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Cost-effectiveness analysis of a pragmatic randomized trial evaluating surgical reconstruction versus rehabilitation in patients with long-standing anterior cruciate ligament injury

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Aims
The aim of this study was to estimate the incremental use of resources, costs, and quality of life outcomes associated with surgical reconstruction compared to rehabilitation for long-standing anterior cruciate ligament (ACL) injury in the NHS, and to estimate its cost-effectiveness.

Methods
A total of 316 patients were recruited and randomly assigned to either surgical reconstruction or rehabilitation (physiotherapy but with subsequent reconstruction permitted if instability persisted after treatment). Healthcare resource use and health-related quality of life data (EuroQol five-dimension five-level health questionnaire) were collected in the trial at six, 12, and 18 months using self-reported questionnaires and medical records. Using intention-to-treat analysis, differences in costs, and quality-adjusted life years (QALYs) between treatment arms were estimated adjusting for baseline differences and following multiple imputation of missing data. The incremental cost-effectiveness ratio (ICER) was estimated as the difference in costs divided by the difference in QALYs between reconstruction and rehabilitation.

Results
At 18 months, patients in the surgical reconstruction arm reported higher QALYs (0.052 (95% confidence interval (CI) -0.012 to 0.117); p = 0.177) and higher NHS costs (£1,017 (95% CI 557 to 1,476); p < 0.001) compared to rehabilitation. This resulted in an ICER of £19,346 per QALY with the probability of surgical reconstruction being cost-effective of 51% and 72% at a willingness-to-pay threshold of £20,000 and £30,000 per QALY, respectively.

Conclusion
Surgical reconstruction as a management strategy for patients with long-standing ACL injury is more effective, but more expensive, at 18 months compared to rehabilitation management. In the UK setting, surgical reconstruction is cost-effective.

Cite this article: *Bone Joint J* 2024;106-B(1):38–45.

Introduction
Anterior cruciate ligament (ACL) rupture is a common debilitating injury causing instability of the knee. For such a common injury, its current management is based on limited evidence,[1–5] and this has led to a highly varied approach to managing both acute and chronic ACL injury,[6] as well as concerns about post-traumatic osteoarthritis (OA).[7] Non-surgical (rehabilitation) or surgical (reconstruction) treatments are common approaches to managing ACL injury. ACL reconstruction is one of the most frequent knee surgeries worldwide with 30,000 being performed each year in England.[6] Rehabilitation is considerably

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doi:10.1302/0301-620X.106B1.BJJ-2023-0175.R1 $2.00

Bone Joint J 2024;106-B(1):38–45.

cheaper than surgery but may not to be as effective in stabilizing the knee. Furthermore, patients with ACL injury often have delayed presentation, and there was no high-quality evidence on which to base practice.[4]

The ACL Surgery Necessity in Non-Acute Patients (ACL SNNAP) trial (ISRCTN10110685) was designed to confirm the best management strategy between reconstructive surgery and rehabilitation for patients with a non-acute ACL injury.[8] It showed surgical reconstruction to be the superior clinical management option. A brief cost-effectiveness analysis reported for this trial suggested reconstruction to be cost-effective at £30,000 per QALY gained threshold.[8]

This study aims to present and expand the cost-effectiveness analysis data in more detail. We compare health-related quality of life (HRQoL), the use of resources and costs of the 316 patients in the ACL SNNAP trial. Furthermore, we examine the impact of including non-NHS healthcare costs. Finally, we evaluate the impact of the COVID-19 pandemic on the cost-effectiveness results, in terms of homogeneity of care being provided as well as the variation in outcomes following the first UK COVID-19 lockdown.

Methods

The ACL SNNAP trial randomized 316 patients from 29 centres in the UK between February 2017 and April 2020, allocating them into one of two options for the management of non-acute ACL injury: surgical reconstruction or rehabilitation. The design included the option for later surgical reconstruction in the rehabilitation group, as required (continued knee instability). Randomization was stratified by baseline Knee injury and Osteoarthritis Outcome Score (KOOS4; < 30 or > 30)[9] and recruitment site. Patients with symptomatic knee instability consistent with an ACL injury were eligible to be included in the trial. Further details on the inclusion and exclusion criteria are reported in the protocol.[10]

The primary analysis of the trial showed a statistically significant difference between surgical reconstruction and rehabilitation arms, as measured by the KOOS4 (7.9 (95% confidence interval (CI) 2.5 to 13.2); p = 0.005) favouring surgical reconstruction. Overall, 65 patients (41%) allocated to rehabilitation underwent subsequent surgery within 18 months from randomization.[8]

The primary outcome of the health economics analysis was the incremental cost per quality-adjusted life year (QALY) gained. This was informed by responses to the EuroQol five-dimension five-level health questionnaire (EQ-5D-5L)[11] during 18-month follow-up. The perspective of the analysis was of the NHS and personal social services. However, we also considered a wider perspective by including private healthcare contacts. The time horizon was 18-month follow-up of the ACL SNNAP trial, and we discounted total costs and QALYs at the recommended 3.5% rate.[12] A health economics analysis plan was developed and approved prior to data lock (available on request to corresponding author).

