaflet whilst ultrasound-guidance conferred no additional benefit over unguided corticosteroid injection [7]. In addition to establishing the effectiveness of interventions for the management of shoulder pain, it is also important to determine whether these interventions offer value for money. Previous studies assessing the cost-effectiveness of interventions for the treatment of SAPS have focused on a comparison of corticosteroid injection and exercise [2] and have not compared different methods of guiding corticosteroid injection, nor the manner in which the exercise intervention was delivered.

The primary aim of this economic analysis was to determine whether a physiotherapist-led exercise intervention is cost-effective compared to a standard advice and exercise leaflet, and

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whether ultrasound-guided subacromial corticosteroid injection is cost-effective when compared to unguided injection.

Methods

A within-trial economic evaluation was conducted alongside a 2x2 factorial randomised trial in patients with SAPS [7]. Using block randomisation, participants who met the inclusion criteria were randomly assigned on a 1:1:1:1 basis to one of four interventions:

1. Ultrasound-guided subacromial corticosteroid injection and physiotherapist-led individualised, supervised and progressed exercise.
2. Ultrasound-guided subacromial corticosteroid injection and an advice and exercise leaflet.
3. Unguided subacromial corticosteroid injection and physiotherapist-led individualised, supervised and progressed exercise
4. Unguided subacromial corticosteroid injection and an advice and exercise leaflet.

The main outcome for the economic analysis was the quality-adjusted life-year (QALY), over a 12-month follow-up period. The base case analysis was carried out from a health care perspective including health care costs incurred by the NHS and patients. To be consistent with the clinical study, the 'at the margins' approach which assumes that interventions are independent was adopted for the base case scenario [8-9]. The trial, including this economic analysis, was approved by The Black Country Research Ethics Committee (10/H1202/72). Trial registration number (ISRCTN42399123).

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Data collection

Resource use and costs

Data on health care resource use were obtained from participant responses to self-report questionnaires administered at 6 weeks, 6 months and 12 months. Resource use data concentrated on visits to health care professionals in primary and secondary care, medical investigations/interventions, and both prescribed and over the counter medications. Data obtained from questionnaire responses were aggregated to generate overall resource use over the 12-month follow-up period. The questionnaires also requested information on time off work over 12 months which was used to estimate productivity losses.

Unit cost data were obtained from the following sources: British National Formulary, NHS reference costs and the PSSRU publication on unit cost of health and social care [10-12] (Supplementary Table 1). 2012/2013 costs were inflated to 2019 prices using the consumer price index.

Trial intervention cost

Information on the intervention costs was obtained from trial data and all resources required to deliver the interventions were determined.

Physiotherapist-led exercise versus advice and leaflet: For the physiotherapist visits, the unit cost associated with a contact with the physiotherapist was multiplied by the number of physiotherapy contacts. Information on the number of physiotherapist contacts was obtained from case report forms that physiotherapists completed. For the advice and exercise leaflet, only the cost associated with the leaflet was included since all participants had the index consultation where the injection was performed on all patients. Full details of the intervention can be found elsewhere [13].

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Ultrasound versus unguided injection: It was assumed that since all patients had a similar injection, the only difference between the ultrasound and unguided injection was the cost of the ultrasound. The cost of the ultrasound machine was estimated to be £35,000, and in order to work out a cost per patient, it was assumed that the life expectancy of the machine is 6 years and that the machine is used about 1872 times a year (this value was obtained through consultation with experts). Applying the annuity factor at an interest rate of 3%, the cost of the ultrasound machine per patient was £3.45.

Health Outcomes

Using participant responses to the 5-level version of the EQ-5D-5L questionnaire [14], quality of life was measured at baseline, 6 weeks, 6 months and 12 months. EQ-5D-5L was mapped back to the EQ-5D 3L valuation set as currently recommended by NICE [15] and used to generate the EQ-5D index scores which were then used to derive QALYs. The mapping algorithm developed by Van Hout et al. 2012 was used for this purpose [16].

Statistical Analysis

The economic analysis was carried out on an intention to treat basis, with the aim to estimate the difference in costs and QALYs between the physiotherapist-led exercise intervention and the advice and exercise leaflet and between the ultrasound-guided and unguided subacromial corticosteroid injections. Over the 12-month period, missing EQ-5D scores and costs at one or more of the time points were accounted for using multiple imputation methodology to impute 25 separate datasets [17]. The number of datasets were chosen in order to adequately account for the level of missing data in the study. The approach adopted in this study used chained equations with predictive mean matching in order to ensure that the missing values are aligned to the nearest best-fitting values in the dataset [18]. This approach is particularly useful for cost and EQ-5D data which have skewed distributions, and ensures that imputed values do not go

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out of the plausible range. The coefficients were then pooled across the multiply imputed datasets using the Rubin's rule to obtain single estimates of the corresponding population parameters [17].

The imputation model was fitted with gender, age, smoking status at baseline, baseline SPADI score and health status at baseline as predictors. Using the area under the curve approach [19], QALYs over the 12-month period were estimated for each participant. Total health care costs over the 12-month period were calculated by multiplying the resource items by the respective unit cost and summing over all resource use items. Differences in mean costs and QALYs between trial arms were estimated and QALYs were adjusted to control for imbalances in baseline utility between the interventions [20].

Incremental cost effectiveness ratios (ICERs) were estimated by dividing the difference in mean cost between two interventions (*physiotherapist-led exercise versus advice and exercise leaflet* and *ultrasound-guided versus unguided injection)* by the difference in mean QALYs. Non-parametric bootstrapping was used to illustrate and quantify uncertainty. To determine the probability of an intervention being deemed cost-effective compared to an alternative intervention (*physiotherapist-led exercise versus advice and exercise leaflet* and *ultrasound-guided versus unguided injection)*, cost-effectiveness acceptability curves (CEACs) were constructed [21]. This shows the probability that an intervention is cost-effective, relative to the chosen comparator, across a range of values that represent a decision makers' willingness to pay for an additional QALY. All the analyses were carried out in STATA version 12 [22].

Costs for productivity losses were computed through the human capital approach using data collected on time off work and employment. Productivity losses were obtained by the product of lost productivity time and the mean hourly wage of patients classified from data on wages

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corresponding to self-reported baseline occupation (derived from the Annual Surveys of Health Evaluation by the Office of National Statistics and based on classification codes under the UK Socio-Economic Occupation Classification, SOC 2000) [23].

Sensitivity analysis was carried out and had three main foci: First, cost-utility analysis was conducted from a UK NHS perspective by excluding private health care costs. Second, as there is a lack of consensus with respect to methods for conducting economic evaluation alongside factorial trials, an alternative approach ('within the table') to analysing the factorial trial treatment options was undertaken. The 'within the table' approach assumes that there is an interaction between the treatments, and considers all four arms of the trial as separate interventions [8-9]. With this analysis, the interventions were ordered in terms of increasing QALYs~~cost~~ and 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 comparator(s)) and extended (weak) dominance (where an intervention is ruled out if the ICER is greater than that of a more effective intervention). Third, cost-utility analysis was conducted using EQ-5D scores generated from the EQ-5D-5L tariff published by Devlin et al. 2018 [24]

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Results

A total of 256 participants were randomised (64 per arm) to one of the four intervention arms. The mean age of participants across all arms was 53.8 years (S.D. 10.2) and 52% of participants were female. The mean (SD) total Shoulder Pain and Disability Index (SPADI) score at baseline was 61.1 (18.1). Full details of other baseline characteristics can be found elsewhere [25].

Resource use and costs

Complete resource use data were obtained for 194 participants (76%). This ranged from 72% in the ultrasound-guided injection and physiotherapist-led exercise arm to 78% in the unguided injection and advice and exercise leaflet arm. A full breakdown of patient responses at each follow-up time point can be found elsewhere [25]. Compared to the advice and exercise leaflet group, significantly fewer visits to the GP were made during the 12 month follow-up period in the physiotherapist-led exercise group. The unguided injection group made more visits to a hospital nurse and specialist over the 12 month follow-up period compared to the ultrasound-guided injection group (Supplementary Table 2). With the exception of diclofenac which was significantly lower in the physiotherapist-led exercise arm, there was no significant difference in prescription medication use across trial arms (Supplementary Table 3). Private health care resource use is presented in Supplementary Table 4.

Mean NHS and private costs per participant by trial arm over the 12-month period prior to imputation are presented in Table 1. Health care costs were higher in the physiotherapist-led exercise group compared to the advice and exercise leaflet group and also in the ultrasound-guided injection group compared to the unguided injection group.

Health outcomes

Health outcomes (EQ-5D and QALYs) using the imputed dataset are presented in table 2. A total of 131 (54%) participants provided complete EQ-5D responses at all time-points. This ranged from 47% in the unguided injection and physiotherapist-led exercise arm to 61% in the ultrasound-guided injection and physiotherapist-led exercise arm. However, it should be noted that the majority of those with missing values were missing just one EQ-5D score. There was an improvement in health outcomes over time, with scores obtained at 12-months higher than the baseline scores in all four arms. With respect to QALYs over the 12-month period, higher scores were obtained in the physiotherapist-led exercise and ultrasound-guided injection

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groups when compared to the advice and exercise leaflet and unguided injection groups, respectively. After adjusting for baseline utility, similar results were obtained.

Cost-utility analysis

The results from the cost-effectiveness analysis using the imputed dataset showed that physiotherapist-led exercise was more expensive (cost difference £155.99) and more effective (QALY difference 0.031) than the advice and exercise leaflet. The resulting ICER was £5,031 per QALY gained (Table 3) with an 85% chance of physiotherapist-led exercise being cost-effective at a cost-effectiveness threshold of £20,000 per QALY gained (Figures 1 and 2). Ultrasound-guided injection was also more expensive (cost difference £15.89) and more effective (QALY difference 0.024) than unguided injection. The resulting ICER was £662 per QALY gained (Table 3) with an 83% chance of ultrasound-guided injection being cost-effective at a willingness to pay threshold of £20,000 per QALY gained (Figures 1 and 2).

Time off work and Productivity Losses

Participants in the advice and exercise leaflet and unguided injection groups took more time off work than those in the physiotherapist-led exercise and ultrasound-guided injection groups. Productivity losses in terms of lost wages were also higher in the advice and exercise leaflet and unguided injection groups. However, these differences were not statistically significant (Supplementary Table 4 and Table 1).

