

THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
We post it as supplied by the authors.

Supplement to: Griffin DR, Dickenson EJ, Wall PDH, et al. Hip arthroscopy versus best conservative care for the treatment of femoroacetabular impingement syndrome (UK FASHIoN): a multicentre randomised controlled trial. *Lancet* 2018; **391**: 2225–35.



Hip arthroscopy versus best conservative care for the treatment of femoroacetabular impingement syndrome (UK FASHIoN): a multi-centre randomised controlled trial

Appendix

Damian R Griffin, Edward J Dickenson, Peter D H Wall, Felix Achana, Jenny L Donovan, James Griffin, Rachel Hobson, Charles E Hutchinson, Marcus Jepson, Nick R Parsons, Stavros Petrou, Alba Realpe, Joanna Smith, Nadine E Foster, on behalf of the UK FASHIoN Study Group

Contents

- 1 Surgeons, physiotherapists and details of treatments
- 3 Details of treatment fidelity assessments
- 4 Randomisation by site
- 5 Details of pre-specified sub group analysis
- 6 Health Economic Evaluation

Surgeons, physiotherapists and details of treatments

Surgeons' training and experience

Surgery was delivered in 23 hospitals by a total of 27 consultants on the UK General Medical Council Specialist Register for Trauma and Orthopaedic Surgery. They had been on the Specialty Register for a mean of 11 years (SD 6.6). The trial surgeons had been performing hip arthroscopy as a consultant for a mean of 9 years (SD 3.6), having received the following dedicated hip preservation training: specialist registrar (n=13), courses (n=24), fellowship (n=14, mean duration 9 months), travelling fellowship (n=8, mean duration 1.6 months). Six surgeons were directors of hip preservation fellowships and 17 were faculty on dedicated hip arthroscopy courses. Trial surgeons reported that they performed a mean of 112 (SD 55) hip arthroscopies a year of which 81 (SD 45) were for FAI syndrome. Each surgeon operated on a mean of 5.3 participants (SD 5.3, median 3, range 1-21) in the FASHIoN trial.

Surgery delivered

144 patients received their surgery within 12 months of randomisation. Operation notes were available for review in 142 patients.

Reshaping surgery:

- 105 cam only resections,
- 26 cam and pincer resection,
- 8 pincer only resections,
- 3 patients did not have a resection; in two participants their hip was found to be degenerate at surgery and in one instance the operative diagnosis was an isolated labral tear not FAI syndrome.

Labral surgery:

- Debridement; n=57
- Thermal shrinkage n=29
- Anchor repair n=35
- Resection n=5
- Resection of ossified labrum n=2 (as part of a pincer resection)

Chondral surgery:

- Microfracture n=21
- Chondroplasty n=29
- Debridement n=10

Post-operative rehabilitation

There was variability in the post-operative rehabilitation protocols between trial centres. Rehabilitation was typically structured in stages over several months and included:

- An immediate post-operative phase to restore hip movement as pain improved
- A phase to restore static stability and movement,
- A phase to restore dynamic stability and movement
- Sports specific training

Physiotherapists' training and experience

Personalised Hip Therapy (PHT) was delivered at 23 hospitals by a total of 47 Chartered Physiotherapists who were registered with the Health and Care Professions Council. In terms of clinical experience, they ranged from NHS Agenda for Change (AfC) band 5 to band 8a (band 5 n=1; band 6 n=11; band 7 n=19; band 8a n=5, band unknown n= 11). AfC is the current NHS grading and pay system, where a band 5 physiotherapist is usually a recently qualified physiotherapist or one with less than three years of experience and a band 8a represents a specialist physiotherapist or an extended scope practitioner.

All PHT physiotherapists treated patients with musculoskeletal conditions within their normal clinical practice. Forty-one (90%) physiotherapists had previously treated patients with FAI syndrome before involvement in the trial. All physiotherapists attended at least one of eight workshops held between 2012 and March 2016. Physiotherapists delivered a median of 7 PHT sessions each and each physiotherapist treated a median of 2 patients. Typically each site had two trained PHT physiotherapists and they often changed jobs, hence the median number of participants treated by each PHT physiotherapist was lower than that of participants operated upon by each surgeon.

PHT delivered

936 PHT treatment sessions were delivered; 867 (93%) were face to face, 31 (3%) were telephone contacts, 4 (1%) were email contacts, and in 34 (3%) the mode of contact was not recorded. 100 (64%) participants received 6 or more sessions. See Table 1. Treatment sessions lasted a mean of 30 minutes per session (SD = 11 minutes), with the first assessment and treatment session usually lasting longer.

Number of PHT treatment sessions attended

Number of sessions attended	Count	Cumulative
1	15 (10%)	15 (10%)
2	5 (3%)	20 (13%)
3	10 (6%)	30 (19%)
4	14 (9%)	44 (29%)
5	10 (6%)	54 (35%)
6	31 (20%)	85 (55%)
7	16 (10%)	101 (66%)
8	20 (13%)	121 (79%)
9	15 (9%)	136 (88%)
10	16 (10%)	152 (99%)
11	2 (1%)	154 (100%)
Total	154	154

Details of treatment fidelity assessments

Members of Surgical Review Panel

John O'Donnell Hip Arthroscopy Surgeon Australia

Marc Philippon Hip Arthroscopy Surgeon USA

Martin Beck Hip Arthroscopy Surgeon Switzerland

Charles Hutchinson Musculoskeletal Radiologist UK

Surgical Review Panel process

Vignettes consisting of an anonymised operation note, two intra operative photographs (usually before and after correction of pathology) and an MRI scan reformatted to show the superior, anterosuperior and anterior head neck junction and acetabular rim, were provided to the surgical review panel. The panel held regular teleconference meetings during the trial to discuss the surgical fidelity. The panel provided an overall rating of either high fidelity or unsatisfactory surgery for each case. This assessment was made subjectively following discussion. When assessing a cam resection the panel assessed the femoral head sphericity and the smoothness of the transition from the head to the femoral neck. When assessing a pincer resection the panel assessed whether the rim remained prominent and whether it was smooth in profile.

Members of PHT Review Panel

All members were part of the group that developed the PHT protocol.

Nadine Foster Professor of Primary Care UK

Peter Wall Academic Orthopaedic Surgeon UK

Ivor Hughes Senior Physiotherapist UK

David Robinson Senior Physiotherapist UK

PHT Review Panel process

The PHT review panel were presented with case report form for each patient. These detailed the physiotherapy delivered. The panel expected PHT was delivered according to the protocol; particularly that there were between 6 and 10 sessions, treatment consisted of the 4 core components (a detailed patient assessment, help and advice about FAI syndrome, help with pain relief and an exercise based programme). The panel assessed whether the exercise programme showed evidence of being individualised, supervised and progressive in time.

