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Corbacho Martín, Belén orcid.org/0000-0002-2359-0379, Brealey, Stephen Derek orcid.org/0000-0001-9749-7014, Keding, Ada orcid.org/0000-0002-1182-887X et al. (5 more authors) (2021) Cost-effectiveness of surgical treatments compared with early structured physiotherapy in secondary care for adults with primary frozen shoulder: economic evaluation of UK FROST trial. Bone & Joint Open. pp. 685-695. ISSN 2633-1462

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SHOULDER & ELBOW

Cost-effectiveness of surgical treatments compared with early structured physiotherapy in secondary care for adults with primary frozen shoulder

AN ECONOMIC EVALUATION OF THE UK FROST TRIAL

B. Corbacho,
S. Brealey,
A. Keding,
G. Richardson,
D. Torgerson,
C. Hewitt,
C. McDaid,
A. Rangan,
On behalf of the UK FROST trial team

From University of York, York, UK

Aims

A pragmatic multicentre randomized controlled trial, UK FROzen Shoulder Trial (UK FROST), was conducted in the UK NHS comparing the cost-effectiveness of commonly used treatments for adults with primary frozen shoulder in secondary care.

Methods

A cost utility analysis from the NHS perspective was performed. Differences between manipulation under anaesthesia (MUA), arthroscopic capsular release (ACR), and early structured physiotherapy plus steroid injection (ESP) in costs (2018 GBP price base) and quality adjusted life years (QALYs) at one year were used to estimate the cost-effectiveness of the treatments using regression methods.

Results

ACR was £1,734 more costly than ESP ((95% confidence intervals (CIs) £1,529 to £1,938)) and £1,457 more costly than MUA (95% CI £1,283 to £1,632). MUA was £276 (95% CI £66 to £487) more expensive than ESP. Overall, ACR had worse QALYs compared with MUA (-0.0293; 95% CI -0.0616 to 0.0030) and MUA had better QALYs compared with ESP (0.0396; 95% CI -0.0008 to 0.0800). At a £20,000 per QALY willingness-to-pay threshold, MUA had the highest probability of being cost-effective (0.8632) then ESP (0.1366) and ACR (0.0002). The results were robust to sensitivity analyses.

Conclusion

While ESP was less costly, MUA was the most cost-effective option. ACR was not cost-effective.

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Keywords: Cost-effectiveness analysis, Frozen shoulder, Physiotherapy

Introduction

Adhesive capsulitis or frozen shoulder is a common disorder affecting 8.2% of men and 10.1% of women of working age,[1] with an estimated cumulative incidence of 2.4 per 1,000 population per year.[2] The capsule of the shoulder joint becomes inflamed, then scarred and contracted, causing pain, stiffness, and loss of function.[3]

A range of treatment options of varying effectiveness and costs are available for the management of frozen shoulder in secondary care.[4] A survey of specialist health professionals conducted in the UK in 2009 identified three interventions as being most commonly used: physiotherapy; manipulation under anaesthesia; and arthroscopic capsular release.[5] The UK national physiotherapy guidelines for frozen shoulder recommend exercise and manual therapy either in isolation, or to supplement with an intra-articular steroid injection.[6] Both manipulation under anaesthesia and capsular release are expected to facilitate quicker recovery, but are costly and invasive, and there is a lack of rigorous evidence.[7-9]

Correspondence should be sent to Belen Corbacho; email: belen.corbacho@york.ac.uk

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The UK FROzen Shoulder Trial (UK FROST) was conducted to provide evidence of clinical effectiveness and cost-effectiveness of manipulation under anaesthesia (MUA), arthroscopic capsular release (ACR), and a specific non-surgical pathway designed for the trial to include intra-articular steroid injection and structured physiotherapy using the best available evidence and consensus from expert shoulder physiotherapists.[6,7,10] We have called this 'Early' Structured Physiotherapy (ESP) as it is more quickly accessible than the surgery interventions and the similarly developed pathway of post-procedural physiotherapy that followed surgery. Therefore, specifically for the purposes of the trial, participants underwent standardized physiotherapy programmes in all three groups as described in detail elsewhere, ESP in the non-surgical group, and post-procedural physiotherapy in the two surgical groups.[11]

The clinical effectiveness results of UK FROST have been reported.[12] In summary, we sought a target difference of five points on the Oxford Shoulder Score (OSS)[13] between early structured physiotherapy (ESP) and either surgical treatment, or a difference of four points between the two surgical treatments. Mean group differences on the OSS at one year were 2.01 points between participants randomized to capsular release and MUA (95% confidence interval (CI) 0.10 to 3.91), 3.06 points between capsular release and ESP (95% CI 0.71 to 5.41), and 1.05 points between MUA and ESP (95% CI -1.28 to 3.39). All of the mean differences on the assessment of shoulder pain and function (OSS) at the primary endpoint of one year were less than the target differences. Therefore, none of the three interventions were considered to be clinically superior.

To inform decision-making, it is important to identify the cost-effective intervention for the treatment of frozen shoulder in secondary care. This paper reports on the economic evaluation conducted alongside the UK FROST trial, which aimed to assess the health-related quality of life, costs and cost-effectiveness of surgical treatments (MUA and capsular release followed by post-procedural physiotherapy) versus non-surgical treatment (ESP) for the management of adults with frozen shoulder within the NHS.

Methods

Overview. Individual patient data (IPD) collected alongside the UK FROST trial were used to perform a cost utility analysis. Costs and health benefits were compared for the three groups over one year, and hence discounting was not required. Costs (2018 price base) were evaluated from the UK NHS and Personal Social Services perspective. Health benefits were expressed in terms of quality-adjusted life years (QALYs), based on patient's health-related quality of life using the EuroQol five-dimension five-level questionnaire (EQ-5D-5L).[14,15] Adjusted differences in mean costs and mean QALYs at one year were used to estimate the cost-effectiveness of the three treatment options. The base-case analysis was conducted on the multiple imputed dataset and followed an intention-to-treat (ITT) approach; thus the treatment groups were compared based on their initial random allocation irrespective of protocol deviations or withdrawal. The National Institute for Health and Clinical Excellence (NICE) guidelines were applied to all methods used for this economic analysis.[16] All analyses and modelling were conducted in StataTM 16 (StataCorp LP, College Station, Texas, USA).

Trial design, interventions, and economic data collection. UK FROST recruited 503 adults with a clinical diagnosis of frozen shoulder from 35 hospital sites in the UK between April 2015 and December 2017. Detailed inclusion and exclusion criteria are published elsewhere.[17] Patients were randomized on a 2:2:1 basis to manipulation under anaesthesia with steroid injection (n = 201), arthroscopic capsular release (n = 203), or ESP with steroid injection (n = 99).