Sensitivity Analysis

From a UK NHS perspective, the results obtained were similar to the base case analysis i.e. physiotherapist-led exercise was cost-effective compared to providing an advice and exercise leaflet and ultrasound-guided injection was cost-effective compared to unguided injection (Table 3). Results from the 'within the table' analysis showed that a combination of ultrasound-guided injection and physiotherapist-led exercise was the most cost-effective intervention

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(£6,225 per QALY gained ~~10,583 per QALY gained~~), supporting findings from the base case analysis (Table 4). The results obtained when the EQ-5D-5L tariff [24] was used are similar to those obtained with the mapping algorithm [16] and support the finding that physiotherapist-led exercise is cost-effective compared to the advice and exercise leaflet, and ultrasound-guided injection is cost-effective when compared to unguided injection (Supplementary Tables 5 and 6).

Discussion

Summary of the main findings

This health economic evaluation showed that for the management of SAPS, physiotherapist-led exercise was cost-effective compared to the advice and exercise leaflet and ultrasound-guided injection was cost-effective when compared to unguided injection. Sensitivity analysis using the within-the-table analysis yielded similar results to the at-the-margins approach indicating that the choice of method did not change the findings of the health economic analysis. Similar findings with respect to the choice of method have been obtained in previous studies [8]. A previous economic evaluation showed that a combination of injection and exercise was cost-effective compared to exercise alone [2]. The results from this study add to this evidence by showing that the approach to providing exercise (physiotherapist-led, individualised, progressed and supervised exercise rather than through a standardised advice and exercise leaflet) and injection (guided using ultrasound rather than unguided) is important in terms of increasing their cost-effectiveness.

The results of the trial on which the economic evaluation is based showed that physiotherapist-led exercise was more effective than an exercise leaflet whilst ultrasound-guidance conferred no additional benefit over unguided corticosteroid injection [25]. The health economic results are similar in terms of the comparison between physiotherapist-led exercise and the advice and

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exercise leaflet, but different in terms of the comparison between ultrasound-guided and unguided injection. It is however important to note that the primary outcome of the clinical trial was the Shoulder Pain and Disability Index whilst that of the economic evaluation was total QALYs obtained from EQ-5D. Although the difference in QALYs obtained for both comparisons was very small and not statistically significant, the agreed approach in health economics is to conduct a cost-effectiveness analysis with costs and effects estimated jointly [26]. Whilst clinical research focuses on hypothesis testing, economic evaluation is aimed at estimation which may produce contradictory results as was seen in this study with the injection comparison [27]. An important issue which the results of this study raise relates to whether the use of generic quality of life measures such as the EQ-5D are sufficient for assessing the cost-effectiveness of interventions in this clinical syndrome. Previous research has shown that generic quality of life measures may be insensitive to changes in some disease areas including musculoskeletal conditions such as osteoarthritis (OA) [28-30].

Strengths and weaknesses of the study

A strength of the study is the factorial nature of the trial, which enabled us to compare four interventions within the same analysis.

A possible limitation of the economic analysis is the fact that the cost of training clinicians to perform ultrasound-guided injection was not included in the analysis and it could be argued that this may have under-estimated the cost of the ultrasound-guided injection. The cost and time required to train clinical staff to perform ultrasound-guided injections is a potential barrier to services. However, it should be noted that there are a number of difficulties associated with the estimation of a per patient training cost within economic evaluation studies and also the training received by clinicians would be used for a large number of patients over a number of years which would result in a low mean cost per patient. A further limitation was that only 76%

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of participants had complete data at all time-points, however, the missing data were accounted for using multiple imputations.

Meaning of the results

This health economic analysis has shown that physiotherapist-led exercise and ultrasound-guided injection are more cost-effective treatment options for SAPS than an advice and exercise leaflet or unguided shoulder injection respectively. However, this conclusion should be interpreted in the light of the clinical results which showed that physiotherapist-led exercise conferred superior benefits for patients compared to the advice and leaflet yet ultrasound guided injection conferred no additional benefit over unguided injection [25].

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Conflicts of interest: None to declare

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Table 1: Mean health care cost (SD) per patient over 12 months (complete cases) (£, 2019 prices)

	Injection intervention group			Exercise intervention group		
	US-guided (n=95)	**Unguided (n=99)**	**Mean difference (95% CI)**	**Physiotherapist-led (n=95)**	**Advice and Exercise Leaflet (n=99)**	**Mean difference (95% CI)**
Intervention cost[a]	186.01 (126.50)	107.12 (127.33)	78.89 (41.98, 113.59)	258.92 (96.73)	37.15 (36.58)	221.77 (196.45, 241.00)
PRIMARY CARE CONTACTS						
General Practitioner	39.16 (75.27)	43.30 (97.90)	-4.14 (-28.39, 20.59)	28.01 (70.66)	53.99 (99.52)	-25.98 (-49.65, -3.08)
Practice Nurse	1.28 (11.11)	0.58 (4.16)	0.70 (-0.84, 3.99)	1.21 (9.73)	0.92 (6.73)	0.29 (-1.69, 3.46)
Other professionals in GP practice	14.48 (40.98)	22.58 (59.73)	-8.10 (-22.99, 4.19)	24.52 (58.25)	12.94 (43.47)	11.58 (-2.64, 26.78)
SECONDARY CARE CONTACTS						
Physiotherapist [b]	37.27 (86.59)	32.69 (86.02)	4.58 (-20.45, 27.03)	53.31 (102.03)	17.30 (63.03)	36.01 (14.52, 62.41)
NHS consultants	26.97 (60.56)	49.08 (93.36)	-22.11 (-43.75, -1.21)	38.15 (74.24)	38.34 (76.12)	-0.19 (-23.44, 21.53)
Private consultants and Physiotherapists	18.07 (83.84)	8.98 (35.80)	9.09 (-5.96, 30.28)	6.17 (27.97)	20.40 (84.94)	-14.23 (-38.09, -0.79)
Other professional in NHS hospitals	1.58 (11.87)	2.07 (11.14)	-0.49 (-3.61, 2.93)	1.46 (11.81)	2.20 (11.19)	-0.74 (-3.82, 2.81)
REPEAT INJECTIONS						
Repeat Injections in NHS	35.96 (98.07)	51.07 (118.07)	-15.11 (-45.35, 17.64)	33.08 (104.93)	53.83 (111.82)	-20.75 (-50.81, 8.58)
Repeat Injections in private practice	1.43 (14.02)	-	1.43 (0, 5.88)	-	1.38 (13.73)	-1.38 (-5.11, 0)
DIAGNOSTIC TESTS						
Diagnostic tests in NHS	36.27 (105.24)	72.97 (144.77)	-36.70 (-70.06, -5.69)	45.44 (114.17)	64.18 (139.89)	-18.74 (-53.69, 17.34)
Diagnostic tests in private practice	-	1.76 (12.98)	-1.76 (-5.38, 0)	-	1.76 (12.98)	-1.76 (-4.96, 0)

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MEDICATION						
Prescribed medication	5.70 (16.62)	7.80 (16.96)	-2.10 (-6.74, 2.51)	3.71 (7.19)	9.71 (22.08)	-6.00 (-10.86, -1.78)
Over the counter medication	10.15 (20.01)	18.86 (57.93)	-8.71 (-22.80, 1.11)	13.85 (45.62)	15.31 (42.19)	-1.46 (-12.94, 11.17)
WORK RELATED OUTCOMES						
Productivity costs	388.06 (1638.82)	823.56 (3924.91)	-435.50 (-1472.23, 239.61)	562.54 (2713.56)	656.13 (3317.80)	-93.59 (-1044.70, 654.54)
TOTAL COSTS						
Total health care costs [c] (n=256)	428.01 (322.83)	412.12 (366.09)	15.89 (-59.36, 109.86)	498.06 (326.05)	342.07 (346.11)	155.99 (69.03, 241.93)

[a] This cost takes into account the fact that participants had more than one intervention e.g. US guided injection plus physiotherapist-led exercise [b] Visits associated with the intervention have been excluded [c] Costs have been imputed

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Table 2: Mean health outcomes (SD) over 12 months (imputed data)

	Injection intervention group			Exercise intervention group		
	US-guided (n=128)	**Unguided (n=128)**	**Mean difference (95% CI)**	**Physiotherapist-led (n=128)**	**Advice & exercise leaflet (n=128)**	**Mean difference (95% CI)**
EQ-5D scores						
Baseline	0.494 (0.255)	0.501 (0.235)	-0.007 (-0.065, 0.052)	0.504 (0.243)	0.492 (0.247)	0.012 (-0.042, 0.078)
6 weeks	0.599 (0.240)	0.574 (0.236)	0.025 (0.031, 0.080)	0.601 (0.242)	0.572 (0.234)	0.029 (-0.025, 0.087)
6 months	0.577 (0.245)	0.549 (0.261)	0.028 (-0.031, 0.088)	0.584 (0.246)	0.541 (0.259)	0.043 (-0.018, 0.103)
12 months	0.599 (0.248)	0.594 (0.271)	0.005 (-0.058, 0.066)	0.606 (0.268)	0.588 (0.252)	0.018 (-0.052, 0.081)
Total QALYs	0.584 (0.225)	0.564 (0.230)	0.020 (-0.035, 0.072)	0.594 (0.227)	0.555 (0.226)	0.039 (-0.013, 0.097)
Total adjusted QALYs [a]	0.586	0.562	0.024 (-0.018, 0.066)	0.589	0.558	0.031 (-0.010, 0.073)

[a] QALYs adjusted for baseline utility

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Table 3: Cost-utility analysis (imputed data)

	Injection intervention group			Exercise intervention group		
	US-guided (n=128)	**Unguided (n=128)**		**Physiotherapist-led (n=128)**	**Advice & Exercise Leaflet (n=128)**	
	Mean	**Mean**	**Mean difference (Confidence Interval)**	**Mean**	**Mean**	**Mean difference (Confidence Interval)**
HEALTHCARE PERSPECTIVE						
Cost	£428.01	£412.12	£15.89 (-59.36, 109.86)	£498.06	£342.07	£155.99 (69.02, 241.93)
QALYs [a]	0.586	0.562	0.024 (-0.018, 0.066)	0.589	0.558	0.031 (-0.010, 0.073)
ICER	£662 per QALY gained			£5,031 per QALY gained		
NHS PERSPECTIVE						
Cost	£398.25	£382.04	£15.85 (-64.32, 90.22)	£476.02	£304.27	£171.75 (98.44, 251.88)
QALYs [a]	0.586	0.562	0.024 (-0.018, 0.066)	0.589	0.558	0.031 (-0.010, 0.073)
ICER	£660 per QALY gained			£5,540 per QALY gained		

[a] Adjusted for baseline utility

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Table 4: Cost-utility analysis "within the table" analysis