Data collection and attribution of health utilities and costs. Resource use and EQ-5D-5L data were collected for each patient in the trial using questionnaires at baseline and at six, 12, and 18 months. At these timepoints, patients were asked to report their use of healthcare resources in the previous six months and their HRQoL on the day of survey. The resource use questionnaires collected data on visits to and from healthcare practitioners (NHS and private) and admissions to hospital.

Hospital admissions related to the knee were identified from data reported in the self-reported questionnaires, clinical events reported, and assessment of hospital records for all patients by local research teams. Where potentially relevant admissions were identified, a data extraction sheet was completed providing details of the admission. Hospital admissions were then converted into a Healthcare Resource Group (HRG). HRGs are groups of International Classification of Diseases (ICD-10)[13] diagnoses and OPCS Classification of Interventions and Procedures codes,[14] which use comparable levels of healthcare resources. Following clinical and hospital coder expert opinion, we identified ICD-10 and OPCS for all hospital admissions (Supplementary Table i) and used these to derive HRGs.

Rehabilitation sessions related to the study knee were identified from data reported in the self-reported questionnaires, and assessment of hospital records for all patients by local research teams. Where rehabilitation sessions were available from hospital records and self-reported questionnaires for the same period, we used data from the source reporting the highest number of sessions. Where rehabilitation session data were available from hospital records but were missing from self-reported questionnaires, we used data from hospital records.

Unit costs applied to all resource use items and were derived from NHS Reference Costs and Unit Costs of Health and Social Care,[15–17] inflated, where necessary, to 2019-20 prices using the healthcare and community health services inflation index.[16] Supplementary Tables i and ii list the unit costs used.

The EQ-5D-5L questionnaire asks patients to report whether they have no problems, slight problems, moderate problems, severe problems, and extreme problems in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses were converted into utility scores using the cross-walk to the three-level version.[18] Utility scores of 1 indicate full health, 0 represents states equal to death, and negative values indicate states considered worse than death. QALYs were calculated using the area under the curve approach, which involves estimating the mean EQ-5D-5L utility between each follow-up time, and weighting it by survival time. Partially completed EQ-5D-5L questionnaires were considered missing.

Missing data. We followed best practice methods for addressing missing data in cost-effectiveness studies.[19] See the Supplementary Material for details on imputation of missing data. Briefly, missing data on patients' characteristics, EQ-5D-5L, and costs at baseline were imputed using unconditional mean imputation. We used multiple imputation by chained equations to impute missing data on EQ-5D-5L utility scores and visual analogue scale (VAS) scores, and cost components, at each follow-up timepoint. We used predictive mean matching to create 30 imputed datasets (proportion of data missing across all time periods × 100) with ten nearest neighbours.

Cost-effectiveness analysis. Our analysis followed intent-to-treat principles wherein healthcare resource use, costs, and EQ-5D-5L scores were analyzed according to treatment allocation, regardless of the treatment actually received. Differences

Table I. Period costs by follow-up and treatment allocation (observed data without imputation for missing data).