Randomisation by site

TABLE 1 Randomised patients summarised by treatment group and centre

Site ID	Surgery (n=171)	PHT (n=177)	Total (n=348)
09	2	3	5
19	5	6	11
13	16	15	31
07	1	1	2
05	6	6	12
18	3	2	5
08	7	7	14
17	7	6	13
21	3	4	7
12	11	12	23
15	4	4	8
06	3	4	7
03	9	9	18
04	20	19	39
23	1	2	3
16	6	5	11
14	5	4	9
10	8	8	16
01	37	41	78
20	1	3	4
11	5	5	10
02	11	11	22

Details of pre-specified sub group analysis

In the pre-specified subgroup analyses: the between group difference on iHOT-33 was 5.0 (-1.2, 11.3) in participants under 40 years and 10.9 (1.7, 20.1) in those over 40 years (p-value for interaction term 0.3023) in favour of HA; the difference was 8.3 (2.5, 14.2) in those with cam morphology, 1.1 (-11.5, 13.7) in those with mixed cam and pincer morphology, and 4.0 (-14.6, 22.7) in those with pincer morphology (p-value for interaction term 0.5672), all in favour of HA.

TABLE 1 Subgroup analyses on the primary outcome iHOT-33: Summary statistics, unadjusted and adjusted treatment results at 12 months.

Subgroup		Hip Arthroscopy (n=171)		PHT (n=177)		Difference		
		Mean (SD)	n	Mean (SD)	n	Unadjusted	Adjusted (95% CI)*	p-value**
Impingement type	Cam	59.4 (27.7)	120	49.1 (24.3)	124	10.4	8.3 (2.5, 14.2)	0.567
	Mixed	56.3 (22.4)	26	51.5 (31.1)	27	4.8	1.1 (-11.5, 13.7)	
	Pincer	57.3 (33.4)	12	51.8 (25.4)	12	5.5	4.0 (-14.6, 22.7)	
Age group (years)	<40	59.1 (26.6)	103	50.0 (24.5)	117	9.1	5.0 (-1.2, 11.3)	0.302
	≥40	58.1 (28.4)	55	48.8 (27.9)	46	9.3	10.9 (1.7, 20.1)	

*Mixed effects regression model based on intention to treat analysis approach with allocated treatment group, impingement type, gender and baseline score as fixed effects, and recruiting centre as a random effect. Also interaction term between subgroup of interest and treatment group.

**p-value is a likelihood ratio test comparing the model with an interaction term to the model without an interaction term.

Health Economic Evaluation

Overview

A prospective within-trial cost-utility analysis was conducted to estimate the cost-effectiveness of arthroscopic surgery versus personalised hip therapy (PHT) as treatment options for femoro-acetabular impingement (FAI) syndrome. Costs were expressed in British pounds sterling (2016 price year) and health outcomes in quality-adjusted life-years (QALYs). The base case analysis was based on the intention-to-treat population and conducted from the perspective of UK National Health and Personal Social Services (NHS/ PSS). The time horizon covered the period from randomisation to end of follow-up at 12 months post-randomisation. Costs and outcomes were not discounted due to the short, one-year time horizon adopted for this within-trial evaluation. Findings are reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.¹

Methods

Measurement of resource use and costs

Data were collected on:

- i) resource use and costs associated with delivery of the interventions,
- ii) health and social care service use during the 12 months of follow-up and
- iii) broader societal resource use and costs – this encompassed private medical costs and lost productivity costs such as lost income over the 12 months of follow-up.

Cost of PHT

PHT was delivered to trial participants primarily by experienced physiotherapists (Agenda for Change NHS band 7 and above) within NHS hospital outpatient clinics. The number and duration of PHT sessions attended were recorded for all patients who received this intervention. The unit cost of a band 7 hospital physiotherapist (including qualifications and overheads) was obtained from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2016 and was £55/hour.² Unit costs were multiplied by duration of physiotherapy contact (in minutes) and summed across sessions attended to give total treatment cost per patient. Indirect costs associated with delivery of the intervention such as use of the treatment room facility, administrative support and overheads are taken into account in PSSRU unit cost calculations, therefore, separate costs for these were not included in our estimate of PHT costs.

Cost of surgery

A micro-costing exercise was undertaken to estimate resource use and costs associated with delivery of arthroscopic surgery for FAI. Resource use data were collected for a sub-sample of trial participants who had received the surgery using a specially designed costing questionnaire that captured the following items:

- duration of surgery
- post-surgical inpatient length of stay
- number, speciality and grade of clinical staff involved in the surgical procedure
- quantity and type of disposable arthroscopic equipment and/or implants used.

Surgery time was defined from start of anaesthesia to time patient left the operating room on completion of surgery. Inpatient length of stay was counted as one day if the patient was admitted and discharged on the same day, two days if the patient was discharged the next day and so on in line with NHS reference costing methodology.³ Anaesthetic drugs and associated consumables such as syringes and needles were separately collected during surgery in a small observational study and assumed to be the same for all patients who had the surgery.

Total cost of surgery was calculated for each patient by summing across the following categories:

- i) staff time,
- ii) theatre use in hours,
- ii) disposal surgical equipment,
- iii) anaesthetic drugs and disposables and
- ii) post-surgery inpatient bed-days.

Operating room/theatre running costs were estimated based on data published by Information Services Scotland.⁴ The Scottish data reported total number of theatre hours used and total allocated costs across NHS hospitals in Scotland for the 2015-2016 financial year. Allocated costs are defined to include expenditure on non-clinical staff, property and equipment maintenance, domestics and cleaning, utilities, fittings and capital expenditure, and excluded clinical staff costs.⁵ The hourly running cost of an operating room/theatre was obtained by dividing the total allocated costs per year by the total theatre time (in hours) per year.

Unit costs of clinical staff time were obtained from the PSSRU Unit Costs of Health and Social Care 2016 compendium.² As stated above, these unit costs already

factor in direct cost of staff salaries and employer on-costs and training costs, as well revenue and capital overhaeds, administrative support, office space and work-related travel. The cost of disposal surgical equipment and implants were primarily obtained from the 2016 online edition of the NHS supply chain catalogue.⁶ Where cost data were not available from the NHS catalogue, procurement department unit costs from the University Hospital Coventry and Warwickshire were applied. Cost of anaesthetic drugs were obtained from the Prescription Costs Analysis database.³

Resource use during follow-up

Health and social care service use data were collected from trial participants for the 3 month period prior to randomisation (to establish baseline data) and the 12 months period post-randomisation. Resource use data were collected at 3 assessment points (baseline, 6 months and 12 months post randomisation) and included:

- details of hospital inpatient and day case admissions
- details of outpatient and accident and emergency attendances
- primary/community care encounters
- use of personal social care services, such as meals on wheels, laundry services, social care contacts, etc.
- prescribed and over the counter medication use
- supplied or self-purchase of walking aids such as crutches, walking sticks and adaptations to home or work environments
- any other additional costs incurred by patients and their families as a result of their hip pain. Examples include private medical costs and out-of-pocket expenditures (e.g. travel costs by patients and family members), childcare costs and lost income.