	Cost (£)*	QALY	QALY*[a]	ICER
		Health care perspective		
Unguided injection and advice and exercise leaflet (n=64)	385.31 (397.70)	0.545 (0.236)	0.542	Dominated by Ultrasound-guided injection and advice and exercise leaflet [b]
Ultrasound-guided injection and advice and exercise leaflet (n=64)	298.82 (281.99)	0.564 (0.218)	0.575	Dominates Unguided injection and advice and exercise leaflet [b]
Unguided injection and Physiotherapist-led exercise (n=64)	438.92 (332.49)	0.583 (0.224)	0.582	£20,014 per QALY gained [c]
Ultrasound-guided injection and Physiotherapist-led exercise (n=64)	557.20 (310.90)	0.604 (0.232)	0.601	£6,225.~~26~~ per QALY gained [d]
		NHS perspective		
	Cost*	**QALY**	**QALY*[a]**	**ICER**
Unguided injection and advice and exercise leaflet (n=64)	347.87 (385.17)	0.545 (0.236)	0.542	Dominated by Ultrasound-guided injection and advice and exercise leaflet [b]
Ultrasound-guided injection and advice and exercise leaflet (n=64)	260.66 (220.67)	0.564 (0.218)	0.575	Dominates Unguided injection and advice and exercise leaflet [b]
Unguided injection and Physiotherapist-led exercise (n=64)	416.21 (324.81)	0.583 (0.224)	0.582	£22,221.~~43~~ per QALY gained [c]

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Ultrasound-guided injection and Physiotherapist-led exercise (n=64)	535.83 (305.61)	0.604 (0.232)	0.601	£6,295 per QALY gained [d]

*Cost and QALYs imputed [a] Adjusted for baseline utility [b] Ultrasound-guided injection and advice and exercise leaflet versus Unguided injection and advice and exercise leaflet [c] Unguided injection and Physiotherapist-led exercise versus Ultrasound-guided injection and advice and exercise leaflet [d] Ultrasound-guided injection and Physiotherapist-led exercise versus Unguided injection and Physiotherapist-led exercise

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Figure 1: Cost-effectiveness plane

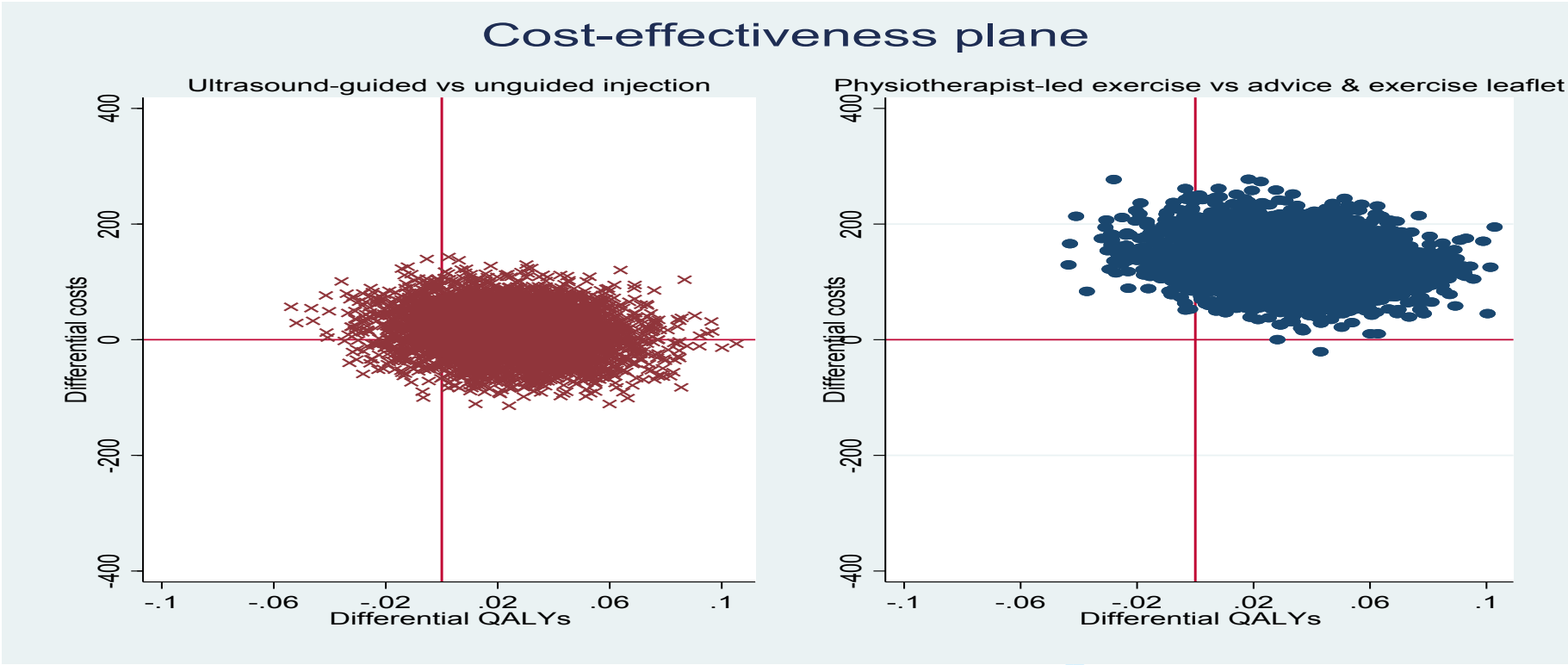
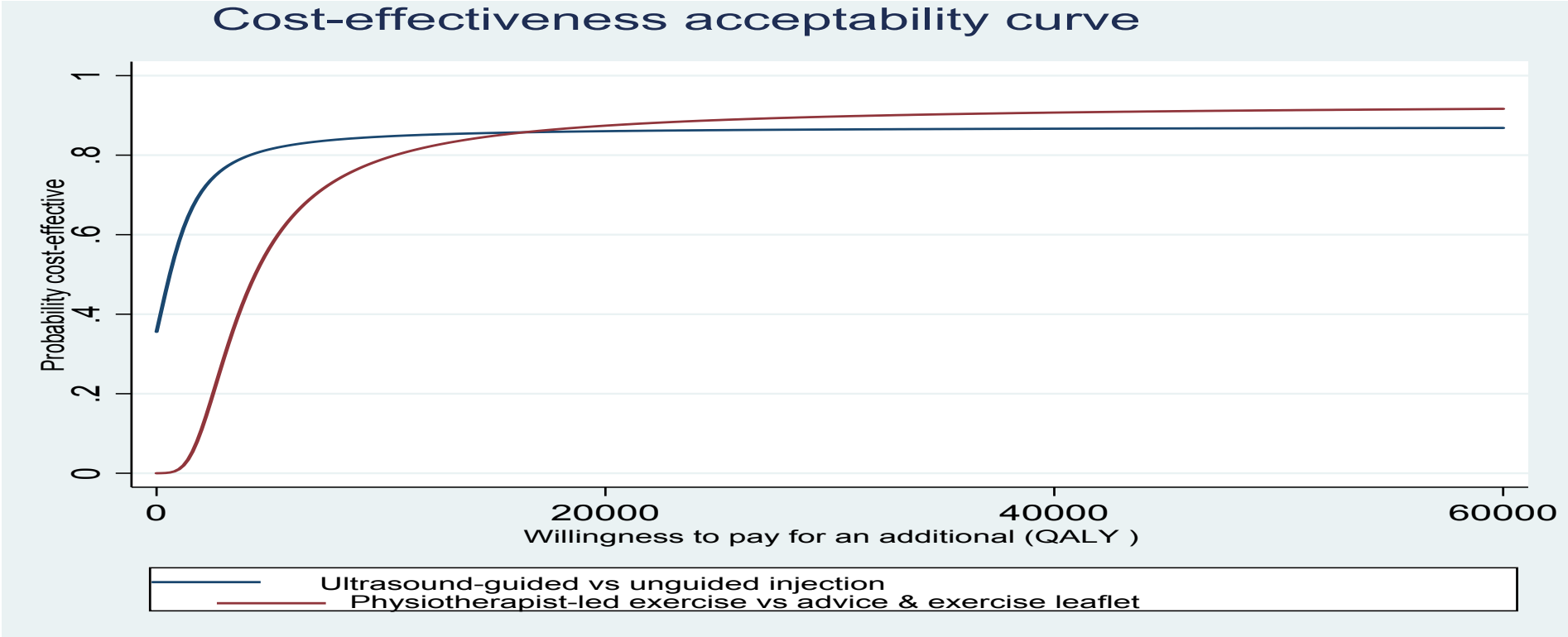


Figure 2: Cost-effectiveness acceptability curve



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The cost-effectiveness of different approaches to exercise and corticosteroid injection for Subacromial pain (impingement) syndrome

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Abstract:

Objectives: To determine whether physiotherapist-led exercise intervention and ultrasound-guided subacromial corticosteroid injection is cost-effective when compared to standard advice and exercise leaflet and unguided injection in patients with subacromial pain (impingement) syndrome.

Methods: An incremental cost–utility analysis using patient responses to the five-level EuroQoL-5D (EQ-5D-5L) questionnaire was undertaken from a health care perspective alongside a 2x2 factorial randomised trial with 256 participants over a 12-month follow-up period. Uncertainty was explored through the use of cost-effectiveness acceptability curves.

Results: The cost–utility analysis indicated that physiotherapist-led exercise was associated with an incremental cost of £155.99 (95% CI: 69.02 to 241.93) and 0.031 (95% CI: −0.01 to 0.07) additional quality-adjusted life-years (QALYs), an incremental cost-effectiveness ratio (ICER) of £5,031 per QALY gained and an 85% chance of being cost-effective at a threshold of £20,000 per QALY gained compared to the advice and exercise leaflet. Ultrasound-guided injection was associated with an incremental cost of £15.89 (95% CI: −59.36 to 109.86) and 0.024 (95% CI: −0.02 to 0.07) additional QALYs, an ICER of £662 per QALY gained and a 83% chance of being cost-effective at a threshold of £20,000 per QALY gained compared to unguided injection.

Conclusion: Physiotherapist-led exercise was cost-effective compared to the advice and exercise leaflet, and ultrasound-guided injection was cost-effective when compared to unguided injection.

Clinical trial registration number: ISRCTN (42399123)

Keywords: Cost-effectiveness, Subacromial pain (impingement) syndrome , Exercise, Corticosteroid injection, EQ-5D

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Rheumatology key messages:

- Guidelines recommend non-surgical options for the management of Subacromial pain (impingement) syndrome.
- Physiotherapist-led exercise and ultrasound-guided corticosteroid injection appear to increase costs but lead to improved quality of life compared to unguided injection and advice and exercise leaflet.
- Physiotherapist-led exercise and ultrasound-guided injection are likely to be cost-effective.

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Introduction

Subacromial pain (impingement) syndrome (SAPS) is the most common cause of shoulder pain. The prevalence of SAPS increases with age and places a substantial burden on health systems, with estimates from GP consultations suggesting that approximately 16% of adults reporting musculoskeletal pain had shoulder pain [1-2]. Shoulder pain poses a considerable burden to society, accounting for a substantial number of days off work and associated productivity costs [3-4]. Treatment guidelines recommend initial non-surgical management including education/self-management advice, exercise, corticosteroid injection, and analgesia [5-6].