For the purposes of the trial, physiotherapy programmes were standardized in all three groups using the best available evidence and consensus of expert shoulder physiotherapists.[6,7,10,11] Physiotherapy in all three groups was to be up to 12 sessions unless, exceptionally, the physiotherapist decided that more than 12 sessions were needed. Patients were also offered an intra-articular steroid (glucocorticoid) injection at the earliest opportunity in the ESP pathway. The injection was administered with or without imaging guidance depending on usual practice of the hospital site, as current evidence did not support superiority of either approach.[18] We did not anticipate that a steroid injection was normally given as part of post-procedural physiotherapy that followed the two surgical interventions. All participants were provided with instructions on a graduated home exercise programme progressing from gentle pendular exercises to firm stretching exercises according to stage, as is accepted good practice.[6,11] The development of the standardized physiotherapy programmes for UK FROST are described in detail elsewhere.[11]

MUA and capsular release were performed as day case surgical procedures. With MUA, the surgeon manipulated the affected shoulder in a controlled fashion to stretch and tear the tight capsule when the patient was under general anaesthesia; and that was supplemented by an intra-articular steroid injection. If the manipulation was judged to be incomplete, the surgeons were asked not to cross over intraoperatively to do capsular release in order to allow assessment of the outcome of the manipulation. ACR was performed under general anaesthesia to surgically divide the contracted anterior capsule in the rotator interval, and that was supplemented with manipulation to complete and confirm optimal capsular

Table I. Unit costs used for the analysis (£, 2018 prices).[19]

Item	Unit cost (£)	Source
Primary and community care		
GP visit at GP practice	37	PSSRU 2018[24]
GP visit at home	94	PSSRU 2018[24]
GP by phone*	15	PSSRU 2018[24]
Nurse visit at GP practice	11	PSSRU 2018[24]
District/community nurse	38	PSSRU 2018[24]
Occupational therapist visit	47	PSSRU 2018[24]
Physiotherapist visit†	57	PSSRU 2018[26]
Hospital care		
Inpatient stay (shoulder)‡	258 (MUA) 449 (ACR)	NHS Reference Costs 2017 to 2018[26]
Inpatient stay (non-shoulder)	384	NHS Reference Costs 2017 to 2018[26]
Day case visit (shoulder)‡	420 (MUA) 2,512 (ACR)	NHS Reference Costs 2017 to 2018[26]
Outpatient visits (shoulder)	125	NHS Reference Costs 2017 to 2018[26]
Outpatient visits (non-shoulder)	124	NHS Reference Costs 2017 to 2018[26]
Hospital physiotherapy visit	55	NHS Reference Costs 2017 to 2018[26]
Other health service visit	74	NHS Reference Costs 2017 to 2018[26]
Consultant surgical	108	PSSRU 2018[24]
Associate specialist	105	PSSRU 2018[24]
Speciality registrar	43	PSSRU 2018[24]
Foundation doctor FY1	32	PSSRU 2018[24]
Foundation doctor FY2	28	PSSRU 2018[24]
Physiotherapist B5	35	PSSRU 2018[24]
Physiotherapist B6	46	PSSRU 2018[24]
Physiotherapist B7	55	PSSRU 2018[24]
Physiotherapist above B8§	72	PSSRU 2018[24]
Nurse B5	37	PSSRU 2018[24]
Nurse B6	45	PSSRU 2018[24]
Nurse B7	54	PSSRU 2018[24]
Medications		
Depomedrone 40 mg	3	BNF[25]
Depomedrone 80 mg	7	BNF[25]
Triamcinolone 40 mg	18	BNF[25]
Triamcinolone 80 mg	36	BNF[25]
Bupivacaine 0.5% (10 ml)	1	BNF[25]
General anaesthesia	31	BNF[25]
Antibiotics	6	BNF[25]
Private care		
Private non-NHS physiotherapy	50	https://www.capitalphysio.com
Private osteopath	42	https://www.nhs.uk/conditions/osteopathy
Private chiropractitioner	55	https://www.nhs.uk/conditions/chiropractic
Community care service	49	Averaged of three above
Private hospital - night	337	PSSRU 2018[23]

*Durations sourced from Personal Social Research Unit (PSSRU) 2015.
†Community Health Services, Physiotherapist, adult, one to one (currency code A08A1).
‡Sum of total expenditure on excess bed days (elective and non-elective) divided by total activity for HRG codes relating to shoulder: MUA (HD24E; non inflammatory, bone or joint disorders, with CC score 8 to 11)); ACR (HN53A, HN53B, HN53C, HN54A, HN54B, HN54C; major and intermediate procedures for non-trauma with CC score 4+, 2 to 3, and 0 to 1).
§Post procedural physiotherapy form is featured to record staff at or above Band 8. Hence unit cost for physio at or above Band is estimated as averaged Band 8a (£66) and Band 8b (£78).
ARC, arthroscopic capsular release; MUA, manipulation under anaesthesia.

release. Procedures like posterior capsular release were permitted at the discretion of the operating surgeon and were recorded.

All interventions were delivered either by participating surgeons who were familiar with the surgical procedures or by qualified physiotherapists (i.e. not students or

Table II. Average primary and community resource use (shoulder-related) and lost days off work per treatment group.[19]

	MUA (n = 201)				ACR (n = 203)				ESP (n = 99)			
Resource type	**n**	**Mean (SD)**	**Median**	**Missing (%)**	**n**	**Mean (SD)**	**Median**	**Missing (%)**	**n**	**Mean (SD)**	**Median**	**Missing (%)**
GP surgery total	137	1.61 (3.04)	0	64 (31.8)	138	1.73 (3.23)	0	65 (32.0)	62	0.90 (1.89)	0	37 (37.4)
3 mths	168	0.82 (1.64)	0	33 (16.42)	171	1.05 (1.97)	0	32 (15.76)	84	0.58 (1.44)	0	15 (15.15)
6 mths	162	0.30 (1.25)	0	39 (19.40)	163	0.49 (1.60)	0	40 (19.70)	76	0.35 (0.89)	0	23 (23.23)
12 mths	169	0.34 (1.20)	0	64.(31.84)	162	0.24 (0.76)	0	65 (32.02)	80	0.25 (0.88)	0	37 (37.37)
GP telephone total	136	0.54 (2.05)	0	65 (32.3)	134	0.44 (1.1)	0	69 (33.9)	61	0.10 (0.47)	0	38 (38.4)
3 mths	168	0.28 (1.24)	0	3 (16.42)	165	0.32 (0.99)	0	28 (18.72)	82	0.06 (0.33)	0	17 (17.17)
6 mths	162	0.16 (1.13)	0	39 (19.40)	161	0.09 (0.41)	0	42 (20.69)	74	0.03 (0.16)	0	25 (25.25)
12 mths	168	0.05 (0.17)	0	33 (16.42)	162	0.03 (0.22)	0	41 (20.20)	83	0.01 (0.011)	0	16 (16.16)
Physiotherapist	135	0.83 (2.8)	0	66 (32.8)	136	1.25 (3.8)	0	67 (33.0)	64	1.17 (4.0)	0	35 (35.3)
3 mths	167	0.66 (2.26)	0	34 (16.92)	167	0.64 (2.95)	0	36 (17.73)	83	0.42 (1.72)	0	16 (16.16)
6 mths	161	0.14 (0.79)	0	40 (19.90)	161	0.31 (1.24)	0	42 (20.69)	77	0.49 (2.25)	0	22 (22.22)
12 mths	170	0.71 (0.92)	0	31 (15.42)	162	0.31 (1.32)	0	41 (20.20)	83	0.24 (0.22)	0	16 (16.16)
Nurse surgery	132	0.07 (0.3)	0	69 (34.3)	129	0.39 (0.8)	0	74 (36.4)	59	0.05 (0.3)	0	40 (40.4)
3 mths	166	0.2 (0.15)	0	35 (17.41)	165	0.34 (1.09)	0	38 (18.72)	79	0.05 (0.32)	0	20 (20.20)
6 mths	160	0.01 (0.08)	0	41 (20.40)	156	0.08 (0.30)	0	47 (23.15)	75	0.04 (0.26)	0	24 (24.24)
12 mths	165	0.05 (0.29)	0	36 (17.91)	160	0.02 (0.14)	0	43 (21.18)	79	0 (0)	0	20 (20.20)
Community nurse	135	0 (0)	0	66 (32.8)	136	0.12 (0.9)	0	67 (33.0)	62	0 (0)	0	37 (37.4)
3 mths	168	0 (0)	0	33 (16.42)	168	0.07 (0.51)	0	35 (17.24)	83	0 (0)	0	16 (16.16)
6 mths	160	0 (0)	0	41 (20.40)	161	0.07 (0.79)	0	42 (20.69)	75	0 (0)	0	24 (24.24)
12 mths	170	0.01 (0.15)	0	31 (15.42)	161	0 (0)	0	42 (20.69)	82	0 (0)	0	17 (17.17)
Occupational therapy	137	0.09 (0.7)	0	64 (31.8)	137	0.06 (0.7)	0	66 (32.5)	63	0 (0)	0	36 (36.4)
3 mths	168	0.03 (0.46)	0	33 (16.42)	167	0 (0)	0	36 (17.73)	83	0 (0)	0	16 (16.16)
6 mths	161	0 (0)	0	40 (19.90)	162	0.01 (0.08)	0	41 (20.20)	76	0 (0)	0	23 (23.23)
12 mths	171	0.05 (0.48)	0	32 (15.92)	162	0.05 (0.63)	0	41 (20.20)	82	0 (0)	0	19 (19.19)
Lost days off work	105	17.5 (26.4)	6	96 (47.8)	92	32.8 (44.2)	14	111 (54.)	34	11.5 (27.8)	0	65 (65.6)
3 mths	138	12.5 (22.0)	2	63 (31.34)	125	13.3 (23.6)	0	78 (38.42)	61	7.2 (20.6)	0	38 (38.38)
6 mths	132	3.5 (10.5)	0	69 (34.32)	125	10.9 (23.2)	0	78 (38.42)	50	5.2 (18.8)	0	49 (49.49)
12 mths	138	2.8 (13.3)	0	63 (31.34)	129	3.1 (13.1)	0	74 (36.45)	57	3.9 (13.1)	0	42 (42.42)