Cost category	Baseline to 6 mths, mean (SD; n)		Mean difference (95% CI)*	6 to 12 mths, mean (SD; n)		Mean difference (95% CI)*	12 to 18 mths, mean (SD; n)		Mean difference (95% CI)*
	Surgical	Rehab		Surgical	Rehab		Surgical	Rehab	
Total NHS costs, £	2,680 (1,805; 88)	1,068 (1,196; 98)	1,612 (1,225 to 1,999)	765 (1,256; 87)	671 (1,144; 78)	93 (-190 to 377)	146 (375; 127)	330 (803; 120)	-184 (-339 to -28)
Hospital admissions (total)	1,803 (1,637; 155)	411 (1,028; 159)	1,392 (1,092 to 1,693)	456 (1161; 155)	518 (1,190; 159)	-62 (-356 to 231)	34 (301; 155)	214 (768; 159)	-180 (-325 to -34)
ACL reconstruction	1,736 (1,649; 155)	394 (1,013; 159)	1,342 (1,029 to 1,656)	402 (1131; 155)	518 (1,190; 159)	-116 (-395 to 163)	34 (301; 155)	214 (768 ;159)	-180 (-325 to -34)
Other admissions	67 (373; 155)	17 (211; 159)	50 (-17 to 117)	54 (337; 155)	0 (0; 159)	54 (8 to 100)	0 (0; 155)	0 (0; 159)	
Physiotherapy sessions	225 (279; 152)	354 (313; 159)	-128 (-200 to -56)	217 (332; 152)	138 (263; 156)	81 (28 to 134)	64 (150; 153)	52 (132; 159)	13 (-16 to 42)
Primary care	41 (75; 88)	23 (62; 93)	17 (-4 to 39)	15 (34; 87)	10 (28; 78)	5 (-1 to 10)	8 (25; 127)	13 (40; 120)	-5 (-11 to 0)
Outpatient care	189 (262; 88)	147 (231; 93)	43 (-49 to 134)	52 (135; 87)	84 (188; 78)	-36 (-78 to 6)	18 (56; 127)	49 (117; 120)	-33 (-51 to -14)
Other healthcare contacts	39 (106; 88)	57 (192; 93)	-18 (-74 to 37)	2 (20; 87)	31 (127; 78)	-29 (-53 to -6)	4 (36; 127)	26 (95; 120)	-22 (-40 to -5)
Total non-NHS costs, £	53 (151; 88)	43 (142; 93)	9 (-35 to 52)	38 (133; 87)	31 (112; 78)	-6 (-50 to 37)	76 (356; 127)	106 (455; 120)	-30 (-106 to 45)
Total healthcare, £	2,733 (1,828; 88)	1,111 (1,220; 93)	1,622 (1,233 to 2,011)	803 (1,285; 87)	702 (1,195; 78)	100 (-193 to 394)	222 (509; 127)	436 (913; 120)	-214 (-400 to -28)

*Difference between treatment arms (surgical vs rehabilitation) were obtained from multilevel mixed-effects models, adjusted for treatment allocation; a time by treatment interaction was included in the model; the follow-up timepoint was used as a categorical variable; robust standard errors were used to account for clustering by site.
ACL, anterior cruciate ligament; CI, confidence interval; SD, standard deviation.

Table II. EuroQol five-dimension utility score and EuroQol Five-dimension visual analogue scale by treatment allocation at each follow-up timepoint (observed data without imputation for missing data).

Follow-up	Surgical reconstruction		Rehabilitation		Mean difference* (95% CI)
	n	Mean (SD)	n	Mean (SD)	
EQ-5D-5L utility					
Baseline	156	0.558 (0.252)	159	0.568 (0.258)	
6 mths	85	0.642 (0.232)	89	0.642 (0.271)	0.016 (-0.068 to 0.100)
12 mths	84	0.781 (0.175)	75	0.730 (0.243)	0.067 (0.007 to 0.127)
18 mths	115	0.766 (0.227)	116	0.724 (0.244)	0.052 (-0.012 to 0.117)
EQ-5D-5L VAS					
Baseline	154	64.2 (20.8)	157	68.4 (20.5)	
6 mths	84	69.8 (18.0)	89	67.6 (19.2)	2.9 (-0.2 to 6.0)
12 mths	84	75.5 (17.1)	75	75.9 (18.5)	-0.4 (-5.2 to 4.4)
18 mths	114	77.7 (16.3)	113	75.9 (16.2)	3.5 (-1.2 to 8.1)

Values are mean (standard deviation) or mean (95% confidence interval).
*Differences between treatment arms (surgical vs rehabilitation) obtained from multilevel mixed-effects models, adjusted for baseline utility, site, and treatment interaction with time, where the follow-up timepoint was used as a categorical variable.
CI, confidence interval; EQ-5D-5L, EuroQol five-dimension five-level health questionnaire; SD, standard deviation; VAS, visual analogue scale.

between arms at each timepoint were estimated using multilevel mixed effects linear regression models to allow for multiple follow-ups clustered within patient and with cluster-robust standard errors (by site). The models were adjusted for treatment allocation, an interaction between follow-up time and treatment allocation, and, in the case of EQ-5D-5L, baseline utility score.

Following multiple imputation, we estimated mean costs (by type) and QALYs from baseline to 18 months using separate linear regression models controlling for treatment allocation, and, for QALYs, baseline EQ-5D-5L utility, and cluster-robust standard errors (by site). Estimates derived from each imputed dataset were combined using Rubin's rule to estimate the adjusted mean difference and standard error for each outcome.