In order to explore how to optimise outcomes from exercise and subacromial corticosteroid injection, a randomised controlled trial was conducted to assess whether better improvements in pain and function were obtained with (1) a physiotherapist-led, individualised, supervised and progressed exercise programme versus a standardised advice and exercise leaflet, and (2) ultrasound-guided subacromial corticosteroid injection versus unguided injection. The clinical results of the trial showed that physiotherapist-led exercise was more effective than an exercise leaflet whilst ultrasound-guidance conferred no additional benefit over unguided corticosteroid injection [7]. In addition to establishing the effectiveness of interventions for the management of shoulder pain, it is also important to determine whether these interventions offer value for money. Previous studies assessing the cost-effectiveness of interventions for the treatment of SAPS have focused on a comparison of corticosteroid injection and exercise [2] and have not compared different methods of guiding corticosteroid injection, nor the manner in which the exercise intervention was delivered.

The primary aim of this economic analysis was to determine whether a physiotherapist-led exercise intervention is cost-effective compared to a standard advice and exercise leaflet, and

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whether ultrasound-guided subacromial corticosteroid injection is cost-effective when compared to unguided injection.

Methods

A within-trial economic evaluation was conducted alongside a 2x2 factorial randomised trial in patients with SAPS [7]. Using block randomisation, participants who met the inclusion criteria were randomly assigned on a 1:1:1:1 basis to one of four interventions:

1. Ultrasound-guided subacromial corticosteroid injection and physiotherapist-led individualised, supervised and progressed exercise.
2. Ultrasound-guided subacromial corticosteroid injection and an advice and exercise leaflet.
3. Unguided subacromial corticosteroid injection and physiotherapist-led individualised, supervised and progressed exercise
4. Unguided subacromial corticosteroid injection and an advice and exercise leaflet.

The main outcome for the economic analysis was the quality-adjusted life-year (QALY), over a 12-month follow-up period. The base case analysis was carried out from a health care perspective including health care costs incurred by the NHS and patients. To be consistent with the clinical study, the 'at the margins' approach which assumes that interventions are independent was adopted for the base case scenario [8-9]. The trial, including this economic analysis, was approved by The Black Country Research Ethics Committee (10/H1202/72). Trial registration number (ISRCTN42399123).

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Data collection

Resource use and costs

Data on health care resource use were obtained from participant responses to self-report questionnaires administered at 6 weeks, 6 months and 12 months. Resource use data concentrated on visits to health care professionals in primary and secondary care, medical investigations/interventions, and both prescribed and over the counter medications. Data obtained from questionnaire responses were aggregated to generate overall resource use over the 12-month follow-up period. The questionnaires also requested information on time off work over 12 months which was used to estimate productivity losses.

Unit cost data were obtained from the following sources: British National Formulary, NHS reference costs and the PSSRU publication on unit cost of health and social care [10-12] (Supplementary Table 1). 2012/2013 costs were inflated to 2019 prices using the consumer price index.

Trial intervention cost

Information on the intervention costs was obtained from trial data and all resources required to deliver the interventions were determined.

Physiotherapist-led exercise versus advice and leaflet: For the physiotherapist visits, the unit cost associated with a contact with the physiotherapist was multiplied by the number of physiotherapy contacts. Information on the number of physiotherapist contacts was obtained from case report forms that physiotherapists completed. For the advice and exercise leaflet, only the cost associated with the leaflet was included since all participants had the index consultation where the injection was performed on all patients. Full details of the intervention can be found elsewhere [13].

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Ultrasound versus unguided injection: It was assumed that since all patients had a similar injection, the only difference between the ultrasound and unguided injection was the cost of the ultrasound. The cost of the ultrasound machine was estimated to be £35,000, and in order to work out a cost per patient, it was assumed that the life expectancy of the machine is 6 years and that the machine is used about 1872 times a year (this value was obtained through consultation with experts). Applying the annuity factor at an interest rate of 3%, the cost of the ultrasound machine per patient was £3.45.

Health Outcomes

Using participant responses to the 5-level version of the EQ-5D-5L questionnaire [14], quality of life was measured at baseline, 6 weeks, 6 months and 12 months. EQ-5D-5L was mapped back to the EQ-5D 3L valuation set as currently recommended by NICE [15] and used to generate the EQ-5D index scores which were then used to derive QALYs. The mapping algorithm developed by Van Hout et al. 2012 was used for this purpose [16].

Statistical Analysis

The economic analysis was carried out on an intention to treat basis, with the aim to estimate the difference in costs and QALYs between the physiotherapist-led exercise intervention and the advice and exercise leaflet and between the ultrasound-guided and unguided subacromial corticosteroid injections. Over the 12-month period, missing EQ-5D scores and costs at one or more of the time points were accounted for using multiple imputation methodology to impute 25 separate datasets [17]. The number of datasets were chosen in order to adequately account for the level of missing data in the study. The approach adopted in this study used chained equations with predictive mean matching in order to ensure that the missing values are aligned to the nearest best-fitting values in the dataset [18]. This approach is particularly useful for cost and EQ-5D data which have skewed distributions, and ensures that imputed values do not go

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out of the plausible range. The coefficients were then pooled across the multiply imputed datasets using the Rubin's rule to obtain single estimates of the corresponding population parameters [17].

The imputation model was fitted with gender, age, smoking status at baseline, baseline SPADI score and health status at baseline as predictors. Using the area under the curve approach [19], QALYs over the 12-month period were estimated for each participant. Total health care costs over the 12-month period were calculated by multiplying the resource items by the respective unit cost and summing over all resource use items. Differences in mean costs and QALYs between trial arms were estimated and QALYs were adjusted to control for imbalances in baseline utility between the interventions [20].

Incremental cost effectiveness ratios (ICERs) were estimated by dividing the difference in mean cost between two interventions (*physiotherapist-led exercise versus advice and exercise leaflet* and *ultrasound-guided versus unguided injection)* by the difference in mean QALYs. Non-parametric bootstrapping was used to illustrate and quantify uncertainty. To determine the probability of an intervention being deemed cost-effective compared to an alternative intervention (*physiotherapist-led exercise versus advice and exercise leaflet* and *ultrasound-guided versus unguided injection)*, cost-effectiveness acceptability curves (CEACs) were constructed [21]. This shows the probability that an intervention is cost-effective, relative to the chosen comparator, across a range of values that represent a decision makers' willingness to pay for an additional QALY. All the analyses were carried out in STATA version 12 [22].

Costs for productivity losses were computed through the human capital approach using data collected on time off work and employment. Productivity losses were obtained by the product of lost productivity time and the mean hourly wage of patients classified from data on wages

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corresponding to self-reported baseline occupation (derived from the Annual Surveys of Health Evaluation by the Office of National Statistics and based on classification codes under the UK Socio-Economic Occupation Classification, SOC 2000) [23].

Sensitivity analysis was carried out and had three main foci: First, cost-utility analysis was conducted from a UK NHS perspective by excluding private health care costs. Second, as there is a lack of consensus with respect to methods for conducting economic evaluation alongside factorial trials, an alternative approach ('within the table') to analysing the factorial trial treatment options was undertaken. The 'within the table' approach assumes that there is an interaction between the treatments, and considers all four arms of the trial as separate interventions [8-9]. With this analysis, the interventions were ordered in terms of increasing QALYs and 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 comparator(s)) and extended (weak) dominance (where an intervention is ruled out if the ICER is greater than that of a more effective intervention). Third, cost-utility analysis was conducted using EQ-5D scores generated from the EQ-5D-5L tariff published by Devlin et al. 2018 [24]

Results

A total of 256 participants were randomised (64 per arm) to one of the four intervention arms. The mean age of participants across all arms was 53.8 years (S.D. 10.2) and 52% of participants were female. The mean (SD) total Shoulder Pain and Disability Index (SPADI) score at baseline was 61.1 (18.1). Full details of other baseline characteristics can be found elsewhere [25].

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Resource use and costs

Complete resource use data were obtained for 194 participants (76%). This ranged from 72% in the ultrasound-guided injection and physiotherapist-led exercise arm to 78% in the unguided injection and advice and exercise leaflet arm. A full breakdown of patient responses at each follow-up time point can be found elsewhere [25]. Compared to the advice and exercise leaflet group, significantly fewer visits to the GP were made during the 12 month follow-up period in the physiotherapist-led exercise group. The unguided injection group made more visits to a hospital nurse and specialist over the 12 month follow-up period compared to the ultrasound-guided injection group (Supplementary Table 2). With the exception of diclofenac which was significantly lower in the physiotherapist-led exercise arm, there was no significant difference in prescription medication use across trial arms (Supplementary Table 3). Private health care resource use is presented in Supplementary Table 4.

Mean NHS and private costs per participant by trial arm over the 12-month period prior to imputation are presented in Table 1. Health care costs were higher in the physiotherapist-led exercise group compared to the advice and exercise leaflet group and also in the ultrasound-guided injection group compared to the unguided injection group.

Health outcomes

Health outcomes (EQ-5D and QALYs) using the imputed dataset are presented in table 2. A total of 131 (54%) participants provided complete EQ-5D responses at all time-points. This ranged from 47% in the unguided injection and physiotherapist-led exercise arm to 61% in the ultrasound-guided injection and physiotherapist-led exercise arm. However, it should be noted that the majority of those with missing values were missing just one EQ-5D score. There was an improvement in health outcomes over time, with scores obtained at 12-months higher than the baseline scores in all four arms. With respect to QALYs over the 12-month period, higher scores were obtained in the physiotherapist-led exercise and ultrasound-guided injection

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groups when compared to the advice and exercise leaflet and unguided injection groups, respectively. After adjusting for baseline utility, similar results were obtained.

Cost-utility analysis

The results from the cost-effectiveness analysis using the imputed dataset showed that physiotherapist-led exercise was more expensive (cost difference £155.99) and more effective (QALY difference 0.031) than the advice and exercise leaflet. The resulting ICER was £5,031 per QALY gained (Table 3) with an 85% chance of physiotherapist-led exercise being cost-effective at a cost-effectiveness threshold of £20,000 per QALY gained (Figures 1 and 2). Ultrasound-guided injection was also more expensive (cost difference £15.89) and more effective (QALY difference 0.024) than unguided injection. The resulting ICER was £662 per QALY gained (Table 3) with an 83% chance of ultrasound-guided injection being cost-effective at a willingness to pay threshold of £20,000 per QALY gained (Figures 1 and 2).