ACR, arthroscopic capsular release; ESP, early structured physiotherapy; MUA, maipulation under anaesthesia; SD, standard deviation.

assistants). There was no minimum number of surgical procedures that the surgeon had to have performed and no grades of surgeon were excluded. No additional training was required for either programme of physiotherapy. However, a standardized booklet was used to record the physiotherapy that participants received in all three trial arms, which provided instructions for delivering the ESP or post-procedural physiotherapy pathways.

NHS ethical approval was obtained on 18 November 2014 from the National Research Ethics Service (NRES Committee North East – Newcastle & North Tyneside 2; Research Ethics Committee Reference 14/NE/1176). Local site-specific NHS research and development approvals were obtained from each participating site. The study was adopted to the UK Clinical Research Network portfolio (17719). Written informed consent was obtained from all trial participants by suitably qualified local study personnel at each participating site.

As detailed in the trial protocol,[17] cost and health outcome data were collected prospectively via patient questionnaires at three months, six months, and one year; and via hospital forms (baseline characteristics, details of surgery, physiotherapy, complications, and hospital care due to additional and further treatments received before/during/after completing randomized treatment). Copies of these forms will be included in the Supplementary Material published alongside the NIHR Health Technology Assessment report.[19]

Health outcomes and quality adjusted life years. The main outcome measure for the economic analysis was QALYs based on the EQ-5D-5L questionnaire. The EQ-5D has been validated for a range of shoulder conditions.[20,21] The EQ-5D-5L was completed by trial participants at baseline, three and six months, and one year. The EQ-5D-5L defines health-related quality of life in terms of five dimensions: 'mobility', 'self-care', 'usual activities', 'pain/discomfort', and 'anxiety/depression'. Responses in each dimension are divided into five ordinal levels coded 1) no problems, 2) slight problems, 3) moderate problems, 4) severe problems, and 5) extreme problems/unable to perform. We used the Van Hout et al[22] 2012 mapping function to derive utilities. QALYs were calculated by combining the utility estimates by the duration of time in each health state using the area under the curve (AUC) method.[23] The difference in mean QALYs between treatments groups was adjusted for baseline utility.[24]

Table III. Costs for cases with complete data by trial allocation and cost category (£, 2018 to 2019 prices) related to the shoulder.[19]

Costs	MUA Mean, £ (SE)	ACR Mean, £ (SE)	ESP Mean, £ (SE)
MUA surgical procedure	349 (192)	5 (56)	0
ACR surgical procedure	0	1,762 (935)	113 (496)
ESP	7 (59)	1 (13)	260 (155)
Physiotherapy hospital setting (i.e. PPP)	176 (164)	175 (162)	7 (36)
Physiotherapy community setting	44 (146)	66 (202)	62 (211)
Further treatments	60 (248	18 (67)	104 (290)
Hospital inpatient care	43 (361)	34 (334)	9 (48)
Hospital outpatient care	19 (84)	12 (61)	34 (113)
GP at surgery	60 (114)	65 (121)	34 (71)
GP on the phone	8 (31)	7 (17)	1 (7)
Nurse at surgery	1 (3)	4 (9)	0.5 (3)
Community nurse	0 (0)	5 (34)	0 (0)
Occupational therapist	4 (34)	3 (32)	0 (0)
Total NHS shoulder costs (a)	834 (753)	2,271 (902)	599 (359)
Total NHS non-shoulder costs – (b)	182 (229)	196 (304)	242 (366)
Productivity costs – (c)	1,995 (2,999)	3,736 (5,031)	1,309 (3,165)
Private care costs – (d)	31 (118)	21 (111)	40 (144)
Total broader costs (a + b + c + d)	3,201 (3,824)	5,377 (4,240)	1,475 (2,368)

ACR, arthroscopic capsular release; ESP, early structured physiotherapy; GP, general practitioner; MUA, manipulation under anaesthesia; PPP, post procedural physiotherapy; SE, standard error.

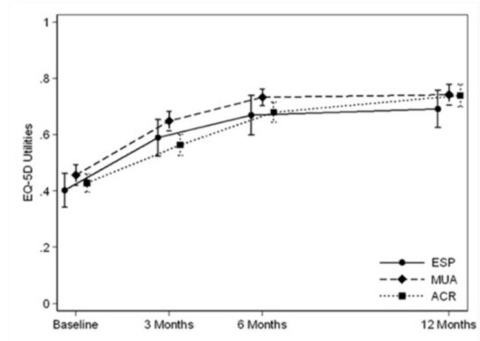

Fig. 1

EuroQol five-dimension five-level (EQ-5D-5L) scores distribution at the different time points over the 12 months. ACR, arthroscopic capsular release; ESP, early structured physiotherapy; MUA, manipulation under anaesthesia.