The incremental cost-effectiveness ratio (ICER) was estimated by dividing the mean cost difference between surgical reconstruction and non-surgical management (rehabilitation) by the mean QALY difference. We estimated the joint uncertainty around incremental total costs and QALYs (i.e. the difference between surgical and non-surgical management), and in the cost-effectiveness, by bootstrapping 1,000 times from each of the *n* imputed datasets (creating at least 1,000 × 30 bootstraps), running the estimation model on each bootstrapped dataset and extracting the estimated treatment effects. From these bootstrapped results, we calculated the probability that surgical reconstruction is more cost-effective than non-surgical management for different threshold values per QALY gained.[20] These were calculated by estimating the proportion of bootstrap

Table III. Quality-adjusted life years, healthcare costs, and cost-effectiveness at 18 months following multiple imputation.

Variable	Surgical reconstruction, mean (SE)	Rehabilitation, mean (SE)	Mean difference (95% CI)*
n	156	160	
QALYs	1.03 (0.02)	0.98 (0.03)	0.052 (-0.03 to 0.13)
Total NHS costs, £	3,186 (155)	2,169 (141)	1,017 (557 to 1,476)
Hospital admissions	2,287 (122)	1,138 (118)	1,150 (773 to 1,523)
Rehabilitation sessions	510 (45)	550 (40)	-40 (-171 to 90)
Total non-NHS healthcare, £	197 (44)	191 (48)	6 (-77 to 90)
Total healthcare costs, £	3,383 (156)	2,360 (147)	1,023 (538 to 1,508)
Incremental cost-effectiveness ratio, £†			
NHS costs only			19,346
Total healthcare costs			19,473
Probability that surgical management is the most cost-effective option, %			
At £20,000 per QALY‡			51
At £30,000 per QALY‡			72

Values are mean (standard error) or mean (95% confidence interval).
*Surgical vs rehabilitation. Based on a linear regression model of each treatment allocation against each outcome adjusted for recruitment site and, for QALYs, baseline utility score.
†Estimated as the difference in costs divided by the difference in QALYs.
‡NHS costs only.
CI, confidence interval; QALYs, quality-adjusted life years; SE, standard error.

replicates with a net monetary benefit (NMB) above 0 for each threshold value, where the NMB is given by the product of the mean difference in QALYs and the threshold value minus the mean difference in costs.

Subgroup analysis examined the cost-effectiveness within patient subgroups defined by age at recruitment (less than 40 years, or 40 years or older), baseline KOOS4 (less than 30 or greater than or equal to 30), sex (male or female), and physical activity prior to injury (high (Tegner Activity Scale (TAS)[21] 5 or above) or moderate/low (TAS below 5).

The COVID-19 pandemic has significantly disrupted all medical research, including the ACL-SNNAP trial, and we wanted to assess the impact of the first national COVID-19 lockdown in terms of homogeneity of care provided, patient outcomes, and resulting cost-effectiveness estimates. This will provide a valuable insight into the value of the interventions in the absence of the pandemic. Hence, we estimated the incremental NHS costs and QALYs of those who completed 18-month follow-up before (n = 159) and after (n = 157) the first UK nationwide lockdown on 23 March 2020. We examined whether there were significant differences between the two periods by allocation group, using cluster-robust standard errors (by recruitment site), in the proportion of individuals receiving surgery (logistic model); time to surgery (Cox proportion hazards model); and physiotherapy sessions received (Poisson model). We judged a difference to be statistically significant at the p-value of 0.05. All analyses were conducted using STATA v. 17.1 MP (StatCorp, USA).

Results

Of the 316 patients recruited to the trial, 156 were allocated to the surgical reconstruction arm and 160 to the rehabilitation arm. The characteristics of the groups were well balanced at baseline. The mean age at baseline was 32.9 years (standard deviation (SD) 9.8) and 208 patients (66%) were male. The mean KOOS4 and EQ-5D-5L utility at baseline were 44.5 (SD 18.9) and 0.56 (SD 0.26), respectively. The randomized intervention was received by 72% (n = 113) and 78% (n = 125) of patients in the surgical reconstruction and rehabilitation arms, respectively.

Overall, the levels of missing data were 30% across all self-reported data items and EQ-5D-5L utility scores (Supplementary Table iii). The levels of missing data were similar between trial arms, and the pattern suggests that data missing at random could be a plausible assumption.

Table I presents mean costs for each cost type and totals by treatment allocation and follow-up period, and adjusted mean differences. Total NHS and healthcare costs were substantially greater between baseline and six months than in subsequent periods. In the first six months, total NHS costs were significantly higher in the surgical arm compared to rehabilitation arm (£1,612 (95% CI 1,225 to 1,999); $p < 0.001$). Relative to the rehabilitation arm, individuals allocated to the surgical arm had higher hospitalization costs in the first six months (£1,392 (95% CI 1,092 to 1,693); $p < 0.001$), and significantly lower hospitalization costs between 12 and 18 months (-£180 (95% CI -325 to -34); p = 0.016). Physiotherapy costs in the rehabilitation arm were significantly higher, relative to the surgery arm, in the first six months (£128 (95% CI 56 to 200); $p < 0.001$) but lower between six and 12 months (-£81 (95% CI -134 to -28); p = 0.003). Non-NHS healthcare costs were substantially smaller than NHS costs in all periods and without significant differences between trial arms.