Time off work and Productivity Losses

Participants in the advice and exercise leaflet and unguided injection groups took more time off work than those in the physiotherapist-led exercise and ultrasound-guided injection groups. Productivity losses in terms of lost wages were also higher in the advice and exercise leaflet and unguided injection groups. However, these differences were not statistically significant (Supplementary Table 4 and Table 1).

Sensitivity Analysis

From a UK NHS perspective, the results obtained were similar to the base case analysis i.e. physiotherapist-led exercise was cost-effective compared to providing an advice and exercise leaflet and ultrasound-guided injection was cost-effective compared to unguided injection (Table 3). Results from the 'within the table' analysis showed that a combination of ultrasound-guided injection and physiotherapist-led exercise was the most cost-effective intervention

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(£6,225 per QALY gained), supporting findings from the base case analysis (Table 4). The results obtained when the EQ-5D-5L tariff [24] was used are similar to those obtained with the mapping algorithm [16] and support the finding that physiotherapist-led exercise is cost-effective compared to the advice and exercise leaflet, and ultrasound-guided injection is cost-effective when compared to unguided injection (Supplementary Tables 5 and 6).

Discussion

Summary of the main findings

This health economic evaluation showed that for the management of SAPS, physiotherapist-led exercise was cost-effective compared to the advice and exercise leaflet and ultrasound-guided injection was cost-effective when compared to unguided injection. Sensitivity analysis using the within-the-table analysis yielded similar results to the at-the-margins approach indicating that the choice of method did not change the findings of the health economic analysis. Similar findings with respect to the choice of method have been obtained in previous studies [8]. A previous economic evaluation showed that a combination of injection and exercise was cost-effective compared to exercise alone [2]. The results from this study add to this evidence by showing that the approach to providing exercise (physiotherapist-led, individualised, progressed and supervised exercise rather than through a standardised advice and exercise leaflet) and injection (guided using ultrasound rather than unguided) is important in terms of increasing their cost-effectiveness.

The results of the trial on which the economic evaluation is based showed that physiotherapist-led exercise was more effective than an exercise leaflet whilst ultrasound-guidance conferred no additional benefit over unguided corticosteroid injection [25]. The health economic results are similar in terms of the comparison between physiotherapist-led exercise and the advice and exercise leaflet, but different in terms of the comparison between ultrasound-guided and

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unguided injection. It is however important to note that the primary outcome of the clinical trial was the Shoulder Pain and Disability Index whilst that of the economic evaluation was total QALYs obtained from EQ-5D. Although the difference in QALYs obtained for both comparisons was very small and not statistically significant, the agreed approach in health economics is to conduct a cost-effectiveness analysis with costs and effects estimated jointly [26]. Whilst clinical research focuses on hypothesis testing, economic evaluation is aimed at estimation which may produce contradictory results as was seen in this study with the injection comparison [27]. An important issue which the results of this study raise relates to whether the use of generic quality of life measures such as the EQ-5D are sufficient for assessing the cost-effectiveness of interventions in this clinical syndrome. Previous research has shown that generic quality of life measures may be insensitive to changes in some disease areas including musculoskeletal conditions such as osteoarthritis (OA) [28-30].

Strengths and weaknesses of the study

A strength of the study is the factorial nature of the trial, which enabled us to compare four interventions within the same analysis.

A possible limitation of the economic analysis is the fact that the cost of training clinicians to perform ultrasound-guided injection was not included in the analysis and it could be argued that this may have under-estimated the cost of the ultrasound-guided injection. The cost and time required to train clinical staff to perform ultrasound-guided injections is a potential barrier to services. However, it should be noted that there are a number of difficulties associated with the estimation of a per patient training cost within economic evaluation studies and also the training received by clinicians would be used for a large number of patients over a number of years which would result in a low mean cost per patient. A further limitation was that only 76% of participants had complete data at all time-points, however, the missing data were accounted for using multiple imputations.

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Meaning of the results

This health economic analysis has shown that physiotherapist-led exercise and ultrasound-guided injection are more cost-effective treatment options for SAPS than an advice and exercise leaflet or unguided shoulder injection respectively. However, this conclusion should be interpreted in the light of the clinical results which showed that physiotherapist-led exercise conferred superior benefits for patients compared to the advice and leaflet yet ultrasound guided injection conferred no additional benefit over unguided injection [25].

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Conflicts of interest: None to declare

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Table 1: Mean health care cost (SD) per patient over 12 months (complete cases) (£, 2019 prices)

	Injection intervention group			Exercise intervention group		
	US-guided (n=95)	**Unguided (n=99)**	**Mean difference (95% CI)**	**Physiotherapist-led (n=95)**	**Advice and Exercise Leaflet (n=99)**	**Mean difference (95% CI)**
Intervention cost[a]	186.01 (126.50)	107.12 (127.33)	78.89 (41.98, 113.59)	258.92 (96.73)	37.15 (36.58)	221.77 (196.45, 241.00)
PRIMARY CARE CONTACTS						
General Practitioner	39.16 (75.27)	43.30 (97.90)	-4.14 (-28.39, 20.59)	28.01 (70.66)	53.99 (99.52)	-25.98 (-49.65, -3.08)
Practice Nurse	1.28 (11.11)	0.58 (4.16)	0.70 (-0.84, 3.99)	1.21 (9.73)	0.92 (6.73)	0.29 (-1.69, 3.46)
Other professionals in GP practice	14.48 (40.98)	22.58 (59.73)	-8.10 (-22.99, 4.19)	24.52 (58.25)	12.94 (43.47)	11.58 (-2.64, 26.78)
SECONDARY CARE CONTACTS						
Physiotherapist [b]	37.27 (86.59)	32.69 (86.02)	4.58 (-20.45, 27.03)	53.31 (102.03)	17.30 (63.03)	36.01 (14.52, 62.41)
NHS consultants	26.97 (60.56)	49.08 (93.36)	-22.11 (-43.75, -1.21)	38.15 (74.24)	38.34 (76.12)	-0.19 (-23.44, 21.53)
Private consultants and Physiotherapists	18.07 (83.84)	8.98 (35.80)	9.09 (-5.96, 30.28)	6.17 (27.97)	20.40 (84.94)	-14.23 (-38.09, -0.79)
Other professional in NHS hospitals	1.58 (11.87)	2.07 (11.14)	-0.49 (-3.61, 2.93)	1.46 (11.81)	2.20 (11.19)	-0.74 (-3.82, 2.81)
REPEAT INJECTIONS						
Repeat Injections in NHS	35.96 (98.07)	51.07 (118.07)	-15.11 (-45.35, 17.64)	33.08 (104.93)	53.83 (111.82)	-20.75 (-50.81, 8.58)
Repeat Injections in private practice	1.43 (14.02)	-	1.43 (0, 5.88)	-	1.38 (13.73)	-1.38 (-5.11, 0)
DIAGNOSTIC TESTS						
Diagnostic tests in NHS	36.27 (105.24)	72.97 (144.77)	-36.70 (-70.06, -5.69)	45.44 (114.17)	64.18 (139.89)	-18.74 (-53.69, 17.34)
Diagnostic tests in private practice	-	1.76 (12.98)	-1.76 (-5.38, 0)	-	1.76 (12.98)	-1.76 (-4.96, 0)

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MEDICATION						
Prescribed medication	5.70 (16.62)	7.80 (16.96)	-2.10 (-6.74, 2.51)	3.71 (7.19)	9.71 (22.08)	-6.00 (-10.86, -1.78)
Over the counter medication	10.15 (20.01)	18.86 (57.93)	-8.71 (-22.80, 1.11)	13.85 (45.62)	15.31 (42.19)	-1.46 (-12.94, 11.17)
WORK RELATED OUTCOMES						
Productivity costs	388.06 (1638.82)	823.56 (3924.91)	-435.50 (-1472.23, 239.61)	562.54 (2713.56)	656.13 (3317.80)	-93.59 (-1044.70, 654.54)
TOTAL COSTS						
Total health care costs [c] (n=256)	428.01 (322.83)	412.12 (366.09)	15.89 (-59.36, 109.86)	498.06 (326.05)	342.07 (346.11)	155.99 (69.03, 241.93)

[a] This cost takes into account the fact that participants had more than one intervention e.g. US guided injection plus physiotherapist-led exercise [b] Visits associated with the intervention have been excluded [c] Costs have been imputed

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Table 2: Mean health outcomes (SD) over 12 months (imputed data)

	Injection intervention group			Exercise intervention group		
	US-guided (n=128)	**Unguided (n=128)**	**Mean difference (95% CI)**	**Physiotherapist-led (n=128)**	**Advice & exercise leaflet (n=128)**	**Mean difference (95% CI)**
EQ-5D scores						
Baseline	0.494 (0.255)	0.501 (0.235)	-0.007 (-0.065, 0.052)	0.504 (0.243)	0.492 (0.247)	0.012 (-0.042, 0.078)
6 weeks	0.599 (0.240)	0.574 (0.236)	0.025 (0.031, 0.080)	0.601 (0.242)	0.572 (0.234)	0.029 (-0.025, 0.087)
6 months	0.577 (0.245)	0.549 (0.261)	0.028 (-0.031, 0.088)	0.584 (0.246)	0.541 (0.259)	0.043 (-0.018, 0.103)
12 months	0.599 (0.248)	0.594 (0.271)	0.005 (-0.058, 0.066)	0.606 (0.268)	0.588 (0.252)	0.018 (-0.052, 0.081)
Total QALYs	0.584 (0.225)	0.564 (0.230)	0.020 (-0.035, 0.072)	0.594 (0.227)	0.555 (0.226)	0.039 (-0.013, 0.097)
Total adjusted QALYs [a]	0.586	0.562	0.024 (-0.018, 0.066)	0.589	0.558	0.031 (-0.010, 0.073)

[a] QALYs adjusted for baseline utility

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Table 3: Cost-utility analysis (imputed data)

	Injection intervention group			Exercise intervention group		
	US-guided (n=128)	**Unguided (n=128)**		**Physiotherapist-led (n=128)**	**Advice & Exercise Leaflet (n=128)**	
	Mean	**Mean**	**Mean difference (Confidence Interval)**	**Mean**	**Mean**	**Mean difference (Confidence Interval)**
HEALTHCARE PERSPECTIVE						
Cost	£428.01	£412.12	£15.89 (-59.36, 109.86)	£498.06	£342.07	£155.99 (69.02, 241.93)
QALYs [a]	0.586	0.562	0.024 (-0.018, 0.066)	0.589	0.558	0.031 (-0.010, 0.073)
ICER	£662 per QALY gained			£5,031 per QALY gained		
NHS PERSPECTIVE						
Cost	£398.25	£382.04	£15.85 (-64.32, 90.22)	£476.02	£304.27	£171.75 (98.44, 251.88)
QALYs [a]	0.586	0.562	0.024 (-0.018, 0.066)	0.589	0.558	0.031 (-0.010, 0.073)
ICER	£660 per QALY gained			£5,540 per QALY gained		