Resource use and costs. The cost for each trial participant was calculated by multiplying health care resource use by the associated unit costs. Total cost comprises the cost of the initial intervention; hospital stays and outpatient appointments after initial intervention, including physiotherapy; and visits to primary and community health care professionals over one year. Costs relating to the surgical interventions was based on operation times, staff, consumables, and length of stay. The hospital-based staff cost per minute was estimated using PSSRU 2018 (Personal Social Services Research Unit) data.[25] These unit cost estimates included staff salaries, salary on-costs, overheads, and capital overheads. Drug tariff per milligram for medications (i.e. anaesthesia, antibiotics, and steroid injections) were obtained from the British National Formulary.[26] To cost length of stay we used NHS Reference costs,[27] taking the weighted mean inpatient bed day for all major and intermediate shoulder procedures. Physiotherapy data (i.e. session duration and staff delivering the session) was collected using physiotherapy forms designed for the trial. Physiotherapists cost per hour was estimated using PSSRU 2018 (Bands 5 to 8). The cost of other hospital-based care and for the primary care and community-based services were estimated by applying unit costs from national tariffs to resource volumes. Other costs included lost productivity measured as number of days off work. The costs of time taken off work were estimated by applying costs from the Office National Statistics (ONS)[28] to occupational information derived from self-reported work status information. Table I presents the unit costs used to calculate the total cost per patient in the trial. The base-case analysis included only shoulder-related resource use, except for hospital stay, which included both shoulder and general medical complications that could apply to the affected shoulder.

Handling missing data. We have previously reported details of the approach applied to handle missing data,[19,29] and we have used the same methods in this study, as described below. Complete case analysis (CCA) excludes all participants with any missing or incomplete data. Excluding patients with missing data leads to loss of statistical power and can bias the results.[30] Multiple imputation (MI) has been recommended as the appropriate method to reflect the uncertainty in the results of an economic evaluation attributable to missing data.[31] Multiple imputation assumes that data are missing at random (MAR), i.e. that the probability that data are unobserved is dependent only on observed variables.[32] We conducted a comprehensive investigation following missing data guidelines,[30,33,34] to prove that MAR was a plausible assumption fitting UK FROST dataset. Thus, incomplete data on costs and QALYs were imputed using multiple imputation with chain equations and predictive mean matching over 60 imputations. Age, sex, baseline OSS score, diabetes (yes/no) at baseline, baseline utility, and all predictors of missingness were included as an explanatory variable in the imputation models. Mean estimates of costs and QALYs, variances, and CI were obtained using Rubin's rules.[35] The MI model was validated using graphical plots to visualize whether the distribution of imputed data resembles the distribution of original data. We explored possible departures from the MAR assumption by means of sensitivity analyses, including complete case analysis. Additionally, a mixed model, which does

Table IV. Adjusted mean differences in costs and quality-adjusted life years between interventions (base case).[19]

Variable	**Adjusted difference in means with SUREG (95% CI)**			
Difference in costs (£)				
MUA vs ESP	276.51 (65.67 to 487.35)			
ACR vs ESP	1,733.78 (1,529.48 to 1,938.06)			
ACR vs MUA	1,457.26 (1,282.73 to 1,631.79)			
Difference in QALYs				
MUA vs ESP	0.0396	(-0.0008 to 0.0800)		
ACR vs ESP	0.0103	(-0.0304 to 0.0510)		
ACR vs MUA	-0.0293	(-0.0616 to 0.0030)		
	ICER (£ per QALY)*	**Probability cost-effective at £13,000/QALY**	**Probability cost-effective at £20,000/QALY**	**Probability cost-effective at £30,000/QALY**
MUA	6,984	0.7942	0.8632	0.8978
ACR	> 100,000	0.0000	0.0002	0.002
ESP	N/A	0.2058	0.1366	0.1002

*Compared with ESP, as it is the alternative with lower costs and health outcomes
ACR, arthroscopic capsular release; CI, confidence interval; ESP, early structured physiotherapy; ICER, incremental cost-effectiveness ratio; MUA, manipulation under anaesthesia; N/A, not applicable; QALY, quality-adjusted life year; SUREG, seemingly unrelated regression.

not require an imputation process, is also presented as per the sensitivity analysis.

Base case analysis. The base case analysis was conducted on the imputed dataset on an ITT basis. Cost-effectiveness was estimated as the difference in mean costs divided by the difference in mean QALYs between the trial comparators at twelve months follow-up, using conventional decision rules and estimating ICERs as appropriate.[36] The mean difference estimates and their 95% CIs were generated by means of seemingly unrelated regression (SUREG) adjusted for age, sex, baseline EQ-5D-5L score, baseline OSS score, and diabetes (yes/no). In order to compute the probability of each intervention being cost-effective at a given cost-effective threshold, the SUREG was conducted with a bootstrapping approach on five imputed datasets to generate 10,000 replicates of incremental costs and benefits. These replicates were represented graphically as cost-effectiveness acceptability curves (CEACs). The probability that each intervention is cost-effective is reported at the cost-effectiveness thresholds applied by NICE of £20,000 to £30,000/QALY,[15] and a threshold of £13,000/QALY as suggested by recent research.[37,38] The ICER was re-expressed in terms of net monetary benefit (NMB) as an estimate of the gain (or loss) in resources of investing in the intervention when those resources might be used somewhere else.

Analyses of uncertainty. The uncertainty around the cost-effectiveness results was explored using sensitivity analyses, all of which controlled for the same covariates: (Scenario 1) recalculating costs including non-shoulder costs (ITT approach); (Scenario 2) adopting a broader perspective that includes productivity and private care costs; (Scenario 3) restricting the analyses to complete cases (ITT approach); (Scenario 4) imputing QALY data at aggregated level rather than at the index-score level; (Scenario 5) mix model approach; and (Scenario 6) missing not at random scenario, which allocated higher costs or worse health outcomes to patients with missing data.

Results

Study population and missing data. The baseline study population for the economic analysis was 503 patients: ESP (n = 99), MUA (n = 201), and capsular release (n = 203). A total of 19 participants fully withdrew from the trial, for whom we used multiple imputation techniques to impute missing economic data. There were 16 participants who crossed over from their initial randomization, i.e. from ESP to capsular release (n = 7), from MUA to ESP (n = 4), from capsular release to ESP (n = 2), and from capsular release to MUA (n = 3). A total of 369 (73%) participants (156 (78%) in manipulation, 149 (73%) in capsular release, and 64 (65%) in ESP) comprised the complete case for utilities, i.e. data for all five EQ-5D-5L dimensions were available for all four assessment timepoints. Overall, the proportion of participants with complete economic data (i.e. both costs and QALYs) were similar between treatment groups: ESP (46.46%), MUA (58.21%), and capsular release (57.14%) (see Supplementary Table i).