Table II presents EQ-5D-5L utility scores and differences by treatment allocation at each timepoint. EQ-5D-5L scores improved between baseline and 18 months. Patients in the surgical arm reported significantly higher EQ-5D-5L scores at 12 months' follow-up compared to the rehabilitation arm (0.067 (95% CI 0.007 to 0.127); p = 0.028). Supplementary Table iv presents the distribution of responses to each EQ-5D-5L domain at each follow-up point. The odds of reporting more severe levels of usual activities in individuals in the surgical arm at 18 months was 0.53 times lower relative to the rehabilitation arm (p = 0.004; Supplementary Table v). No other significant

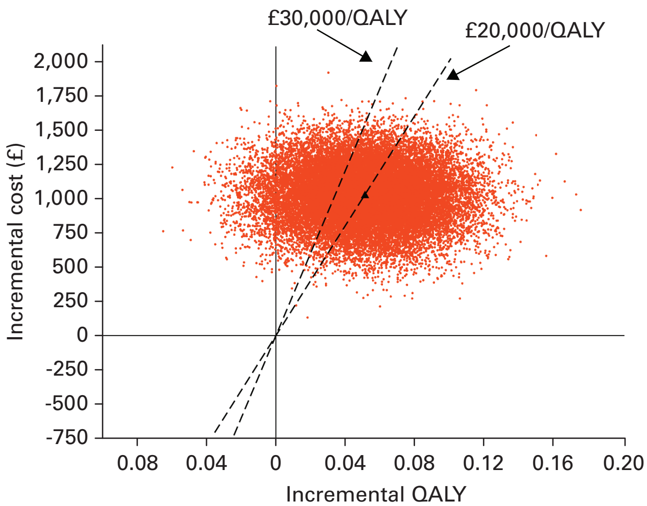

Fig. 1

Cost-effective scatter plot for the base case analysis. Scatter plot of estimated joint density of incremental costs and quality-adjusted life-years (QALYs) of surgical reconstruction relative to rehabilitation obtained by bootstrap resampling from each of the 30 imputed datasets, running the regression models on each bootstrapped dataset and extracting the estimated incremental costs and QALYs. Dashed lines represent threshold values of £20,000 and £30,000 per QALY gained. Bootstrapped results falling below the lines are deemed cost-effective. From the bootstrapped results, we calculated the probability that surgical management was more cost-effective than rehabilitation for different threshold values per QALY gained.

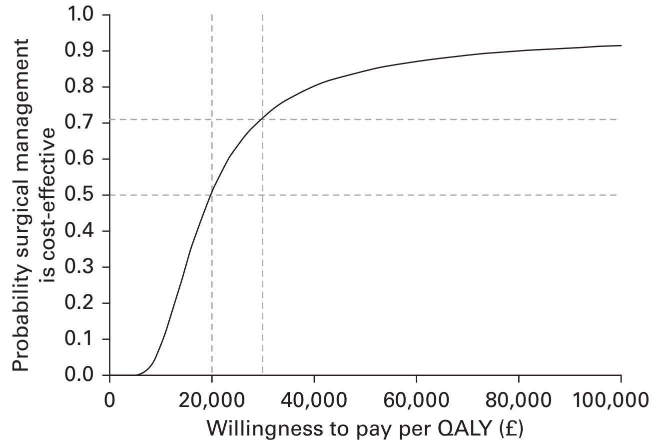

Fig. 2

Cost-effectiveness acceptability curve. Probability captures the joint uncertainty in incremental costs and quality-adjusted life-years (QALYs) of surgical reconstruction compared to rehabilitation, and was obtained by estimating the proportion of bootstrapped results that were cost-effective for each threshold value. Given a willingness-to-pay threshold of £30,000 per QALY gained, the probability that surgical management is cost-effective compared to rehabilitation is 0.72.

differences were identified across EQ-5D-5L domains and follow-up periods between treatment arms.

Following multiple imputation, patients in the surgical arm reported significantly higher EQ-5D-5L scores at 12 months' follow-up compared to the rehabilitation arm (0.077 (95% CI 0.008 to 0.146); $p = 0.030$) and no significant differences were found for the remaining follow-up periods (Supplementary Table vi). In terms of total healthcare costs (NHS and non-NHS), patients in the surgical reconstruction arm reported significantly higher costs between baseline and six months (£1,295 (95% CI 988 to 1,602) and £1,313 (95% CI 969 to 1,657), respectively; both $p < 0.001$) relative to the rehabilitation arm (Supplementary Table vii). The NHS and healthcare costs were significantly lower in the surgical arm between 12 months and 18 months (-£236 (95% CI -392 to -79); $p = 0.003$; and -£256 (95% CI -434 to -79); $p = 0.005$, respectively) relative to the rehabilitation arm.