[a] Adjusted for baseline utility

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Table 4: Cost-utility analysis "within the table" analysis

	Cost (£)*	QALY	QALY*[a]	ICER
		Health care perspective		
Unguided injection and advice and exercise leaflet (n=64)	385.31 (397.70)	0.545 (0.236)	0.542	Dominated by Ultrasound-guided injection and advice and exercise leaflet [b]
Ultrasound-guided injection and advice and exercise leaflet (n=64)	298.82 (281.99)	0.564 (0.218)	0.575	Dominates Unguided injection and advice and exercise leaflet [b]
Unguided injection and Physiotherapist-led exercise (n=64)	438.92 (332.49)	0.583 (0.224)	0.582	£20,014 per QALY gained [c]
Ultrasound-guided injection and Physiotherapist-led exercise (n=64)	557.20 (310.90)	0.604 (0.232)	0.601	£6,225 per QALY gained [d]
		NHS perspective		
	Cost*	**QALY**	**QALY*[a]**	**ICER**
Unguided injection and advice and exercise leaflet (n=64)	347.87 (385.17)	0.545 (0.236)	0.542	Dominated by Ultrasound-guided injection and advice and exercise leaflet [b]
Ultrasound-guided injection and advice and exercise leaflet (n=64)	260.66 (220.67)	0.564 (0.218)	0.575	Dominates Unguided injection and advice and exercise leaflet [b]
Unguided injection and Physiotherapist-led exercise (n=64)	416.21 (324.81)	0.583 (0.224)	0.582	£22,221 per QALY gained [c]

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Ultrasound-guided injection and Physiotherapist-led exercise (n=64)	535.83 (305.61)	0.604 (0.232)	0.601	£6,295 per QALY gained [d]

*Cost and QALYs imputed [a] Adjusted for baseline utility [b] Ultrasound-guided injection and advice and exercise leaflet versus Unguided injection and advice and exercise leaflet [c] Unguided injection and Physiotherapist-led exercise versus Ultrasound-guided injection and advice and exercise leaflet [d] Ultrasound-guided injection and Physiotherapist-led exercise versus Unguided injection and Physiotherapist-led exercise

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Figure 1: Cost-effectiveness plane

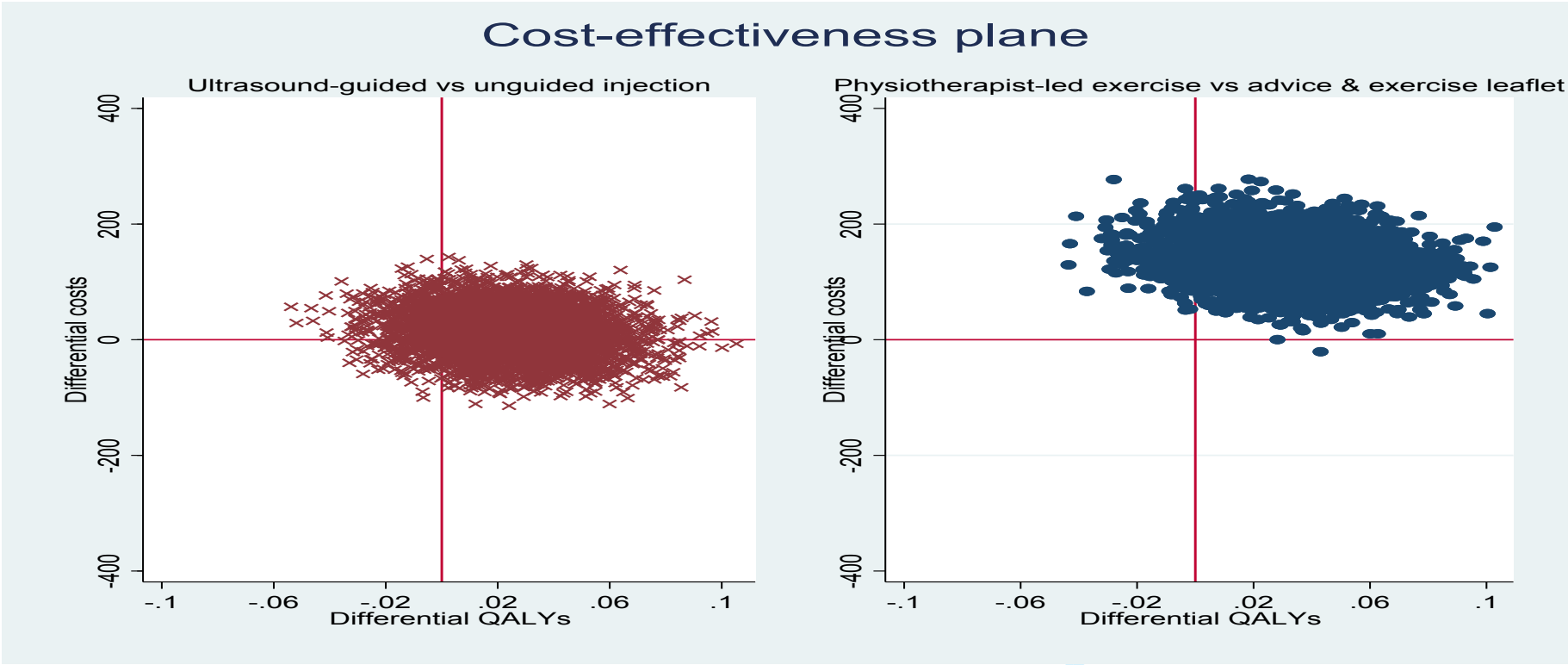
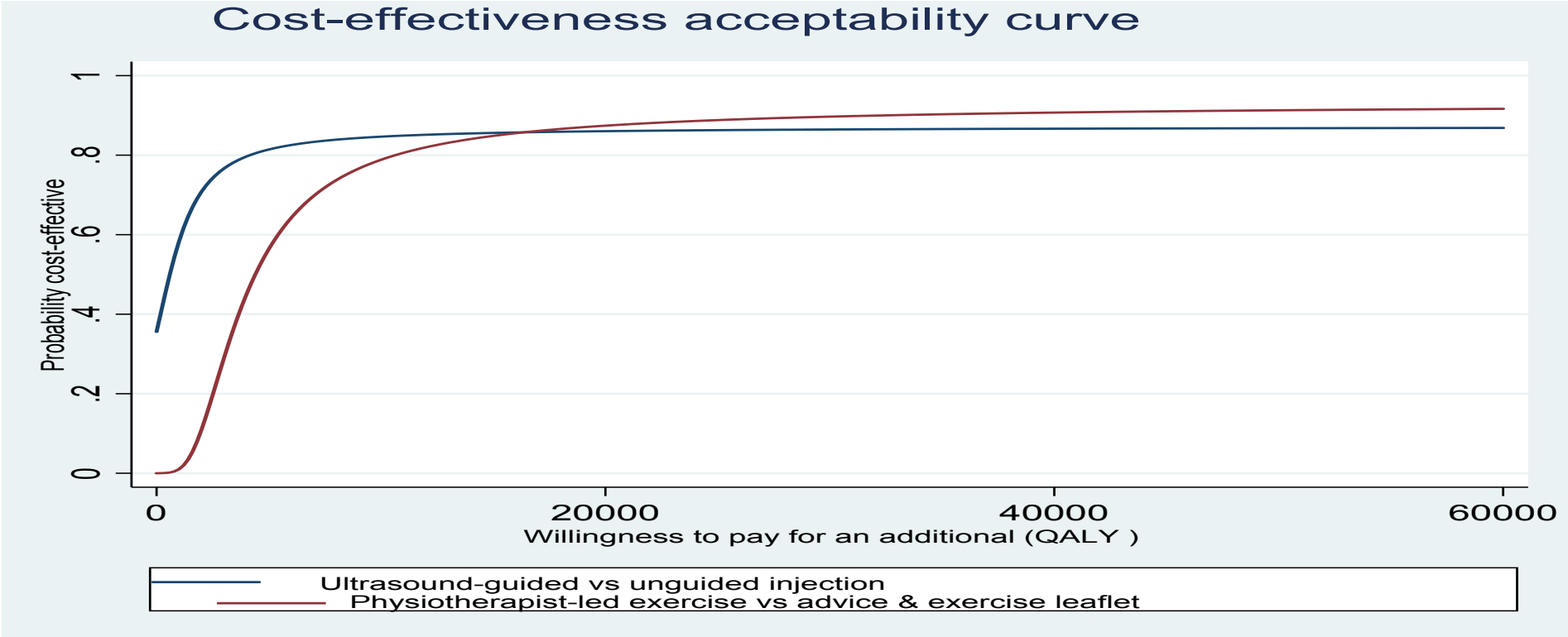


Figure 2: Cost-effectiveness acceptability curve



For Peer Review

Supplementary Table 1: Unit cost of health care resource use

Health care resource	Unit cost (£) 2012/13 prices
Primary care contacts	
GP at practice	43
GP at home	53.58
Nurse at practice	10.30
Nurse at home	23.30
Secondary care contacts	
Physiotherapist visits	34
Consultants	52
Specialists A&E visits	62
Intervention cost[a]	
Physiotherapist-led exercise	34 per visit[b]
Advice and exercise leaflet	1[c]
Ultrasound-guided injection	65[d]
Unguided injection	0[e]
Prescribed Medication	Participant specific
Over the counter medication	Participant specific
Medical investigations/Interventions	Participant specific

[a] These costs are what was actually used for the analysis [b] This value was multiplied by the number of times a participant saw a physiotherapist. Thus, the cost varied from participant to participant [c] This is the cost of the leaflet [d] Includes cost of the ultrasound procedure [e] Assumed to be zero since all patients had a similar injection and the only difference between the ultrasound-guided and unguided injection was the cost of the ultrasound.