A description of economic variables in UK FROST and figures representing the distribution of economic data before and after the imputation can be found in Supplementary Table ii and Supplementary Figure a). Missing data were non-monotonic, since in all groups, individuals with missing data at one follow-up point may provide data subsequently (i.e. more individuals are observed at year one than in month 6). The results of logistic

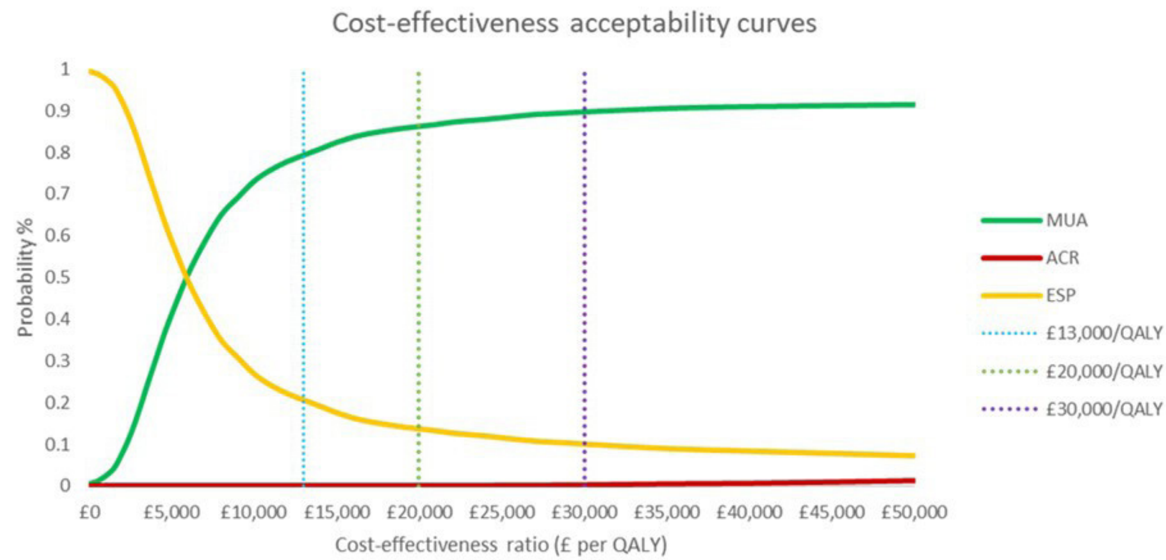

Fig. 2

Base case cost-effectiveness acceptability curves. ACR, arthroscopic capsular release; ESP, early structured physiotherapy; MUA, manipulation under anaesthesia; QALY, quality-adjusted life year.

regression analysis (see Supplementary Table iii) showed that participants with lower EQ-5D-5L at baseline were significantly more likely to have missing data on costs (OR 0.28; 95% CI 0.14 to 0.57) and QALYs (OR 0.31; 95% CI 0.14 to 0.67). Baseline age predicted missing data on quality of life (OR 0.95; 95% CI 0.93 to 0.98); sex and diabetes were associated with missingness but not statistically significant ($p = 0.05$, logistic regression). Regarding the association between missingness and the observed outcomes, missing QALYs at one year were significantly associated with QALYs at three months (OR 0.00; 95% CI 0.00 to 0.50); while missing costs at one year were significantly associated with QALYS at three months (OR 0.003; 95% CI 0.00 to 0.09) and QALYs at six months (OR 0.007; 95% CI 0.00 to 0.306).

Healthcare resource use and costs. The mean cost of MUA was £425 (standard deviation (SD) 115). For 97% (163 of 168) of the cases manipulation was delivered as a day case, only 3% (5 of 168) of the cases required hospitalization (only one night); the mean duration of the manipulation was 25.11 minutes (SD 14.20). The mean cost of arthroscopic capsular release was £2,170 (SD 431). For 90% (153/170) of the cases it was delivered as a day case; 10% (17/170) of the cases required hospitalization for on average 2.8 nights (median = 1; min = 1; max = 31) in hospital; and the mean duration of the intervention was 76.61 minutes (SD 24.22). A total of 160 (80%) participants allocated to MUA and 159 (78%) allocated to capsular release received post-procedural physiotherapy. The mean (SD/max) number of sessions was similar for both groups (MUA: 6.42 (4.95/18) vs capsular release: 6.65 (4.81/18)). The mean (SD) cost of post procedural physiotherapy was £214 (157) for MUA compared with £209 (153) for capsular release. A total of 162 (97%) patients who had MUA received an injection compared with 46 (27%) who received capsular release. The mean cost of ESP was £260 (155) (i.e. mean cost of physiotherapy was £217 (SD 147); mean cost of a steroid injection was £43 (SD 32)). A total of 85 (86%) patients who had ESP received an injection as part of their treatment. The mean (SD) number of sessions received in the ESP pathway was 8.28 (3.45), with a maximum of 15 sessions and a minimum of two.

Resource use related to primary and community care was slightly higher for the capsular release group, although differences between the groups appeared small (Table II). Over the entire follow-up period, a higher proportion of participants in the capsular release group had more days lost off work. Inpatient hospital costs related to complications after initial treatment up to one year was greater for the manipulation group. However, participants who received ESP were more likely to need further treatment following their index intervention and accumulated greater outpatient costs after discharge. Participants in the capsular release group received fewest further treatments, however, they accumulated greater total costs over the trial follow-up; as expected, costs of the surgery were the major cost driver for this group (Table III). Participants waited a median of 14 days for ESP, a median of 56.5 days for MUA, and a median of 71.5 days for capsular release.[11] The longer waiting times were reflected in the actual days off work and increased productivity costs, which were greater for the capsular release arm. Private costs were similar among the three arms. It should be noted that total cost estimates shown in Table III are unadjusted means, and relate to complete

Table V. Sensitivity analysis (Scenario 1 and Scenario 2): summary for incremental analysis, cost-effectiveness results, and uncertainty under different costs scenarios.[19]

Approach	MI of costs (shoulder – NHS perspective) and QALYs analysis with SUREG base case analysis	MI of costs (shoulder and non-shoulder – NHS perspective) and QALYs analysis with SUREG SA (Scenario 1)	MI of costs (broader perspective) and QALYs analysis with SUREG SA (Scenario 2)
MUA vs ESP			
Mean difference in costs, £ (SE; 95% CI)	276 (107; 66 to 487)	163 (113; -58 to 384)	1,032 (595; -137 to 2,201)
Mean difference in QALYs (SE; 95% CI)	0.039 (0.0206; -0.001 to 0.080)	0.0375 (0.0207; -0.0032 to 0.0782)	0.0375 (0.0207; -0.0032 to 0.0781)
ICER	6,984	4,336	27,522
ACR vs ESP			
Mean difference in costs, £ (SE; 95% CI)	1,734 (104; 1,529 to 1,938)	1,555 (112; 1,335 to 1,775)	4,110 (648; 2,836.20 to 5,383.73)
Mean difference in QALYs (SE; 95% CI)	0.0103 (0.0207555; -0.0304 to 0.0510)	0.0080 (0.0208; -0.0328 to 0.0488)	0.0081 (0.0208; -0.0327 to 0.0488)
ICER	168,613	194,895	507,707
ACR vs MUA			
Mean difference in costs, £ (SE; 95% CI)	1,457 (89; 1,282.73 to 1,631.79)	1,393 (91; 1,213 to 1,572)	3,078 (548; 1,999 to 4,157)
Mean difference in QALYs (SE; 95% CI)	-0.0293 (0.0164678; -0.0616 to 0.0030)	-0.0296 (0.0165; -0.0619 to 0.0028)	-0.0294 (0.0165; -0.0618 to 0.0030)
ICER	ACR dominated by MUA	ACR dominated by MUA	ACR dominated by MUA

ACR, arthroscopic capsular release; CI, confidence interval; ESP, early structured physiotherapy; ICER, incremental cost-effectiveness ratio; MUA, manipulation under anaesthesia; QALY, quality-adjusted life year; SE, standard error; SUREG, seemingly unrelated regression.

cases, therefore there is limited value in interpreting differences between treatments. Mean differences for each surgical treatment versus ESP and corresponding 95% CIs, adjusted for patient covariates, and taking into consideration the correlation between costs and QALYs, are shown in Table IV (i.e. cost-effectiveness results).