Cost-effectiveness analysis. Table III shows the cost-effectiveness analysis results at 18 months following multiple imputation of missing data. Patients in the surgical reconstruction arm reported higher QALYs compared to rehabilitation but the difference was not statistically significant (0.052 (95% CI -0.03 to 0.13); $p = 0.177$). Total NHS costs were larger in the surgical reconstruction arm (£1,017 (95% CI 557 to 1,476); $p < 0.001$), as a result of higher hospitalization costs (£1,150 (95% CI 773 to 1,523); $p < 0.001$).

Adopting an NHS perspective, the ICER for surgical management programme versus rehabilitation was £19,346 per QALY gain, below the standard threshold for cost-effectiveness in the UK (£20,000 to £30,000 per QALY gain). Similar results were derived when using all healthcare costs (NHS and non-NHS), with the ICER for surgical management versus rehabilitation being £19,473.

Figure 1 presents the cost-effectiveness scatter plot giving differences in mean total costs and QALYs for surgical versus rehabilitation management adopting the NHS perspective. Most bootstrap replicates remained largely in the north-east quadrant of the cost-effectiveness scatter plot, indicating that surgical reconstruction resulted in higher QALYs but also higher costs relative to rehabilitation. Figure 2 shows that the probability that surgical reconstruction is cost-effective was 51% and 72% at a threshold value of £20,000 and £30,000 per QALY, respectively.

Subgroup analysis. Table IV presents cost-effectiveness results at 18 months by subgroups of patients. There is considerable variation in the cost-effectiveness estimates between patient subgroups by age and physical activity prior to injury. Adopting a £30,000 per QALY threshold, surgical management was cost-effective for patients aged under 40 years and for those with a high level of physical activity prior to injury. All subgroups by baseline KOOS4 and sex reported ICERs below the £30,000 per QALY threshold.

COVID-19 lockdown. We found no significant differences at baseline between individuals completing the trial before and after lockdown (Supplementary Table viii). Patients in the surgical arm reported significantly higher EQ-5D-5L scores at 12 and 18 months' follow-up compared to the rehabilitation arm before lockdown (0.124 (95% CI 0.066 to 0.183); $p < 0.001$; and 0.079 (95% CI 0.007 to 0.151); $p = 0.032$, respectively) but no significant differences after lockdown (Supplementary Table ix).

Table IV reports the ICER for surgical management programme versus rehabilitation to be £10,782/QALY for the

Table IV. Quality-adjusted life years, NHS costs, and cost-effectiveness at 18 months following multiple imputation in patient subgroups.

Variable	Total, n		Mean NHS costs, £ (SE)		Mean difference (95% CI)*	QALYs		Mean difference (95% CI)*	ICER, £/ QALY
	Surgical	Rehab	Surgical	Rehab		Surgical	Rehab		
Sex									
Female	46	61	3,776 (279)	2,123 (230)	1,653 (842 to 2,464)	1.00 (0.04)	0.97 (0.04)	0.07 (-0.06 to 0.20)	23,369
Male	110	99	2,939 (181)	2,198 (180)	741 (213 to 1,270)	1.04 (0.03)	0.98 (0.03)	0.05 (-0.04 to 0.13)	15,501
Age at baseline									
< 40 yrs	114	122	3,093 (174)	2,154 (163)	939 (413 to 1,466)	1.04 (0.02)	0.97 (0.03)	0.07 (-0.02 to 0.15)	13,597
≥ 40 yrs	42	38	3,438 (325)	2,218 (284)	1,219 (144 to 2,295)	1.01 (0.04)	0.97 (0.04)	< 0.01 (-0.13 to 0.14)	313,069
Baseline KOOS4									
< 30	40	36	3,471 (250)	2,363 (266)	1,108 (456 to 1,760)	0.93 (0.04)	0.79 (0.05)	0.11 (-0.07 to 0.29)	10,047
≥ 30	116	124	3,087 (188)	2,113 (165)	975 (379 to 1,570)	1.06 (0.02)	1.03 (0.03)	0.03 (-0.03 to 0.10)	27,849
Activity prior to injury†									
Moderate/low	17	24	4,120 (548)	1,644 (377)	2,476 (1,336 to 3,615)	0.95 (0.07)	0.90 (0.06)	0.06 (-0.15 to 0.27)	43,416
High	139	136	3,078 (159)	2,262 (151)	810 (337 to 1,283)	1.04 (0.02)	0.98 (0.03)	0.05 (-0.02 to 0.13)	15,262
Completion of follow-up									
Before 23 March 2020	80	79	3,251 (222)	2,326 (210)	925 (417 to 1,434)	1.06 (0.03)	0.97 (0.03)	0.09 (-0.01 to 0.18)	10,782
After 23 March 2020	76	81	3,117 (214)	2,016 (187)	1,101 (412 to 1,789)	0.99 (0.03)	0.99 (0.04)	0.02 (-0.08 to 0.12)	54,789