Resource inputs were valued by attaching unit costs derived from national compendia to resource inputs.

Hospital based services included inpatient admissions, day care and outpatient and accident and emergency attendances, and diagnostic tests and scans. Unit costs for these services were obtained primarily from the 2015/2016 NHS reference costs main schedules.⁷ Per diem costs were calculated for each inpatient admission as a weighted average of Healthcare Resource Group (HRG) codes of related procedures and/or clinical conditions. For example, the average cost per day for inpatient stay in an orthopaedic ward with procedures carried out on the hip/leg was calculated as a sum total of the weighted average of lower limb orthopaedics (trauma) HRG codes divided by average length of stay across elective and non-elective inpatient services.

Primary and community health and social care services included face-to-face or telephone contacts and/or home visits by a general practice doctor, practice nurse, community physiotherapy or other community health or social care professionals. Consultation costs were derived from the PSSRU Unit Costs of Health and Social Care 2016 compendium.²

The cost of private physiotherapy and other private medical costs were obtained from online sources and referenced appropriately in the unit cost tables.

The cost of prescribed medication was obtained primarily from the prescription cost analysis 2016 database and electronic searches of the British National Formulary (BNF) 2016 edition.³ Typical dosage and duration of treatment reported in the BNF for each medication were used in calculating quantity of individual preparations if the daily dose and/or duration of course of medication were not reported. The quantity of over the counter medicines were rounded to the nearest pack and unit costs obtained from online sources.

The cost of walking aids and adaptations were either provided by the patients themselves (if self-purchased) or taken from the NHS supply chain catalogue if supplied by a health provider during the trial follow-up period. It was assumed that walking aids such as crutches, sticks, grab rail, dressing aids and specially adapted shoes were supplied as part of treatment if the cost of purchase were not provided by trial participants.⁶

Patient-level costs were generated for each resource variable by multiplying the quantity reported by the respective unit cost weighted by duration of contact where appropriate. Summary statistics were generated for resource use variables by treatment allocation and assessment point. Between treatment-group differences in resource use and costs at each assessment point were compared using the two-sample t-test. Statistical significance was assessed at the 5% significance level. Standard errors are reported for treatment group means and bootstrap 95% confidence intervals for the between-group differences in mean resource use and cost estimates.

Measurement of outcomes

The health-related quality of life of trial participants was assessed at baseline and at 6 and 12 months post randomisation using the EuroQol EQ-5D-3L in the feasibility study, the EQ-5D-5L in the main trial, and the SF-12 version 1 in both feasibility and main trial samples. Responses to each health dimension were categorised as optimal or sub-optimal with respect to function where optimal level of function indicates no impairment (for example "no problem" on the EQ-5D-3L dimensions)

and sub-optimal indicates any functional impairment.⁸⁻¹⁰ Between-group differences in optimal versus sub-optimal level of function for each health dimension were compared for each outcome measure using chi-squared (χ^2) tests.

The responses to each health-related quality of life instrument were converted into health-related quality of life weights (also referred to as utility weights) using established algorithms for each instrument. Utility values were generated using the UK value set for the EQ-5D-3L, the interim cross-walk value set for mapping from the EQ-5D-5L to the EQ-5D-3L, the newly published EQ-5D-5L tariffs for the EQ-5D-5L, and the SF-6D tariff based on SF-12 version 1 responses.¹¹⁻¹⁴

Quality-adjusted life-years (QALYs) were generated for each patient using the area under the baseline-adjusted utility curve, assuming linear interpolation between the three utility measurements. QALYs were generated for patients in the feasibility sample using utilities derived from EQ-5D-3L and SF-6D tariffs and for those in the main study sample using the EQ-5D-5L cross-walk tariff, new UK EQ-5D-5L tariff and the SF-6D tariff.¹¹⁻¹⁴ Health utility values and QALYs accrued over the 12 month follow-up were summarised by treatment group and assessment point and presented as means and associated standard errors; between-group differences were compared using the two-sample t-test, similar to the summary analyses of resource inputs and costs.

Cost-effectiveness analysis methods

Missing data

Multiple imputation by chain equations implemented through the MICE package¹⁵ was used to handle missing costs and health utility data at each assessment point. Multiple imputation avoids problems associated complete case analyses, is consistent with good practice and only requires data to be missing at random.¹⁶ Appropriateness of this missing at random assumption was assessed by comparing the characteristics of patients with and without missing costs and health-related quality of life data at each follow-up time point. Imputations were generated separately by treatment group as recommended by Faria *et al.*¹⁷ using the predictive mean matching method which has the advantage of preserving non-linear relationships and correlations between variables within the data. Twenty imputed datasets were generated and the analyses fitted to each imputed dataset. The results from the 20 datasets were then combined using Rubin's rules. The imputation, analysis and pooling of results steps were performed simultaneously within the MICE package.¹⁵ The imputed data were used to inform the base case and all subgroup and sensitivity analyses with the exception of one sensitivity analysis, which was conducted using only complete data.

Base case cost-effectiveness analysis

The base-case took the form of an intention-to-treat analysis conducted from a UK health and social service perspective. Health outcomes were expressed in QALYs using utilities generated from the EQ-5D-3L (feasibility study participants) and the EQ-5D-5L to EQ-5D-3L cross-walk tariff for the main trial participants. Total costs accrued over 12 months of follow-up were calculated for each patient by summing the delivery costs of the intervention(s) received (irrespective of treatment allocation), and a sum total of follow-up costs reported at the 6 and 12 month assessment points relevant to the perspective of interest.

Two seemingly unrelated normal error regressions were fitted to the data using the Systems fit implementation in R.¹⁸ These were used to simultaneously estimate incremental costs and benefits of surgery compared with PHT whilst accounting for correlation between the two. The regressions controlled for treatment allocation, sex, recruitment site, type of impingement, baseline costs (regression equation for costs only) and baseline health-related quality of life (regression equation for outcomes). The incremental cost-effectiveness ratio (ICER) was calculated by dividing the between-group difference in adjusted mean total costs by the difference in adjusted mean QALYs. The cost-effectiveness of hip arthroscopy was determined by comparing the ICER value to cost-effectiveness thresholds of £20,000 and £30,000 per QALY gained in line with NICE guidance¹⁹ and to the recent empirical £13,000 per QALY estimate suggested by Claxton *et al.*²⁰ The incremental net (monetary) benefit of the surgery compared with PHT was calculated for a range of cost-effectiveness thresholds. Net benefit values reflect the opportunity cost of (or the benefits forgone) from adopting a new treatment when resources could be put to use elsewhere. A positive net benefit would suggest that, on average, the new treatment provides net gain compared with the alternative and can be considered cost-effective at the given cost-effectiveness threshold.

Uncertainty around the mean cost-effectiveness estimates was characterised through a monte carlo method.²¹ This involved simulating 1,000 replicates of the ICER from a joint distribution of the incremental costs and QALYs and plotting the simulated ICERs on a cost-effectiveness plane. Cost-effectiveness acceptability curves were also plotted to give graphical display of the probability that surgery is cost-effective across a wide range of cost-effectiveness thresholds.