Health outcomes and quality-adjusted life years. The overall distribution of the EQ-5D scores (utilities) for the different follow-up assessments is illustrated in Figure 1. Patients allocated to MUA started from a higher utility value compared to the other groups (manipulation (mean 0.456) vs capsular release (mean 0.428) vs ESP (mean 0.402)). Patients allocated to the surgical groups had similar utility values (adjusted for baseline utility) at 12 months' follow-up (capsular release (mean 0.739) vs MUA (mean 0.734)); both MUA and capsular release had better utility values compared to ESP at 12 months (mean 0.693). QALYs estimates at one year, when controlling for baseline utility (for available cases), show that patients allocated to MUA accrued more QALYs than the other two groups: MUA (0.6765) > ESP (0.6492) > capsular release (0.6475).

Cost-effectiveness analysis. The incremental analysis for the base case is summarized in Table IV. Compared to ESP, MUA cost a mean of £276 more per patient (95% CI £66 to £487) and marginally improved health outcomes over the 12 months (a mean 0.0396 more QALYs per participant than structured physiotherapy (95% CI -0.0008 to 0.0800)). The resulting incremental cost-effectiveness ratio (ICER) for MUA was £6,984 per additional QALY when compared to ESP. ACR is considerably more costly than ESP (on average £1,734 more expensive per participant (95% CI (£1,529 to £1,938)); and despite the QALY gained by capsular release participants (on average 0.0396 more QALYs per participant than physiotherapy (95% CI -0.0008 to 0.0800)) this was not sufficient to support capsular release as being a cost-effective use of NHS resources when compared with ESP. Similarly, capsular release is dominated by MUA, with higher mean costs and lower QALYs. As illustrated by the CEAC in Figure 2, at a £20,000 per QALY threshold the probability of MUA being cost-effective was high (86%) compared with ESP (13%) and capsular release (0%).

Sensitivity analysis. Table V shows that the base case analysis results were robust to including non-shoulder costs, with MUA continuing to be a cost-effective use of NHS resources. In contrast, cost-effectiveness results were sensitive to a broader perspective scenario, suggesting the ICER from a wider perspective was higher than the thresholds that NICE normally considered for reimbursement decisions. Capsular release continued to be dominated by MUA in both costs' scenarios. Given that capsular release was dominated in all scenarios, sensitivity analyses around missing data were restricted to the comparison of MUA compared with ESP (Table VI). Both multiple imputation and the mixed model agree that MUA is the cost-effective alternative, although mean difference in costs and QALYs changed according to the method. The mixed

Table VI. Sensitivity analysis (Scenario 3, Scenario 4, and Scenario 5): summary for incremental analysis, cost-effectiveness results, and uncertainty under different missing data assumptions.[19]

Variable	Complete case analysis with SUREG (Scenario 3)	MI of costs and utilities followed by SUREG (Scenario 4)	Mixed model with adjustment for covariates (Scenario 5)
Mean difference in costs, £ (SE; 95% CI)	339 (136; 72 to 606)	193 (107; -14 to 399)	256 (129; 2 to 509)
Mean difference in QALYs (SE; 95% CI)	0.016 (0.026; -0.034 to 0.066)	0.0357 (0.020; -0.004 to 0.076)	0.030 (0.022; -0.014 to 0.073)
ICER	21,443	5,395	8,562
Probability that MUA is cost-effective	0.48	0.89	0.76

CI, confidence interval; ICER, incremental cost-effectiveness ratio; MUA, manipulation under anaesthesia; QALY, quality-adjusted life year; SE, standard error; SUREG, seemingly unrelated regression.

model has slightly larger standard errors than MI in both the incremental costs and QALYs, possibly because of the large number of parameters to estimate compared with the analysis model post-imputation. Finally, increasing costs or decreasing QALYs (scenario 6) in both patient groups make little difference to results (see Appendix, table D). MUA remains the intervention most likely to be cost-effective even if its imputed QALYS are reduced by 10% or its cost is increased by 50%.

Discussion

Main findings. UK FROST is the largest randomized clinical trial to our knowledge to date that provides robust evidence on the cost-effectiveness of common surgical interventions followed by post-procedural physiotherapy, compared with a non-surgical pathway of ESP and steroid injection for the treatment of patients with a frozen shoulder. Participants' health-related quality of life improved with all three treatments during the trial follow-up. Overall, participants who had MUA accrued more QALYs compared to those who had capsular release and ESP. The greater costs of capsular release make this intervention difficult to justify. In particular, capsular release was dominated by manipulation, with higher mean costs and lower QALYs. Compared to ESP, participants who had capsular release accrued on average more QALYs, but this was not sufficient to support capsular release as a cost-effective alternative to ESP. At a £20,000 per QALY threshold the probability of MUA being cost-effective was high (86%) compared with early structured physiotherapy (13%) and capsular release (0%). Therefore, from an NHS perspective, this is clear evidence that MUA is the most cost-effective option and would represent good value for money.

This analysis presents an up-to-date estimate of the cost-effectiveness of three common treatment pathways for the management of frozen shoulder in the NHS setting. The strengths of this study were the pragmatic design and the recruitment of patients from 35 hospitals across a range of rural and urban areas, involving 90 surgeons and 285 physiotherapists. There were minimal exclusions of patients and the rate of crossovers was low. We also used very detailed hospital forms designed for the trial, together with multiple sources of cost data available for the analyses, to permit an exhaustive microcosting to optimize the accuracy of the estimation of the treatment costs. The UK FROST trial, therefore, provides timely and direct evidence of clinical and resource implications for the NHS that may also be generalizable to other healthcare systems that offer these treatment options.

The EQ-5D instrument has been well validated in patients with a frozen shoulder.[19,20] However, a systematic review identified a lack of use of generic preference-based measures in existing frozen shoulder clinical studies.[7] The elicitation of the EQ-5D-5L from patients with frozen shoulder is another strength of our study, providing further evidence on the impact of this condition on patient's overall health related quality of life.

There are two potential limitations with the analysis. The first relates to the problem of missing data, which is a common issue in economic evaluations nested within clinical trials. We conducted a comprehensive analysis of missing data and a number of sensitivity analyses to test the assumptions we used to impute missing data in our economic models. Sensitivity analyses showed that results were robust to alternative assumptions on missing data, indicating that MUA continued to be a cost-effective use of NHS resources. It is therefore highly unlikely that such assumptions regarding missing data will change the conclusions of our analysis.