*Surgical versus rehabilitation, based on a linear regression model of each treatment allocation against each outcome adjusted for recruitment site and, for QALYs, baseline utility score.
†Modified Tenger score.
CI, confidence interval; ICER, incremental cost-effectiveness ratio; KOOS, Knee injury and Osteoarthritis Outcome Score; QALY, quality-adjusted life year; SE, standard error.

patients who completed follow-up before lockdown in contrast with £54,789/QALY for patients who completed it after (Supplementary Figure a). This was largely due to higher incremental QALYs (0.09 QALYs (95% CI -0.01 to 0.18); p = 0.080) and lower incremental costs (£925 (95% CI 417 to 1,434); p = 0.001) before lockdown compared to after the lockdown date (0.02 QALYs (95% CI -0.08 to 0.12); p = 0.668, and £1,101 (95% CI 412 to 1,789); p = 0.003). Hence, among patients who completed follow-up before and after the lockdown, the probability that surgical reconstruction is cost-effective was 92% and 35%, respectively, at a threshold value £30,000 per QALY (Supplementary Figures a and b).

There were no significant differences before and after the lockdown date in odds of receiving surgery in both the surgical (odds ratio (OR) 1.13 (95% CI 0.54 to 2.39) after lockdown; p = 0.749) and rehabilitation arms (OR 0.74 (95% CI 0.35 to 1.57); p = 0.433); time to surgery in both the surgical (hazard ratio (HR) 1.03 (95% CI 0.68 to 1.54) after lockdown; p = 0.900) and rehabilitation arms (HR 0.77 (95% CI 0.43 to 1.38); p = 0.376); or number of physiotherapy sessions received in the rehabilitation arm (incidence rate ratio (IRR) 1.21 (95% CI 0.96 to 1.53) after lockdown; p = 0.110), relative to those completing the trial after lockdown. However, in the surgical arm, patients received fewer physiotherapy sessions after lockdown compared to those completing the trial before lockdown (IRR 0.64 (95% CI 0.48 to 0.86) after lockdown; p = 0.003).

Discussion

Over 18 months of follow-up in the ACL-SNNAP trial, we found that surgical management led to improved HRQoL compared to non-surgical management, but with higher healthcare costs. Using £20,000 to £30,000 per QALY thresholds, we report surgical management to be cost-effective in the UK setting.

A recent trial in the Netherlands comparing surgical management with rehabilitation in individuals with recent or acute ACL injury (less than two months) concluded that early ACL reconstruction was not cost-effective.[22] However, our study looked at long-standing ACL injury whereby patients in the Dutch study were recruited following recovery from their acute symptoms. Furthermore, the study conducted in the Netherlands was a smaller clinical trial where patients were followed up for two years. Consistent with our findings, the authors reported early reconstruction to be more effective, albeit with smaller gains (0.04 QALYs vs 0.05 QALYs in our study), but more costly than rehabilitation. The difference in costs between the two trial arms was considerably higher than what we found in the ACL-SNNAP trial, due to higher rehabilitation and hospitalization costs in the Dutch study compared to our UK study among those allocated to surgical management. The other major difference between studies is that the smaller Dutch study completed follow-up prior to the COVID-19 pandemic, whereas our study was impacted by the resulting lockdown.

We evaluated the homogeneity in care over the pandemic and its impact on the cost-effectiveness results by dividing trial patients into those completing the trial prior to or after the UK national lockdown. We found differences in the QALY gains associated with the surgical management arm to be higher prior to lockdown compared to after lockdown. These resulted in surgical management being cost-effective in the cohort of patients who completed the trial prior to national lockdown, but not cost-effective in those who completed it after the national lockdown. The number of reported rehabilitation sessions among those allocated to the surgical arm was significantly lower for those who completed the trial after the lockdown, with four fewer sessions per individual. Rehabilitation sessions involve physical attendance, which would have been affected due to the lockdown. However, there was no significant difference in rehabilitation sessions before and after lockdown for those allocated to the rehabilitation arm.