Sensitivity analysis

Sensitivity analyses were conducted to investigate aspects of study design and data collection for which alternative methods exist, but where there is uncertainty regarding which method or approach is best. For example, the cost of surgery was estimated based on data from a sub-sample

of patients who had the surgery in the study. Surgery costs can also be obtained through the healthcare resource groups case-mix method. Other sensitivity analyses included broadening the perspective of the analysis to capture wider societal costs and their impact on relative cost-effectiveness of the interventions. A list of all sensitivity analyses carried out are presented in Table 1.

TABLE 1 List of sensitivity analysis considered

Analysis	Description of changes to base case considered in sensitivity analysis
Pre-specified	Unadjusted analysis
Pre-specified	Complete case analysis
Pre-specified	Per protocol sample 1: Restricted analysis to patients who received allocated treatment
Pre-specified	Per protocol sample 2: Restricted analysis to patients whose surgery or PHT was deemed to be of good quality as assessed by clinical panel
Pre-specified	Adopting a societal perspective that includes both direct health and social care costs and broader societal costs
Pre-specified	Use QALYs generated using the SF-6D utility algorithm
post-hoc	Altering the cost of surgery from £3,042 (estimate from the micro-costing) to £1,430 based on HRG code HN15A (Minor Hip Procedures for Non-Trauma, 19 years and over), short-stay
post-hoc	Altering the cost of surgery from £3,042 (estimate from the micro-costing) to £6,387 based on HRG code HN13A (Major Hip Procedures for Non-Trauma, 19 years and over, with CC Score 10+) short-stay

Sub-group analysis

Heterogeneity in cost-effectiveness estimates was explored through the following pre-specified and post-hoc subgroup analyses.

The pre-specified analyses were the following:

- Recruitment period (feasibility versus main trial samples)
- Type of impingement (CAM versus mixed/pincer)
- Age (less than 40 years old versus 40 years or older).

Post-hoc subgroup analyses were the following:

- Sex (female versus male).
- Subgroup of patients in the surgery arm who had surgery within 4 months of randomisation.
- Subgroup of patients in the surgery arm who did not undergo surgery within 4 months of randomisation. These last two subgroup analyses were conducted in response to a suggestion at peer-review investigated the impact of the delay to surgery on the within-trial cost-effectiveness results. Patients in the surgery group were categorised

based on the median time to surgery of 122 days observed in the trial into (i) those who had surgery within the first 4 months of randomisation (i.e. within 122 days of randomisation) (n=74) and those who did not have surgery within 4 months of randomisation (n=75). Each group of patients in the surgery arm was then compared to the whole PHT group (n=177) in a separate subgroup analyses that adjusted for baseline covariates and used imputed costs and QALYs as was done in the base case analysis.

Long-term modelling

The study protocol had also allowed for trial participants to be follow-up beyond the initial 12 month period for up to 3 years and outcome data collected at the end of the second and third year post-randomisation. Given that the 12-month within-trial economic analysis did not show evidence of cost-effectiveness in favour of the surgery, it is doubtful whether long-term economic modelling would be meaningful without this additional data. Also, 14 patients representing 7.3% of the PHT group had crossed-over and received the surgery during the 12 months follow-up period. The net effect of patients crossing over to surgery may increase costs in the PHT arm and decrease the incremental costs between surgery and PHT. If more and more PHT patients continue to cross-over to surgery in subsequent years, then they will be picked up at second and third year assessments. Therefore, an assessment of the utility of a long term economic model should be delayed until the second and third year data becomes available. This would provide a more accurate assessment of outcomes over a longer follow-up period and determine whether modelling is needed to capture the long term (i.e. lifetime) costs and consequences of treatment.

Further Health Economics Results

Cost of PHT

Table 2 presents a summary PHT attendance by type of consultation, impingement classification, missed appointments and recruitment site. A total of 1219 physiotherapy appointments were offered to 166 (93.8%) of the 177 patients in the PHT group. Of these, 909 (75%) were face-to-face consultations, 38 (3%) were telephone consultations, 7 (0.6%) were email contacts and 256 (21%) were recorded as unknown or missed appointments. The mean number of physiotherapy contacts among those who attended at least one PHT session was 6 (range 1 to 11) and mean duration across all sessions attended was 178.17 minutes (mean 29min per session).

TABLE 2 Resource use and costs associated with delivery of PHT

Attendance/consultation type	Mean (standard error)			
	Number of participants (% of 177, number in PHT arm)	Number of consultations	Duration (minutes)	Total cost ²
OVERALL ATTENDANCE				
Did not receive intervention	11 (6.2%)	0.00 (0.00)	0.00 (0.00)	£0.00 (0.00)
Offered ≥ 1 appointments (exc. DNAs)	166 (93.8%)	7.31 (0.22)	220.87 (6.45)	£192.16 (5.62)
Attended ≥ 1 sessions (exc. DNAs)	166 (93.8%)	5.99 (0.21)	178.17 (6.04)	£155.01 (5.25)
Offered ≥ 6 appointments (exc. DNAs)	110 (62.1%)	7.74 (0.17)	225.93 (5.24)	£196.56 (4.56)
Attended ≥ 6 sessions (exc. DNAs)	105 (59.3%)	7.68 (0.15)	222.59 (4.81)	£193.65 (4.18)
ATTENDANCE BY TYPE OF CONSULTATION				
Face-to-face	160 (90.4%)	5.66 (0.21)	170.94 (6.02)	£148.71 (5.23)
Telephone	27 (15.3%)	1.15 (0.07)	13.65 (1.56)	£11.88 (1.35)
Email	4 (2.3%)	1.00 (0.00)	27.70 (9.66)	£24.10 (8.41)
Unknown	22 (12.4%)	2.00 (0.35)	65.37 (11.76)	£56.87 (10.23)
MISSED APPOINTMENTS BY TYPE OF CONSULTATION				
Face-to-face	3 (1.7%)	1.00 (0.00)	26.67 (3.33)	£23.20 (2.90)
Telephone	5 (2.8%)	1.20 (0.20)	13.24 (1.83)	£11.52 (1.59)
Email				
Unknown	96 (54.2%)	2.24 (0.19)	73.68 (6.16)	£64.10 (5.36)
ATTENDANCE BY RECRUITMENT SITE				
University Hospital Coventry and Warwickshire	33 (18.6%)	7.09 (0.48)	25.81 (0.77)	£152.90 (8.97)
Yeovil	8 (4.5%)	3.50 (0.96)	36.88 (3.55)	£104.34 (27.03)
Royal Exeter and Devon	8 (4.5%)	6.62 (0.65)	30.72 (1.48)	£180.53 (22.96)
Royal Orthopaedic	14 (7.9%)	6.93 (0.71)	25.64 (1.23)	£148.20 (14.66)
Frimley Park	4 (2.3%)	6.25 (1.75)	31.72 (1.18)	£175.09 (50.18)
Royal Cornwall	3 (1.7%)	4.33 (0.88)	33.57 (1.99)	£126.50 (25.19)
Elective Orthopaedic Centre	1 (0.6%)	6.00 (-)	23.33 (-)	£121.80 (-)
Guys and St Thomas	7 (4.0%)	7.00 (1.02)	33.37 (1.40)	£206.18 (31.91)
St Bartholomew's Hospital	3 (1.7%)	5.33 (1.67)	33.95 (2.64)	£150.28 (41.57)
University College Hospital	7 (4.0%)	7.43 (0.95)	34.83 (0.82)	£223.71 (27.93)
Wrightington	5 (2.8%)	6.40 (1.12)	34.70 (1.37)	£190.20 (30.82)
Northumbria	9 (5.1%)	5.22 (0.68)	32.49 (1.86)	£140.45 (16.53)
Doncaster & Bassetlaw	11 (6.2%)	6.27 (0.70)	29.85 (0.29)	£162.84 (18.34)
Stanmore	3 (1.7%)	7.67 (0.33)	32.68 (0.80)	£217.50 (4.35)
Oswestry (A) & RH)	3 (1.7%)	8.00 (0.00)	31.67 (1.10)	£220.40 (7.67)
South Tees	4 (2.3%)	7.00 (1.08)	30.17 (0.81)	£181.96 (25.87)
Llandough (Cardiff)	2 (1.1%)	3.50 (1.50)	47.25 (5.25)	£137.02 (45.67)
Glasgow	2 (1.1%)	9.50 (0.50)	34.11 (1.89)	£282.75 (30.45)
Wrexham	2 (1.1%)	7.00 (1.00)	31.72 (0.88)	£193.93 (32.98)
Kings College Hospital	4 (2.3%)	5.25 (0.48)	36.15 (1.46)	£163.93 (12.54)
North Bristol	4 (2.3%)	6.75 (0.48)	27.75 (1.89)	£162.04 (11.42)
Spire	1 (0.6%)	6.00 (-)	40.00 (-)	£208.80 (-)
Plymouth and Duchy	0 (0.0%)	0.00 (-)	0.00 (-)	£0.00 (-)