The second limitation relates to the length of follow-up, as one year could be argued to be too short to capture the full effects of all the treatments. Clinical effectiveness results showed that at the primary endpoint of 12 months, many participants had improved to nearly full shoulder functioning, with a median overall OSS of 43 (out of 48), compared with an initial median overall OSS of 20 points.[11] It is notable that the difference in OSS scores and the difference in quality of life are found in the same direction, with only a small difference in QALYs observed across groups. It could be argued that there is a possible trend of the capsular release group improving over time, which might continue with longer time follow-up. This could be explained by the timing of the delivery of the interventions. However, additional analysis adjusting for delivery times of interventions confirmed this did not alter the interpretation of the primary findings, which in turn also suggests that it is unlikely that any important difference in QALYs would emerge beyond the trial follow-up.[12] Regarding costs, we are confident that important costs, including costs of complications, have been captured during the trial follow-up.

It is important to consider that all three treatment groups received standardized physiotherapy specifically designed for the purposes of the trial. This is likely to have resulted in patients receiving more physiotherapy and possibly steroid injections in the ESP pathway than would be received routinely in the NHS and consequently increased its costs. More physiotherapy, however, was also likely to have been received in both the surgical pathways than that provided in the NHS. Furthermore, the rationale for the number of physiotherapy sessions that patients were encouraged to receive in the ESP intervention was to give every opportunity for the physiotherapy to be effective. Despite this, ESP was not found to be clinically superior compared with the surgical treatments or to be the most cost-effective option to the NHS.

Finally, it should be noted that this study did not take into consideration the economic impact of hydrodilatation. This is because when we undertook a survey of practice to inform the design of UK FROST, only 6% of UK practitioners were using hydrodilatation. Consequently, this was not identified as a priority intervention for evaluation.[39] Its popularity has increased since then, and although hydrodilatation has been compared with manipulation, capsular release, and intra-articular steroid injections,[40,41] evidence of its effectiveness and cost-effectiveness is inconclusive.

In summary, to the best of our knowledge there is very limited evidence regarding the cost-effectiveness of the three commonly used treatments for the frozen shoulder that were compared in UK FROST. We found that while our specifically designed non-surgical pathway of ESP and steroid injection was the least costly intervention, MUA was the most cost-effective management pathway for the NHS as the extra cost was good value for money for the benefits gained by patients. Evidence presented from this economic evaluation should help clinicians discuss treatment options with patients during shared decision-making and encourage surgeons to use capsular release more selectively when less costly and less invasive interventions fail.[42]

Take home message

- UK FROST is the largest randomized clinical trial to date that provides robust evidence on the cost-effectiveness of common interventions for the treatment of adult patients with a frozen shoulder in secondary care: manipulation under anaesthesia (MUA), arthroscopic capsular release (ACR), and physiotherapy with steroid injection.
- While our specifically designed non-surgical pathway of early structured physiotherapy was the least costly intervention, MUA was the most cost-effective option to the NHS. ACR was not cost-effective.

Supplementary material

Additional information about how we handled missing data in the analysis and the impact on cost-effectiveness results.

References

1. **Walker-Bone K**, **Palmer KT**, **Reading I**, **et al**. Prevalence and impact of musculoskeletal disorders of the upper limb in the general population. *Arthritis Rheum*. 2004;51(4):642–651.
2. **Van der Windt DA**, **Koes BW**, **de Jong BA**, **et al**. Shoulder disorders in general practice: incidence, patient characteristics, and management. *Ann Rheum Dis*. 1995;54(12):959–964.
3. **Hand GC**, **Athanasou NA**, **Matthews T**, **et al**. The pathology of frozen shoulder. *J Bone Joint Surg Br*. 2007;89-B(7):928–932.
4. **Rangan A**, **Hanchard N**, **McDaid C**. What is the most effective treatment for frozen shoulder. *BMJ*. 2016;354:i4162.
5. **Dennis L**, **Brealey S**, **Rangan A**, **Rookmoneea M**, **Watson J**. Managing Idiopathic Frozen Shoulder: A Survey of Health Professionals' Current Practice and Research Priorities. *Shoulder & Elbow*. 2010;2(4):294–300.
6. **Hanchard NCA**, **Goodchild L**, **Thompson J**, **O'Brien T**, **Davison D**, **Richardson C**. Evidence-Based clinical guidelines for the diagnosis, assessment and physiotherapy management of contracted (frozen) shoulder: quick reference summary. *Physiotherapy*. 2012;98(2):117–120.
7. **Maund E**, **Craig D**, **Suekarran S**, **et al**. Management of frozen shoulder: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2012;16(11):1–264.
8. **Grant JA**, **Schroeder N**, **Miller BS**, **et al**. Comparison of manipulation and arthroscopic capsular release for adhesive capsulitis: a systematic review. *J Shoulder Elbow Surg*. 2013;22(8):1135–1145.
9. **Uppal HS**, **Evans JP**, **Smith C**. Frozen shoulder: A systematic review of therapeutic options. *World J Orthop*. 2015;6(2):263–268.
10. **Hanchard NC**, **Goodchild L**, **Thompson J**, **et al**. A questionnaire survey of UK physiotherapists on the diagnosis and management of contracted (frozen) shoulder. *Physiotherapy*. 2011;97(2):115–125.
11. **Hanchard NCA**, **Goodchild L**, **Brealey SD**, **Lamb SE**, **Rangan A**. Physiotherapy for primary frozen shoulder in secondary care: Developing and implementing stand-alone and post operative protocols for UK frost and inferences for wider practice. *Physiotherapy*. 2020;107(6):150):160–160:.
12. **Rangan A**, **Brealey SD**, **Keding A**, **et al**. Management of adults with primary frozen shoulder in secondary care (UK frost): a multicentre, pragmatic, three-arm, superiority randomised clinical trial. *The Lancet*. 2020;396(10256):977–989.
13. **Dawson J**, **Fitzpatrick R**, **Carr A**. Questionnaire on the perceptions of patients about shoulder surgery. *J Bone Joint Surg Br*. 1996.
14. **Brooks R**. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53–72.
15. **Van Hout B**, **Janssen MF**, **Feng YS**, **et al**. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15(5):708–715.
16. **National Institute for Health and Care Excellence**. Guide to the Methods of Technology Appraisal. London: NICE. 2013.
17. **Brealey S**, **Armstrong AL**, **Brooksbank A**, **et al**. United Kingdom frozen shoulder trial (UK frost), multi-centre, randomised, 12 month, parallel group, superiority study to compare the clinical and cost-effectiveness of early structured physiotherapy versus manipulation under anaesthesia versus arthroscopic capsular release for patients referred to secondary care with a primary frozen shoulder: study protocol for a randomised controlled trial. *Trials*. 2017;18(1):1–5.
18. **Bloom JE**, **Rischin A**, **Johnston RV**, **Buchbinder R**. Image-guided versus blind glucocorticoid injection for shoulder pain. *Cochrane Database Syst Rev*. 2012;2012(8):CD009147.
19. **Brealey S**, **Northgraves M**, **Kottam L**, **et al**. Surgical treatments compared with early structured physiotherapy in secondary care for adults with primary frozen shoulder: the UK frost three-arm RCT. *Health Technol Assess*. 2020;24(71):71–.
20. **Holmgren T**, **Björnsson Hallgren H**, **Öberg B**, **Adolfsson L**, **Johansson K**. Effect of specific exercise strategy on need for surgery in patients with subacromial impingement syndrome: Randomised controlled study. *BMJ*. 2012;344(1):e787.
21. **Angst F**, **Schwyzer HK**, **Aeschlimann A**, **Simmen BR**, **Goldhahn J**. Measures of adult shoulder function: Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH) and its short version (QuickDASH), Shoulder Pain and Disability Index (SPADI), American Shoulder and Elbow Surgeons (ASES) Society standardized shoulder assessment form, Constant (Murley) Score (CS), Simple Shoulder Test (SST), Oxford Shoulder Score (OSS), Shoulder Disability Questionnaire (SDQ), and

Western Ontario Shoulder Instability Index (WOSI). *Arthritis Care Res (Hoboken)*. 2011;63 Suppl 11:S174:S174-88:.