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Supplementary Table 2: Mean (SD) NHS resource use per patient (complete cases)

	Injection intervention group			Exercise intervention group		
	US-guided (n=95)	Unguided (n=99)	Difference (Confidence Interval)	Physiotherapist-led (n=95)	Advice and Exercise Leaflet (n=99)	Difference (Confidence Interval)
PRIMARY CARE CONTACTS						
GP (surgery)	0.80 (1.51)	0.90 (2.03)	**-0.10 (-0.62, 0.38)**	0.57 (1.41)	1.12 (2.07)	**-0.55 (-1.07,-0.07)**
GP (home visit)	0.01 (0.10)	0	**0.01 (0.00, 0.04)**	0.01 (0.10)	0	**0.01 (0.00, 0.04)**
Nurse visits (surgery)	0.14 (0.96)	0.05 (0.36)	**0.09 (-0.08, 0.35)**	0.11 (0.84)	0.08 (0.58)	**0.03 (-0.14, 0.28)**
Nurse (home visit)	0	0	**0**	0	0	**0**
Other professionals attached to GP practice (surgery)	0.35 (0.91)	0.48 (1.31)	**-0.13 (-0.46, 0.17)**	0.52 (1.22)	0.32 (1.04)	**0.20 (-0.13, 0.50)**
[a] Other professionals attached to GP practice (home)	0.04 (0.29)	0.08 (0.80)	**-0.04 (-0.26, 0.08)**	0.13 (0.87)	0	**0.13 (0.02 , 0.38)**
SECONDARY CARE CONTACTS						
Consultant	0.46 (1.04)	0.75 (1.48)	**-0.29 (-0.64, 0.08)**	0.60 (1.27)	0.62 (1.31)	**-0.02 (-0.40, 0.35)**
Physiotherapist [b]	2.79 (3.96)	2.45 (3.78)	**0.34 (-0.67, 1.47)**	4.87 (4.21)	0.45 (1.66)	**4.42 (3.51, 5.35)**
Specialist A&E	0	0.06 (0.42)	**-0.06 (-0.19, -0.01)**	0.04 (0.41)	0.02 (0.14)	**0.02 (-0.04, 0.12)**
Hospital Nurse	0	0.08 (0.34)	**-0.08 (-0.17, -0.03)**	0.02 (0.14)	0.06 (0.31)	**0.04 (-0.12, 0.02)**
Acupuncturist	0	0.01 (0.10)	**-0.01 (-0.03, 0)**	0	0.01 (0.10)	**-0.01 (-0.03, 0)**
[c] Other professionals	0.06 (0.35)	0.06 (0.31)	**0 (-0.08, 0.10)**	0.04 (0.32)	0.08 (0.34)	**-0.04 (-0.13, 0.07)**
Repeat Injections	0.26 (0.72)	0.37 (0.86)	**-0.11 (-0.28, 0.07)**	0.24 (0.77)	0.39 (0.82)	**-0.15 (-0.30, 0.05)**

[a] This includes contacts with professionals such as work nurse sister and consultant [b] Physiotherapy visits that were part of the intervention have been included here [c] Includes contacts with professionals such as work nurse sister, sports therapist, massage masseur and kinesiologist

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Supplementary Table 3: Mean (SD) prescribed drugs and medical investigations per patient over 12 months (complete cases)

	Injection intervention group			Exercise intervention group		
	US-guided (n=95)	**Unguided (n=99)**	**Difference (Confidence Interval)**	**Physiotherapist-led (n=95)**	**Advice and Exercise Leaflet (n=99)**	**Difference (Confidence Interval)**
PRESCRIBED DRUGS						
Paracetamol	0.38 (1.45)	0.52 (2.00)	**-0.14 (-0.62, 0.32)**	0.37 (1.39)	0.53 (2.04)	**-0.16 (-0.72, 0.27)**
Ibuprofen	0.31 (1.38)	0.75 (2.89)	**-0.44 (-1.14, 0.08)**	0.28 (1.29)	0.78 (2.92)	**-0.5 (-1.24, 0.06)**
Co-codamol	0.77 (2.11)	1.19 (2.71)	**-0.42 (-1.13, 0.24)**	1 (2.46)	0.97 (2.43)	**0.03 (-0.64, 0.77)**
Diclofenac	0.04 (0.25)	0.09 (0.81)	**-0.05 (-0.28, 0.06)**	0.01 (0.10)	0.12 (0.84)	**-0.11 (-0.34, -0.001)**
MEDICAL INVESTIGATIONS						
Blood test	0.09 (0.41)	0.26 (0.79)	**-0.17 (-0.04, -0.03)**	0.05 (0.22)	0.30 (0.85)	**-0.25 (-0.46, -0.10)**
X-ray	0.13 (0.39)	0.29 (0.72)	**-0.16 (-0.33, -0.16)**	0.16 (0.55)	0.26 (0.62)	**-0.10 (-0.25, 0.06)**
Ultrasound	0.11 (0.35)	0.33 (0.73)	**-0.22 (0.39, -0.06)**	0.17 (0.54)	0.28 (0.62)	**-0.11 (-0.28, 0.04)**
MRI scan	0.01 (0.10)	0.04 (0.24)	**-0.03 (-0.10, 0.01)**	0.01 (0.10)	0.04 (0.24)	**-0.03 (-0.10, 0.01)**
CT scan	0	0.03 (0.22)	**-0.03 (-0.10, 0)**	0	0.03 (0.22)	**-0.03 (-0.10, 0)**

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Supplementary Table 4: Mean (SD) private resource use per patient over 12 months (complete cases)

	Injection intervention group			Exercise intervention group		
	US-guided (n=95)	**Unguided (n=99)**	**Difference (Confidence Interval)**	**Physiotherapist-led (n=95)**	**Advice and Exercise Leaflet (n=99)**	**Difference (Confidence Interval)**
Consultant	0.12 (0.63)	0.05 (0.36)	**0.07 (-0.06, 0.24)**	0.03 (0.33)	0.13 (0.65)	**-0.1 (-0.26, 0.03)**
Physiotherapist	0.11 (0.83)	0.06 (0.42)	**0.05 (-1.1, 0.28)**	0.07 (0.44)	0.09 (0.81)	**-0.02 (-0.26, 0.13)**
Specialist	0.02 (0.21)	0	**0.02 (0, 0.08)**	0	0.02 (0.20)	**-0.02 (-0.10, 0)**
Hospital Nurse	0.01 (0.10)	0.01 (0.10)	**0 (-0.02, 0.03)**	0.01 (0.10)	0.01 (0.10)	**0 (-0.02, 0.04)**
Acupuncturist	0.01 (0.10)	0	**0.01 (0, 0.04)**	0	0.01 (0.10)	**-0.01 (-0.04, 0)**
Osteopath	0.07 (0.72)	0.06 (0.60)	**0.01 (-0.13, 0.27)**	0	0.13 (0.92)	**-0.13 (-0.35, 0)**
Other professionals	0.08 (0.58)	0.06 (0.45)	**0.02 (-0.12, 0.17)**	0.04 (0.41)	0.10 (0.60)	**-0.06 (-0.24, 0.08)**
Over the counter medication	2.86 (5.52)	6.22 (22.15)	**-3.36 (-9.61, -0.09)**	5.24 (21.60)	3.94 (8.78)	**1.30 (-2.08, 7.57)**
Repeat Injection	0.01 (0.11)	0	**0.01 (0, 0.04)**	0	0.01 (0.10)	**-0.01 (-0.04, 0)**
			WORK RELATED ITEMS			
Time off work due to shoulder problems (mean days)	3.49 (14.63)	8.70 (44.50)	**-1.68 (-13.44, 6.33)**	5.29 (24.00)	6.97 (40.57)	**-5.21 (-16.73, 1.93)**

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Supplementary Table 5: Cost-utility analysis 'at the margins' approach (with EQ-5D-5L tariff)

	Injection intervention group			Exercise intervention group		
	US-guided (n=128)	**Unguided (n=128)**		**Physiotherapist-led (n=128)**	**Advice & Exercise Leaflet (n=128)**	
	Mean	**Mean**	**Mean difference (Confidence Interval)**	**Mean**	**Mean**	**Mean difference (Confidence Interval)**
HEALTHCARE PERSPECTIVE						
Cost	£428.01	£412.12	£15.89 (-59.36, 109.86)	£498.06	£342.07	£155.99 (69.02, 241.93)
QALYs [a]	0.697	0.667	0.030 (-0.009, 0.070)	0.693	0.671	0.023 (-0.017, 0.062)
ICER	£529.7 per QALY gained			£6,782 per QALY gained		
NHS PERSPECTIVE						
Cost	£398.25	£382.04	£15.85 (-64.32, 90.22)	£476.02	£304.27	£171.75 (98.44, 251.88)
QALYs [a]	0.697	0.667	0.030 (-0.009, 0.070)	0.693	0.671	0.023 (-0.017, 0.062)
ICER	£528.3 per QALY gained			£7,467 per QALY gained		

[a] Adjusted for baseline utility

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Supplementary Table 6: Cost-utility analysis "within the table" analysis (With EQ-5D-5L tariff)

	Cost (£)*	QALY*[a]	ICER
	Health care perspective		
Unguided injection and advice and exercise leaflet (n=64)	385.31 (397.70)	0.652	N/A
Unguided injection and Physiotherapist-led exercise (n=64)	438.92 (332.49)	0.681	£1,848 per QALY gained [b]
Ultrasound-guided injection and advice and exercise leaflet (n=64)	298.82 (281.99)	0.689	Dominates Unguided injection and Physiotherapist-led exercise [c]
Ultrasound-guided injection and Physiotherapist-led exercise (n=64)	557.20 (310.90)	0.705	£16,148 per QALY gained [d]
	NHS perspective		
Unguided injection and advice and exercise leaflet (n=64)	347.87 (385.17)	0.652	N/A
Unguided injection and Physiotherapist-led exercise (n=64)	416.21 (324.81)	0.681	£2,356 per QALY gained [b]
Ultrasound-guided injection and advice and exercise leaflet (n=64)	260.66 (220.67)	0.689	Dominates Unguided injection and Physiotherapist-led exercise [c]

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Ultrasound-guided injection and Physiotherapist-led exercise (n=64)	535.83 (305.61)	0.705	£17,198 per QALY gained [d]

*Cost and QALYs imputed [a] Adjusted for baseline utility [b] Unguided injection and Physiotherapist-led exercise versus Unguided injection and advice and exercise leaflet [c] Ultrasound-guided injection and advice and exercise leaflet versus Unguided injection and Physiotherapist-led exercise [d] Ultrasound-guided injection and Physiotherapist-led exercise versus Ultrasound-guided injection and advice and exercise leaflet

For Peer Review

Supplementary Table 1: Unit cost of health care resource use

Health care resource	Unit cost (£) 2012/13 prices
Primary care contacts	
GP at practice	43
GP at home	53.58
Nurse at practice	10.30
Nurse at home	23.30
Secondary care contacts	
Physiotherapist visits	34
Consultants	52
Specialists A&E visits	62
Intervention cost[a]	
Physiotherapist-led exercise	34 per visit[b]
Advice and exercise leaflet	1[c]
Ultrasound-guided injection	65[d]
Unguided injection	0[e]
Prescribed Medication	Participant specific
Over the counter medication	Participant specific
Medical investigations/Interventions	Participant specific

[a] These costs are what was actually used for the analysis [b] This value was multiplied by the number of times a participant saw a physiotherapist. Thus, the cost varied from participant to participant [c] This is the cost of the leaflet [d] Includes cost of the ultrasound procedure [e] Assumed to be zero since all patients had a similar injection and the only difference between the ultrasound-guided and unguided injection was the cost of the ultrasound.