The age range of our population is worthy of note. The somewhat older population in SNNAP, compared to some other ACL-related studies,[4,23] is likely a manifestation of both inclusion criteria and the characteristics of a more chronic (long-standing) ACL insufficient population. Our age inclusion criteria of 18 years or older resulted in a more representative sample of the population in England undergoing ACL reconstruction, and allowed for the examination of the cost-effectiveness of surgery relative to rehabilitation by age. ACL injuries are more common in younger populations. However, older adults are remaining active for longer, continuing to participate in sports. In a study of national hospital data in England between 1997 and 2007, the mean age at surgery was 29.5 years, and the greatest percentage increase in rate of surgery was observed in the 40 to 49 and 50 to 59 year age groups.[6] As our trial focused on those with a long-standing injury, it is likely that younger, physically active patients may have already pursued a treatment pathway of reconstruction excluding them from eligibility. This was not considered a limitation of the study, but an expected profiling of the investigated population adding evidence beyond other studies with lower overall age. This is relevant as older patients are more likely to have the presence of pre-existing degenerative osteoarthritis and higher rates of hospital readmission following surgery, while rehabilitation may have better outcomes in older populations due to higher compliance with rehabilitation protocol and greater financial stability.[24] Our study showed that surgery was more cost-effective than rehabilitation in patients aged under 40 years compared to those above 40 years.

Our cost-effectiveness analysis is based on the largest randomized trial comparing surgical and non-surgical management of non-acute ACL in the world. However, the analysis is not without limitations, including the sizeable amount of missing data on healthcare resource utilization and EQ-5D-5L. We accounted for this using multiple imputation.[19] This assumes data are missing at random, conditional on modelled covariates, and we found no strong evidence to contradict this assumption. In addition, results were calculated over only 18 months, and the potential long-term implications of ACL injury and reconstruction such as post-traumatic OA, revisions, or conversions to total knee arthroplasty and their impact on costs and HRQoL were not captured within the analysis.[7,23] Notwithstanding this, most patients had established their level of instability at 18 months since being included in the trial. Hence, longer follow-up is needed to confirm whether the observed differences in costs and QoL are maintained. Finally, we were not able to collect data concerning medication use, equipment, informal care, and lost earnings due to absence from work. We expect the differences in medication, informal care, and equipment to be small between groups.[22] However, lost earnings could be high in patients similar to ACL-SNNAP, given their age and working status, and may favour one of the trial interventions. Further research is needed to ascertain differences between the two groups.

In conclusion, this study suggests that surgical reconstruction is cost-effective during the 18-month follow-up period. In the absence of the COVID-19 pandemic, it is likely that surgery would be considerably more cost-effective than rehabilitation. Furthermore, the benefits of surgery for younger individuals were considerable making it more cost-effective to this subgroup relative to older patients.

Take home message

- Surgical reconstruction is cost-effective in the UK setting for unstable patients with non-acute anterior cruciate ligament injury relative to management with rehabilitation therapy.
- Surgery resulted in greater gains in health-related quality of life but also higher costs compared to rehabilitation.

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Supplementary material

The supplementary material provides additional information on the methods used in our study as well as additional supporting results.

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Funding statement:
The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: the ACL SNNAP study was funded by the National Institute for Health Research Health Technology Assessment (HTA) Programme (HTA 14/140/63).

ICMJE COI statement:
The authors report funding from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (HTA 14/140/63), paid to the University of Oxford as the institution sponsoring the trial. A. Price reports royalties or licenses from Zimmer Biomet and consulting fees from Zimmer Biomet and Medacta, all of which are unrelated to this study. D. J. Beard reports NIHR Senior Investigator grant (April 2022 to April 2026).

Data sharing:
All data requests should be submitted to the corresponding author for consideration. Access to anonymized data may be granted following review.

Acknowledgements:
The ACL SNNAP study was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (HTA 14/140/63). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NHS, the NIHR, Medical Research Council, Central Commissioning Facility, NIHR Evaluation, Trials, and Studies Coordinating Centre, the NIHR HTA Programme or the Department of Health. The study sponsor is the University of Oxford (Oxford, UK). The study was managed by the Oxford Surgical Intervention Trials Unit (SITU) in collaboration with the Oxford Clinical Trials Research Unit. SITU is supported by the Royal College of Surgeons (RCS) Surgical Trials Initiative and the Oxford NIHR Biomedical Research Centre. DJB's RCS Trials Chair is supported by the Rosetrees Trust. The authors wish to thank the PIs and their teams at each of the ACL SNNAP sites.

Ethical review statement:
Ethical approval was given by the National Research Ethics Service, Oxfordshire Research Ethics Committee in October 2016 (16/SC/0502).

Open access funding:
The ACL SNNAP study was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (HTA 14/140/63).

Trial registration number:
ISRCTN10110685

This article was primary edited by D. Johnstone.