22. **Van Hout B**, **Janssen MF**, **Feng YS**, **et al**. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15(5):708–715.
23. **Billingham LJ**, **Abrams KR**, **Jones DR**. Methods for the analysis of quality-of-life and survival data in health technology assessment. *Health Technol Assess*. 1999;3(10):10):1–152:.
24. **Manca A**, **Hawkins N**, **Sculpher MJ**. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ*. 2005;14(5):487–496.
25. **Curtis L**, **Burns A**. Unit costs of health and social care 2018. Canterbury: Personal Social Services Research Unit, University of Kent, 2018.
26. **Joint Formulary Committee**. British National formulary London: BMJ Group and Pharmaceutical Press. www.medicinescomplete.com
27. NHS Reference Costs 2017 to 2018. www.england.nhs.uk/national-costcollection/
28. **Office for national statistics. EARN01: average Weekly earnings**. London: Office for National Statistics. 2019.
29. **Corbacho B**, **Cockayne S**, **Fairhurst C**, **et al**. Cost-effectiveness of a multifaceted podiatry intervention for the prevention of falls in older people: the reducing falls with orthoses and a multifaceted podiatry intervention trial findings. *Gerontology*. 2018;64(5):503–512.
30. **Faria R**, **Gomes M**, **Epstein D**, **White IR**. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics*. 2014;32(12):1157–1170.
31. **Manca A**, **Palmer S**. Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials. *Appl Health Econ Health Policy*. 2005;4(2):65–75.
32. **White IR**, **Horton NJ**, **Carpenter J**, **Pocock SJ**. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ. 2011;342:d40.
33. **Leurent B**, **Gomes M**, **Faria R**, **Morris S**, **Grieve R**, **Carpenter JR**. Sensitivity analysis for not-at-random missing data in trial-based cost-effectiveness analysis: a tutorial. Aug 1. *PharmacoEconomics*. 2018;36(8):889–901.
34. **Faria R**, **Bojke L**, **Epstein D**, **Corbacho B**, **Sculpher M**, **REFLUX trial group**. Cost-Effectiveness of laparoscopic fundoplication versus continued medical management for the treatment of gastro-oesophageal reflux disease based on long-term follow-up of the reflux trial. *Br J* Surg. 2013;100(9):1205–1213.
35. **Rubin DB**. Multiple imputation for nonresponse in surveys. John Wiley & Sons, 2004.
36. **Johannesson M**, **Weinstein MC**. On the decision rules of cost-effectiveness analysis. *J Health Econ*. 1993;12(4):459–467.
37. **Claxton K**, **Martin S**, **Soares M**, **et al**. Methods for the estimation of the nice cost effectiveness threshold In: Che Research Paper 81. York, England: University of York. 2013.
38. **Lomas J**, **Claxton K**, **Martin S**, **Soares M**. Resolving the “cost-effective but unaffordable” paradox: estimating the health opportunity costs of nonmarginal budget impacts. *Value Health*. 2018;21(3):266–275.
39. **Dennis L**, **Brealey S**, **Rangan A**, **Rookmoneea M**, **Watson J**. Managing Idiopathic Frozen Shoulder: A Survey of Health Professionals' Current Practice and Research Priorities. *Shoulder Elbow*. 2010;2(4):294–300.
40. **Gallacher S**, **Beazley JC**, **Evans J**, **et al**. A randomized controlled trial of arthroscopic capsular release versus hydrodilatation in the treatment of primary frozen shoulder. *J Shoulder Elbow Surg*. 2018;27(8):1401–1406.
41. **Mun SW**, **Baek CH**. Clinical efficacy of hydrodistention with joint manipulation under interscalene block compared with intra-articular corticosteroid injection for frozen shoulder: a prospective randomized controlled study. *J Shoulder Elbow Surg*. 2016;25(12):1937–1943.
42. **Science Animated**. Frozen shoulder: which treatment should you choose? October 1, 2020. https://youtu.be/I88uzfD8Y4s

Author information:

- B. Corbacho, MSc, Health Economist
- S. Brealey, PhD, Research Fellow
- A. Keding, MSc, Statistician
- D. Torgerson, MSc, PhD, Director York Trials Unit (YTU), Professor
- C. Hewitt, BSc, MSc, PhD, Deputy Director of the York Trials Unit (YTU), Professor
- C. McDaid, BSSc, MSc, PhD, Reader in Trials
  York Trials Unit, Department of Health Sciences, University of York, York, UK.
- G. Richardson, PhD, Professor of Health Economics, Centre for Health Economics, University of York, York, UK.
- A. Rangan, FRCS, Professor of Orthopaedic Surgery, York Trials Unit, Department of Health Sciences, University of York, York, UK; Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, UK; The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK.

Author contributions:

- B. Corbacho: Formal analysis, Writing - original draft, Writing - review & editing.
- S. Brealey: Writing - original draft, Writing - review & editing.
- A. Keding: Formal analysis, Writing - original draft, Writing - review & editing.
- G. Richardson: Supervision, Writing - review & editing.
- D. Torgerson: Supervision, Conceptualization, Methodology, Writing - review & editing.
- C. Hewitt: Methodology, Writing - review & editing.
- C. McDaid: Conceptualization, Writing - review & editing.
- A. Rangan: Project administration, Investigation, Writing - original draft, Writing - review & editing.

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  Matthew Northgraves, University of York; Lucksy Kottam, South Tees Hospitals NHS Foundation Trust; Lorna Goodchild, South Tees Hospitals NHS Foundation Trust; Cynthia Srikesavan, University of Oxford; Saleema Rex, University of York; Charalambos P. Charalambous, Blackpool Victoria Hospital; University of Central Lancashire; Nigel Hanchard, University; Alison Armstrong, University Hospitals of Leicester NHS Trust; Andrew Brooksbank, Glasgow Royal Infirmary; Andrew Carr, University of Oxford; Cushla Cooper, University of Oxford; Joseph Dias, University Hospitals of Leicester NHS Trust; Ioana Donnelly, Glasgow Royal Infirmary; Sarah E. Lamb, University of Exeter; Sara Rodgers, University of York; Emma Sharp, Glasgow Royal Infirmary; Sally Spencer, Edge Hill University; Francine Toye, Oxford University Hospitals NHS Foundation Trust.

Ethical review statement:

- Ethics approval was obtained on 18 November 2014 from the National Research Ethics Service (NRES Committee North East – Newcastle & North Tyneside 2; Research Ethics Committee Reference 14/NE/1176). Local site-specific NHS research and development approvals were obtained from each participating site. The study was adopted to the UK Clinical Research Network portfolio (17719).