Cost of surgery

Estimates of resource use associated with delivery of the surgery and sources of unit cost data for resource inputs are presented Tables 3 to 5. The mean duration of surgery was 2.12 (range: 1 to 3) hours and the mean length of inpatient stay was 1.6 (range: 1 to 3) days (Table 3). The composition of the surgical team/staff remained broadly similar across centres and consisted of 2 surgeons (a consultant and an

assistant or registrar), one anaesthetist, a radiographer, up to 2 nurses, 2 operating department practitioners and a healthcare assistant. Unit costs of clinical staff time were obtained from the 2016 edition of the PSSRU Unit Costs of Health and Social care services and ranged from £28 per hour for a healthcare assistant to £137 per hour for consultant surgeon (including qualifications and overheads). The running cost of an operating theatre was estimated

based on data published by the Information Services Scotland (ISD).^{22,23} Inpatient stay was assumed to cost £332.77 per day, the excess bed day cost for elective orthopaedics procedures [HN14E: Intermediate Hip Procedures for Non-Trauma, 19 years and over, with CC Score 0] in the 2016 reference costs schedules.²⁴ The unit cost of anaesthetic drugs were obtained from NHS Prescription Cost Analysis 2016 database,²⁵ electronic searches of the British National Formulary (BNF) 2016 and searches of the literature where necessary. Unit cost of syringes and needles and other medical consumables were obtained from online sources when more direct NHS sources were unavailable.

Across all the 22 centres, the overall mean cost was £3,042 (range of means £2,286 to £40,076), 35.3% of which were staffing costs, 23.5% disposal surgical equipment and implants, 19.4% theatre running costs, 17.8% inpatient costs and 4% represent the cost of anaesthesia including drugs, syringes and needles (Table 4).

TABLE 3 Unit cost of operating room/surgery staff

Resource category	Sample (n=40)			Source of unit cost
	Mean (SE)	Unit cost	Unit	
Theatre time (hours)	2.09 (0.08)	£298.68	Hour	ISD Scotland (2016)
Inpatient length of stay (days)	1.57 (0.09)	£332.77	Day	Reference costs (2016)
CLINICAL STAFF				
Consultant surgeon	1.00 (0.00)	£137	Hour	PSSRU 2016, section 15
Consultant anaesthetist	1.00 (0.00)	£135	Hour	PSSRU 2016, section 15
Assistant surgeon	1.00 (0.07)	£59	Hour	PSSRU 2016, section 15
Radiographer (band 6)	0.95 (0.05)	£46.00	Hour	PSSRU 2016, p.221
Nurse (band 6)	0.86 (0.10)	£44.00	Hour	PSSRU 2016, section 14
Nurse (band 5)	0.81 (0.09)	£35	Hour	PSSRU 2016, section 14
ODP (band 4)	1.07 (0.07)	£30.00	Hour	PSSRU 2016, p.221
Healthcare assistant (band 4)	1.20 (0.09)	£28.00	Hour	PSSRU 2016, section 14

ODP = Operating department practitioner

TABLE 4 Unit cost of disposable surgical equipment

Equipment/Implant	Quantity (n=40); Mean (SE)	Unit cost	Supplier number	Source
SMITH & NEPHEW				
Ligament chisel (rf probe ¹)	0.100 (0.048)	£340.79	72200682	NHS supply chain catalogue 2016 and Personal communication with finance department
Ablator (rf probe)	0.650 (0.105)	£340.79	72200683	
Tac-s (rf probe)	0.125 (0.053)	£349.31	72200681	
Hook (rf probe)	0.125 (0.053)	£149.32	7209646	
Incisor plus elite shaver	0.075 (0.042)	£104.92	72200081	
4.5mm long curved shaver	0.200 (0.082)	£137.25	7205332	
4.0/5.5mm abrader burr	0.175 (0.071)	£161.47	72200082	
4.0/5.5mm flat top burr	0.025 (0.025)	£161.47	72203130	
4.0/5.5mm barrel burr	0.200 (0.073)	£161.47	72203132	
Accupass suture	0.225 (0.076)	£104.29	7210425	
All suture cefix	0.125 (0.089)	£255.93	72201993	
Banana blade	0.150 (0.057)	£35.00	72203307	
Ambient super multivac 50	0.075 (0.042)	£167.07	ASHA4830-01	
Hip pac	0.025 (0.025)	£38.56	7209874	
Dyonics water pump	0.075 (0.042)	£66.95	7211006	
Starvac 90	0.025 (0.025)	£142.27	ASC4251-01	
Super turbovac 90	0.050 (0.035)	£154.64	ASH4250-01	
Hip disposable needle	0.025 (0.025)	£96.52	72201811	
110mm hip cannula	0.050 (0.035)	£40.60	72200436	
Cross 50	0.025 (0.025)	£139.05	72202140	
ARTHREX				
coolcut ablator 90	0.100 (0.048)	£123.04	AR-9705A-90	NHS supply chain catalogue 2016 and Personal communication with finance department
coolcut ablator 30/50/90	0.025 (0.025)	£125.45	AR-9703A-90	
4.2mm bone cutter (excalibur)	0.025 (0.025)	£77.20	AR-6420EX	
4.2mm bone cutter	0.050 (0.035)	£90.46	AR-6420XBC	
4.2mm sabre tooth shaver	0.025 (0.025)	£77.20	AR-6420CST	
4.2mm dissector	0.025 (0.025)	£90.46	AR-6420XDS	
4mm burr	0.250 (0.069)	£77.20	AR-8550RBE	