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Supplementary Table 2: Mean (SD) NHS resource use per patient (complete cases)

	Injection intervention group			Exercise intervention group		
	US-guided (n=95)	Unguided (n=99)	Difference (Confidence Interval)	Physiotherapist-led (n=95)	Advice and Exercise Leaflet (n=99)	Difference (Confidence Interval)
PRIMARY CARE CONTACTS						
GP (surgery)	0.80 (1.51)	0.90 (2.03)	**-0.10 (-0.62, 0.38)**	0.57 (1.41)	1.12 (2.07)	**-0.55 (-1.07,-0.07)**
GP (home visit)	0.01 (0.10)	0	**0.01 (0.00, 0.04)**	0.01 (0.10)	0	**0.01 (0.00, 0.04)**
Nurse visits (surgery)	0.14 (0.96)	0.05 (0.36)	**0.09 (-0.08, 0.35)**	0.11 (0.84)	0.08 (0.58)	**0.03 (-0.14, 0.28)**
Nurse (home visit)	0	0	**0**	0	0	**0**
Other professionals attached to GP practice (surgery)	0.35 (0.91)	0.48 (1.31)	**-0.13 (-0.46, 0.17)**	0.52 (1.22)	0.32 (1.04)	**0.20 (-0.13, 0.50)**
[a] Other professionals attached to GP practice (home)	0.04 (0.29)	0.08 (0.80)	**-0.04 (-0.26, 0.08)**	0.13 (0.87)	0	**0.13 (0.02 , 0.38)**
SECONDARY CARE CONTACTS						
Consultant	0.46 (1.04)	0.75 (1.48)	**-0.29 (-0.64, 0.08)**	0.60 (1.27)	0.62 (1.31)	**-0.02 (-0.40, 0.35)**
Physiotherapist [b]	2.79 (3.96)	2.45 (3.78)	**0.34 (-0.67, 1.47)**	4.87 (4.21)	0.45 (1.66)	**4.42 (3.51, 5.35)**
Specialist A&E	0	0.06 (0.42)	**-0.06 (-0.19, -0.01)**	0.04 (0.41)	0.02 (0.14)	**0.02 (-0.04, 0.12)**
Hospital Nurse	0	0.08 (0.34)	**-0.08 (-0.17, -0.03)**	0.02 (0.14)	0.06 (0.31)	**0.04 (-0.12, 0.02)**
Acupuncturist	0	0.01 (0.10)	**-0.01 (-0.03, 0)**	0	0.01 (0.10)	**-0.01 (-0.03, 0)**
[c] Other professionals	0.06 (0.35)	0.06 (0.31)	**0 (-0.08, 0.10)**	0.04 (0.32)	0.08 (0.34)	**-0.04 (-0.13, 0.07)**
Repeat Injections	0.26 (0.72)	0.37 (0.86)	**-0.11 (-0.28, 0.07)**	0.24 (0.77)	0.39 (0.82)	**-0.15 (-0.30, 0.05)**

[a] This includes contacts with professionals such as work nurse sister and consultant [b] Physiotherapy visits that were part of the intervention have been included here [c] Includes contacts with professionals such as work nurse sister, sports therapist, massage masseur and kinesiologist

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Supplementary Table 3: Mean (SD) prescribed drugs and medical investigations per patient over 12 months (complete cases)

	Injection intervention group			Exercise intervention group		
	US-guided (n=95)	**Unguided (n=99)**	**Difference (Confidence Interval)**	**Physiotherapist-led (n=95)**	**Advice and Exercise Leaflet (n=99)**	**Difference (Confidence Interval)**
PRESCRIBED DRUGS						
Paracetamol	0.38 (1.45)	0.52 (2.00)	**-0.14 (-0.62, 0.32)**	0.37 (1.39)	0.53 (2.04)	**-0.16 (-0.72, 0.27)**
Ibuprofen	0.31 (1.38)	0.75 (2.89)	**-0.44 (-1.14, 0.08)**	0.28 (1.29)	0.78 (2.92)	**-0.5 (-1.24, 0.06)**
Co-codamol	0.77 (2.11)	1.19 (2.71)	**-0.42 (-1.13, 0.24)**	1 (2.46)	0.97 (2.43)	**0.03 (-0.64, 0.77)**
Diclofenac	0.04 (0.25)	0.09 (0.81)	**-0.05 (-0.28, 0.06)**	0.01 (0.10)	0.12 (0.84)	**-0.11 (-0.34, -0.001)**
MEDICAL INVESTIGATIONS						
Blood test	0.09 (0.41)	0.26 (0.79)	**-0.17 (-0.04, -0.03)**	0.05 (0.22)	0.30 (0.85)	**-0.25 (-0.46, -0.10)**
X-ray	0.13 (0.39)	0.29 (0.72)	**-0.16 (-0.33, -0.16)**	0.16 (0.55)	0.26 (0.62)	**-0.10 (-0.25, 0.06)**
Ultrasound	0.11 (0.35)	0.33 (0.73)	**-0.22 (0.39, -0.06)**	0.17 (0.54)	0.28 (0.62)	**-0.11 (-0.28, 0.04)**
MRI scan	0.01 (0.10)	0.04 (0.24)	**-0.03 (-0.10, 0.01)**	0.01 (0.10)	0.04 (0.24)	**-0.03 (-0.10, 0.01)**
CT scan	0	0.03 (0.22)	**-0.03 (-0.10, 0)**	0	0.03 (0.22)	**-0.03 (-0.10, 0)**

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Supplementary Table 4: Mean (SD) private resource use per patient over 12 months (complete cases)

	Injection intervention group			Exercise intervention group		
	US-guided (n=95)	Unguided (n=99)	Difference (Confidence Interval)	Physiotherapist-led (n=95)	Advice and Exercise Leaflet (n=99)	Difference (Confidence Interval)
Consultant	0.12 (0.63)	0.05 (0.36)	**0.07 (-0.06, 0.24)**	0.03 (0.33)	0.13 (0.65)	**-0.1 (-0.26, 0.03)**
Physiotherapist	0.11 (0.83)	0.06 (0.42)	**0.05 (-1.1, 0.28)**	0.07 (0.44)	0.09 (0.81)	**-0.02 (-0.26, 0.13)**
Specialist	0.02 (0.21)	0	**0.02 (0, 0.08)**	0	0.02 (0.20)	**-0.02 (-0.10, 0)**
Hospital Nurse	0.01 (0.10)	0.01 (0.10)	**0 (-0.02, 0.03)**	0.01 (0.10)	0.01 (0.10)	**0 (-0.02, 0.04)**
Acupuncturist	0.01 (0.10)	0	**0.01 (0, 0.04)**	0	0.01 (0.10)	**-0.01 (-0.04, 0)**
Osteopath	0.07 (0.72)	0.06 (0.60)	**0.01 (-0.13, 0.27)**	0	0.13 (0.92)	**-0.13 (-0.35, 0)**
Other professionals	0.08 (0.58)	0.06 (0.45)	**0.02 (-0.12, 0.17)**	0.04 (0.41)	0.10 (0.60)	**-0.06 (-0.24, 0.08)**
Over the counter medication	2.86 (5.52)	6.22 (22.15)	**-3.36 (-9.61, -0.09)**	5.24 (21.60)	3.94 (8.78)	**1.30 (-2.08, 7.57)**
Repeat Injection	0.01 (0.11)	0	**0.01 (0, 0.04)**	0	0.01 (0.10)	**-0.01 (-0.04, 0)**
WORK RELATED ITEMS						
Time off work due to shoulder problems (mean days)	3.49 (14.63)	8.70 (44.50)	**-1.68 (-13.44, 6.33)**	5.29 (24.00)	6.97 (40.57)	**-5.21 (-16.73, 1.93)**

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Supplementary Table 5: Cost-utility analysis 'at the margins' approach (with EQ-5D-5L tariff)

	Injection intervention group			Exercise intervention group		
	US-guided (n=128)	**Unguided (n=128)**		**Physiotherapist-led (n=128)**	**Advice & Exercise Leaflet (n=128)**	
	Mean	**Mean**	**Mean difference (Confidence Interval)**	**Mean**	**Mean**	**Mean difference (Confidence Interval)**
HEALTHCARE PERSPECTIVE						
Cost	£428.01	£412.12	£15.89 (-59.36, 109.86)	£498.06	£342.07	£155.99 (69.02, 241.93)
QALYs [a]	0.697	0.667	0.030 (-0.009, 0.070)	0.693	0.671	0.023 (-0.017, 0.062)
ICER	£529.7 per QALY gained			£6,782 per QALY gained		
NHS PERSPECTIVE						
Cost	£398.25	£382.04	£15.85 (-64.32, 90.22)	£476.02	£304.27	£171.75 (98.44, 251.88)
QALYs [a]	0.697	0.667	0.030 (-0.009, 0.070)	0.693	0.671	0.023 (-0.017, 0.062)
ICER	£528.3 per QALY gained			£7,467 per QALY gained		

[a] Adjusted for baseline utility

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Supplementary Table 6: Cost-utility analysis "within the table" analysis (With EQ-5D-5L tariff)

	Cost (£)*	QALY*[a]	ICER
	Health care perspective		
Unguided injection and advice and exercise leaflet (n=64)	385.31 (397.70)	0.652	N/A
Unguided injection and Physiotherapist-led exercise (n=64)	438.92 (332.49)	0.681	£1,848 per QALY gained [b]
Ultrasound-guided injection and advice and exercise leaflet (n=64)	298.82 (281.99)	0.689	Dominates Unguided injection and Physiotherapist-led exercise [c]
Ultrasound-guided injection and Physiotherapist-led exercise (n=64)	557.20 (310.90)	0.705	£16,148 per QALY gained [d]
	NHS perspective		
Unguided injection and advice and exercise leaflet (n=64)	347.87 (385.17)	0.652	N/A
Unguided injection and Physiotherapist-led exercise (n=64)	416.21 (324.81)	0.681	£2,356 per QALY gained [b]
Ultrasound-guided injection and advice and exercise leaflet (n=64)	260.66 (220.67)	0.689	Dominates Unguided injection and Physiotherapist-led exercise [c]

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Ultrasound-guided injection and Physiotherapist-led exercise (n=64)	535.83 (305.61)	0.705	£17,198 per QALY gained [d]

*Cost and QALYs imputed [a] Adjusted for baseline utility [b] Unguided injection and Physiotherapist-led exercise versus Unguided injection and advice and exercise leaflet [c] Ultrasound-guided injection and advice and exercise leaflet versus Unguided injection and Physiotherapist-led exercise [d] Ultrasound-guided injection and Physiotherapist-led exercise versus Ultrasound-guided injection and advice and exercise leaflet

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