Equipment/Implant	Quantity (n=40); Mean (SE)	Unit cost	Supplier number	Source
CONMED LINVATEC				
4.2mm great white shaver	0.025 (0.025)	£81.35	HPS-C001	NHS supply chain catalogue 2016 and Personal communication with finance department
4.2mm full radius resector	0.050 (0.035)	£193.86	C9144	
4.5/5.5mm spherical burr	0.050 (0.035)	£193.86	C9014	
4.5/5mm oval burr	0.050 (0.035)	£59.12	702139600	
STRYKER				
5mm resector	0.100 (0.048)	£86.60	385552000	NHS supply chain catalogue 2016
5.5mm pear burr	0.075 (0.055)	£94.39	5820016050	
5.5mm barrel burr	0.100 (0.048)	£94.39	5820017050	
4.5mm burr	0.025 (0.025)	£86.60	375941000	
Pivot slingshot	0.025 (0.025)	£120.00	CAT02589	
Pivot nanopass	0.050 (0.035)	£120.00	CAT02298	
Pivot injector	0.025 (0.025)	£95.00	CAT01857	
Pivot cinchlock ss	0.225 (0.121)	£230.00	CAT02462	
Pivot nanotack	0.100 (0.070)	£200.00	CAT01858	
Samurai blade	0.050 (0.035)	£124.21	CAT00227	
Microfx blade	0.025 (0.025)	£151.60	234-200-200	
OTHER MANUFACTURERS				
Juggerknot (Biomet)	0.075 (0.075)	£173.00	912068	Personal communication

1. Rf probe = radio frequency probe

TABLE 5 Cost of hip arthroscopy surgery by resource category

Centre (number of patients)	Mean cost (standard error)					
	Equipment	Staff	Theatre running costs	Anaesthetic drugs and disposables	In-patient stay	Total
University Hospital Coventry and Warwickshire (n=7)	£1083 (155)	£1154 (96)	£626 (45)	£122 (0)	£711 (0)	£3695 (202)
Yeovil (n=2)	£458 (32)	£1119 (172)	£571 (86)	£122 (0)	£711 (0)	£2980 (290)
Royal Exeter and Devon (n=1)	£495 (-)	£845 (-)	£606 (-)	£122 (-)	£711 (-)	£2779 (-)
Frimley Park (n=1)	£502 (-)	£558 (-)	£358 (-)	£122 (-)	£355 (-)	£1895 (-)
Guys and St Thomas (n=1)	£657 (-)	£1244 (-)	£728 (-)	£122 (-)	£355 (-)	£3105 (-)
University College London Hospital (n=3)	£902 (305)	£1197 (180)	£674 (96)	£122 (0)	£592 (118)	£3487 (506)
Wrightington (n=3)	£856 (221)	£1260 (74)	£749 (40)	£122 (0)	£355 (0)	£3343 (200)
Northumbria (n=2)	£685 (7)	£958 (404)	£515 (157)	£122 (0)	£355 (0)	£2634 (567)
Doncaster and Bassetlaw (n=6)	£522 (122)	£1058 (126)	£564 (61)	£122 (0)	£533 (79)	£2798 (256)
Stanmore (n=1)	£734 (-)	£1556 (-)	£598 (-)	£122 (-)	£1066 (-)	£4076 (-)
Oswestry (A) & RH (n=1)	£1014 (-)	£1097 (-)	£753 (-)	£122 (-)	£711 (-)	£3697 (-)
South Tees (n=2)	£925 (380)	£1172 (78)	£587 (0)	£122 (0)	£355 (0)	£3161 (458)
Llandough (Cardiff) (n=4)	£563 (98)	£970 (77)	£564 (32)	£122 (0)	£355 (0)	£2574 (200)
Wrexham (n=1)	£446 (-)	£1446 (-)	£846 (-)	£122 (-)	£711 (-)	£3570 (-)
North Bristol (n=4)	£429 (145)	£827 (154)	£465 (76)	£122 (0)	£444 (89)	£2286 (448)
Spire (n=1)	£843 (-)	£455 (-)	£282 (-)	£122 (-)	£711 (-)	£2412 (-)
All centres (n=40)	£719 (58)	£1067 (47)	£591 (23)	£122 (0)	£542 (31)	£3042 (116)

Economic costs

Estimates of the economic costs associated with each intervention are summarised in Table 6 by type of resource and treatment allocation. Among the complete cases, and across the 12-month follow-up period, the mean total cost from a UK health and personal social service perspective were £3,742 in the surgery group and £1531 in the PHT group, generating an unadjusted mean cost-difference of £2,211 and adjusted mean cost-difference of £2,281 (95%CI £1,809, £2,575). Surgery costs accounted for approximately 70% of total unadjusted costs in the surgery group whilst the treatment costs (including surgery costs for PHT patients who had surgery) accounted for only 29% of the total adjusted costs in the PHT group. The corresponding mean total costs estimated from a societal perspective were £5,023 in the surgery group of which 52% is surgery costs, and £1,730 in the PHT group, 26% of which were accounted for by treatment costs, generating an unadjusted cost-difference of £3,354 (95%CI £1,809, £2,757).

Cost-effectiveness results

Base case analysis results

Table 7 presents estimates of the cost-effectiveness of hip arthroscopy versus PHT for FAI. In the base case analysis, surgery was associated with adjusted mean additional cost of £2,372 (95%CI £938, £3,805) and adjusted mean additional QALYs of -0.018 (95%CI -0.051 to 0.015) per patient compared with PHT over the 12 months of follow-up. On average, surgery was more expensive and marginally less effective than PHT in the adjusted analysis during the first year of follow-up. The mean base case incremental cost-effectiveness ratio (ICER) thus suggest that surgery was dominated by PHT at 12 months post-randomisation. Figure 1 shows the uncertainty around this central estimate of the ICER. The graph on the left-hand-side of the figure displays 1,000 simulated replicates of the ICER on a cost-effectiveness plane whilst the right graph display the probability that surgery is cost-effective compared with PHT for a range of cost-effectiveness thresholds. Almost all simulated replicates of the ICER fell to the left-hand side of the £30,000 and £50,000 per QALY cost-effectiveness threshold lines with the central estimate (indicated by

the black diamond) falling in the north-west quadrant. This suggests that surgery is unlikely to be cost-effective at the £20,000 to £30,000 per QALY threshold range (right plot), which NICE currently uses to determine the cost-effectiveness of health technologies.²⁶ The graph on the right-hand-side of the plot show that probability that surgery is cost-effective compared with PHT is close to zero for threshold values less than £100,000 per QALY.

Sensitivity analysis results

Of the sensitivity analyses performed, only the unadjusted analysis generated a difference in mean QALYs of 0.001 in favour of the surgery (Table 7). The probability that surgery is cost-effective was 0.005 at £30,000 per QALY and no more than 0.08 at £50,000 per QALY. All other sensitivity analyses adjusted for baseline characteristics such as sex, impingement type, study site, healthcare service use prior to randomisation and health-related quality of life. In the adjusted sensitivity analyses, surgery was significantly more expensive (adjusted mean difference in costs ranged from £2,186 to £6,389) and generated fewer QALYs (adjusted mean difference in QALYs ranged from -0.028 to -0.002) on average than PHT over 12 months of follow-up.

Subgroup analysis results

The subgroup analyses revealed substantial uncertainty around the central estimates of incremental costs and incremental QALYs because of the reduced sample size in each subgroup but the direction of relative cost-effectiveness of the interventions remained mostly the same as in the base-case analysis (see Table 7). Surgery generated fewer QALYs on average (adjusted mean difference in QALYs ranged from -0.002 to -0.029) and was significantly more expensive (adjusted mean difference in costs ranged from £1,863 to £3,442) than PHT. The only exception is the subgroup of patients in the surgery arm who had surgery within first 4 months after randomisation (n=74). In this post-hoc analysis conducted in response to a suggestion at peer-review, surgery generated mean incremental costs of £4,323 and adjusted mean incremental QALYs of 0.004 compared with PHT with an ICER of £1,080,750 per QALY gained at 12 months from randomisation.

TABLE 7 Cost-effectiveness results for the within-trial economic analysis with 1-year time horizon

Description	Cost-effectiveness outcomes			Probability surgery is cost-effective at cost-effectiveness threshold of			
	Mean incremental costs (95% CI), £	Mean incremental QALYs (95% CI)	ICER ^a	£13,000 per QALY	£20,000 per QALY	£30,000 per QALY	£50,000 per QALY
Base case analysis ¹	2372 (938, 3805)	-0.015 (-0.048, 0.018)	Dominated	0	0.001	0.002	0.005
SENSITIVITY ANALYSES (PRE-SPECIFIED)							
Unadjusted analysis	2370 (957, 3783)	0.004 (-0.045, 0.053)	592500	0.003	0.005	0.013	0.076
Adjusted complete case analysis	2186 (1743, 2630)	-0.016 (-0.049, 0.018)	Dominated	0	0	0	0.003
Per protocol sample ²	2908 (1343, 4473)	-0.008 (-0.042, 0.026)	Dominated	0	0.002	0.002	0.007
Per protocol sample ³	3702 (1910, 5494)	-0.003 (-0.039, 0.033)	Dominated	0	0	0	0.004
Societal costs	3446 (1698, 5194)	-0.017 (-0.050, 0.016)	Dominated	0	0	0	0
SF-12/SF-6D	2288 (839, 3738)	-0.002 (-0.017, 0.013)	Dominated	0.003	0.003	0.004	0.004
SENSITIVITY ANALYSES (POST HOC)							
Assume surgery costs £1,430 ^a	1283 (-254, 2820)	-0.017 (-0.050, 0.016)	Dominated	0.032	0.03	0.03	0.033
Assume surgery costs £6,387 ^b	6239 (4703, 7776)	-0.017 (-0.050, 0.016)	Dominated	0	0	0	0
Sub-group analyses (pre-specified)							
Feasibility sample (EQ-5D-3L)	2064 (1303, 2825)	-0.002 (-0.069, 0.065)	Dominated	0.002	0.003	0.029	0.119
Main study sample (EQ-5D-5L cross-walk value set)	2662 (492, 4832)	-0.015 (-0.053, 0.024)	Dominated	0.005	0.006	0.008	0.019
Main study sample (EQ-5D-5L new UK value set)	2859 (227, 5492)	-0.013 (-0.046, 0.021)	Dominated	0.012	0.013	0.011	0.016
Impingement type (CAM)	1960 (1443, 2477)	-0.011 (-0.045, 0.023)	Dominated	0	0	0	0.001
Impingement type (Pincer / Mixed)	3797 (-1996, 9590)	-0.034 (-0.114, 0.047)	Dominated	0.088	0.092	0.09	0.094
Age less than 40 years old	1863 (1163, 2563)	-0.009 (-0.048, 0.030)	Dominated	0	0	0.002	0.025
Age 40 years or more	3442 (-722, 7606)	-0.010 (-0.075, 0.055)	Dominated	0.054	0.063	0.068	0.083
SUB-GROUP ANALYSES (POST HOC)							
Restricted analysis to women only	1736 (821, 2651)	-0.002 (-0.055, 0.050)	Dominated	0	0.006	0.039	0.125
Restricted analysis to men only	2906 (477, 5335)	-0.012 (-0.052, 0.027)	Dominated	0.013	0.017	0.017	0.024
Had surgery within 4 months of randomisation	4323 (1862, 6784)	0.004 (-0.039, 0.046)	1080750	0	0	0.002	0.007
Had surgery after months from randomisation	1779 (917, 2640)	-0.029 (-0.072, 0.014)	Dominated	0	0	0.001	0.007

ICER = Incremental cost-effectiveness ratio; CI = confidence interval

1. Adjusted for age, sex, treatment allocation, study site, impingement type, baseline health-related quality of life and baseline costs.

2. Per protocol sample 1: Restricted analysis to patients who received the allocated treatment-arm intervention (i.e. excluded cross-overs, surgery patients who did not have surgery and patients in the PHT arms who did not have PHT).

3. Per protocol sample 2 - Restricted analysis to patients whose surgery or PHT was deemed to be of good quality as assessed by clinical panel.

4. Mean ICERs for base case, sensitivity and subgroup analyses all fell in the north-

west quadrant of the cost-effectiveness plane where surgery is more costly and less effective than PHT.

a. HRG code HN15A (Minor Hip Procedures for Non-Trauma, 19 years and over), short-stay.

b. HRG code HN13A (Major Hip Procedures for Non-Trauma, 19 years and over, with CC Score 10+) short-stay.

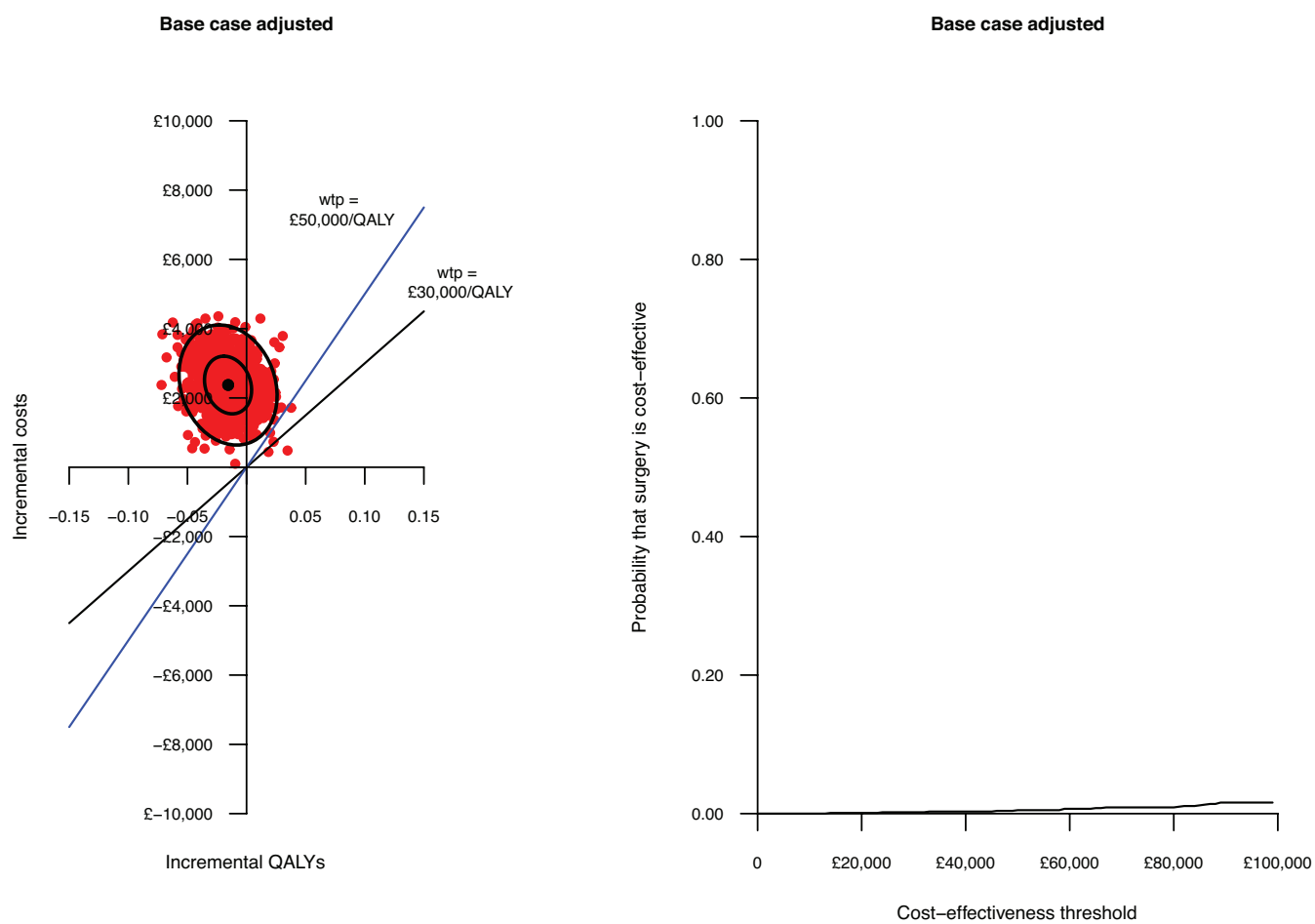


FIGURE 1 Base case analysis comparing the cost-effectiveness of arthroscopic surgery versus PHT for FAI. The analysis accounted for missing data using multiple imputation and adjusting for age, sex, baseline health-related quality of life (effectiveness regression)

References

- Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value in Health* 2013; **16**(2): 231-50.
- Curtis L. Unit Costs of Health and Social Care 2016. 2016. <http://www.pssru.ac.uk/project-pages/unit-costs/2016/>.
- Digital N. Prescription Cost Analysis England 2016. 2016 <http://www.content.digital.nhs.uk/catalogue/PUB23631> (accessed 27/04/2017).
- Scotland IS. SFR 5.10 Theatre Costs 2016. <http://www.isdscotland.org/Health-Topics/Finance/Costs/Detailed-Tables/Theatres.asp>.
- Scotland N. Scottish Health Service Costs Book User Manual June 2016 Version: 3.0. In: Scotland N, editor.; 2016.
- Chain NS. NHS Supply Chain Catalogue 2016. <https://www.supplychain.nhs.uk/clinical-and-consumables/2016>).
- Health Do. National schedule of Reference Costs (2014-2015): the main schedule 2015.
- EuroQol G. EuroQol—a new facility for the measurement of health-related quality of life. *Health policy (Amsterdam, Netherlands)* 1990; **16**(3): 199.
- Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research* 2011; **20**(10): 1727-36.
- Tarlov A. The medical outcome study: an application of methods for monitoring the results of medical care. *JAMA* 1989; **262**: 907-13.
- Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *Bmj* 1998; **316**(7133): 736-41.
- Van Hout B, Janssen M, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health* 2012; **15**(5): 708-15.
- Devlin NJ, Shah KK, Feng Y, Mulhern B, Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health economics* 2017.

14. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Medical care* 2004; **42**(9): 851-9.
15. Buuren Sv, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *Journal of statistical software* 2010: 1-68.
16. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II—an ISPOR Good Research Practices Task Force report. *Value in Health* 2015; **18**(2): 161-72.
17. 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): 1157-70.
18. Henningsen A, Hamann JD. systemfit: A package for estimating systems of simultaneous equations in R. *Journal of Statistical Software* 2007; **23**(4): 1-40.
19. Excellence NIoHaC. Guide to the methods of technology appraisal. NICE Guideline (PMG9) 2013.
20. Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health technology assessment (Winchester, England)* 2015; **19**(14): 1.
21. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic evaluation in clinical trials: OUP Oxford; 2014.
22. Curtis L. Unit Costs of Health and Social Care 2016, Personal Social Services Research Unit, University of Kent, Canterbury. Available from <http://www.pssru.ac.uk/project-pages/unit-costs/2016/>. 2016.
23. Information Services Scotland. SFR 5.10: THEATRE COSTS. Available from <http://www.isdscotland.org/Health-Topics/Finance/Costs/Detailed-Tables/Theatres.asp>. Accessed 10/05/2017. 2016.
24. Department of Health. National schedule of reference costs (2015 to 2016): the main schedule. Available from <https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016>. 2016.
25. NHS Digital. Prescription Cost Analysis, England - 2016. Available from <http://www.content.digital.nhs.uk/catalogue/PUB23631>. Accessed 27 April 2017. 2016.
26. Excellence NIoHaC. Guide to the methods of technology appraisal 2013 (PMG9). London: National Institute of Health and Care Excellence 2013.