Rehabilitation versus surgical reconstruction for non-acute anterior cruciate ligament injury (ACL SNNAP): a pragmatic randomised controlled trial

BEARD, D.J., DAVIES, L., COOK, J.A., STOKES, J., LEAL, J., FLETCHER, H., ABRAM, S., CHEGWIN, K., GRESHON, A., JACKSON, W., BOTTOMLEY, N., DODD, M., BOURKE, H., SHIRKEY, B.A., PAEZ, A., LAMB, S.E., BARKER, K., PHILLIPS, M., BROWN, M., LYTHE, V., MIRZA, B., CARR, A., MONK, P., MORGADO AREIA, C., O'LEARY, S., HADDAD, F., WILSON, C., PRICE, A., EMSLEY, R., PEAT, George <http://orcid.org/0000-0002-9008-0184>, SNOW, M., CAMPBELL, M., HOWELL, T., JOHNSON, H., MCDONNELL, S., PINKNEY, T., WILLIAMS, M., CAMPBELL, H., DAVIES, J., LI, J., BAGG, C., HAYWOOD, L., NICHOLSON, A., RICHES, J., SYMONS, S., VERTUE, M., AL MOUAZZEN, L., BRAY, R., CLARK, D., COULTHARD, J., HOLLAND, T., HOWELLS, N., JONES, A., KAPUR, R., KISZELY, A., KRISHNAN, H., MACDONALD-TAYLOR, K., MANARA, J., MURRAY, J., NEGRUT, C., PAI, V., PORTEOUS, A., PUTNIS, S., ROBINSON, J., RUPASINGHE, S., SELVARATNAM, V., SMITH, J., SMITH, N., STEVENS, J., TAYLOR, C., THEODORIDES, A., VETHARAJAN, N., VINT, H., YOUNG, L., BULLOCK, S., COOK, R., DODDS, A., FREEMAN-HICKS, A., HILLOUT, P., CORNELL, T., COUTTS, A., DEAN, S., DEVOOGHT-JOHNSON, N., FERRELL, E., FLETCHER, E., HALL, C., KENT, B., KESSLY, S., KINCAID, R., LAZIZI, M., MOSTAFA, A., NISBETT, T., POWELL, T., RIDDLESTONE, P., ROBERTON, A., SUMMERS, J., WHITBREAD, L., WROATH, B., FENLON, E. and HALL, A.

Rehabilitation versus surgical reconstruction for non-acute anterior cruciate ligament injury (ACL SNNAP): a pragmatic randomised controlled trial

*David J Beard, Loretta Davies, Jonathan A Cook, Jamie Stokes, Jose Leal, Heidi Fletcher, Simon Abram, Katie Chegwin, Akiko Greshon, William Jackson, Nicholas Bottomley, Matt Dodd, Henry Bourke, Beverly A Shirkey, Arsenio Paez, Sarah E Lamb, Karen Barker, Michael Phillips, Mark Brown, Vanessa Lythe, Burhan Mirza, Andrew Carr, Paul Monk, Carlos Morgado Areia, Sean O'Leary, Fares Haddad, Chris Wilson, Andrew Price, on behalf of the ACL SNNAP Study Group**

Summary

Background Anterior cruciate ligament (ACL) rupture is a common debilitating injury that can cause instability of the knee. We aimed to investigate the best management strategy between reconstructive surgery and non-surgical treatment for patients with a non-acute ACL injury and persistent symptoms of instability.

Methods We did a pragmatic, multicentre, superiority, randomised controlled trial in 29 secondary care National Health Service orthopaedic units in the UK. Patients with symptomatic knee problems (instability) consistent with an ACL injury were eligible. We excluded patients with meniscal pathology with characteristics that indicate immediate surgery. Patients were randomly assigned (1:1) by computer to either surgery (reconstruction) or rehabilitation (physiotherapy but with subsequent reconstruction permitted if instability persisted after treatment), stratified by site and baseline Knee Injury and Osteoarthritis Outcome Score—4 domain version (KOOS4). This management design represented normal practice. The primary outcome was KOOS4 at 18 months after randomisation. The principal analyses were intention-to-treat based, with KOOS4 results analysed using linear regression. This trial is registered with ISRCTN, ISRCTN10110685, and ClinicalTrials.gov, NCT02980367.

Findings Between Feb 1, 2017, and April 12, 2020, we recruited 316 patients. 156 (49%) participants were randomly assigned to the surgical reconstruction group and 160 (51%) to the rehabilitation group. Mean KOOS4 at 18 months was 73·0 (SD 18·3) in the surgical group and 64·6 (21·6) in the rehabilitation group. The adjusted mean difference was 7·9 (95% CI 2·5–13·2; p=0·0053) in favour of surgical management. 65 (41%) of 160 patients allocated to rehabilitation underwent subsequent surgery according to protocol within 18 months. 43 (28%) of 156 patients allocated to surgery did not receive their allocated treatment. We found no differences between groups in the proportion of intervention-related complications.

Interpretation Surgical reconstruction as a management strategy for patients with non-acute ACL injury with persistent symptoms of instability was clinically superior and more cost-effective in comparison with rehabilitation management.

Funding The UK National Institute for Health Research Health Technology Assessment Programme.

Lancet 2022; 400: 605–15

See **Comment** page 543

*ACL SNNAP Study Group members are listed at the end of the Article

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre (Prof D J Beard DPhil, L Davies DPhil, J A Cook PhD, J Stokes MSc, H Fletcher BSc, S Abram DPhil, K Chegwin, A Greshon, B A Shirkey PhD, A Paez PhD, Prof A Carr FRCS, P Monk FRCS, C Morgado Areia MSc, Prof A Price FRCS) **and Nuffield Department of Population Health** (J Leal DPhil, V Lythe MSc, B Mirza MBBS)**, University of Oxford, Oxford, UK; Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK** (W Jackson FRCS, N Bottomley FRCS, Prof K Barker PhD)**; College of Medicine and Health, University of Exeter** (Prof S E Lamb DPhil)**; Swansea Bay University Health Board, Swansea, UK** (M Dodd FRCS)**; Heatherwood & Wexham Park Hospitals, Frimley Health NHS Foundation Trust , Slough, UK** (H Bourke FRCS)**; Fr3dom UK, Brighton, UK** (M Phillips, M Brown)**; Royal Berkshire Hospital, Royal Berkshire NHS Foundation Trust, Reading, UK** (S O'Leary FRCS)**; University College Hospitals, University College London Hospitals NHS Foundation Trust, London, UK** (Prof F Haddad FRCS)**; University Hospital of Wales, Cardiff and Vale University Health Board, Cardiff, UK** (Prof C Wilson FRCS)

Introduction

Anterior cruciate ligament (ACL) rupture is a common knee injury that can have a profound effect on knee kinematics (knee movement and forces) with recurrent knee instability (giving way) as the main problem. The injury mainly affects young, active individuals, with an estimated 200 000 injuries annually in the USA.[1,2] The instability leads to poor quality of life, decreased activity, and increased risk of secondary osteoarthritis of the knee.[3] Management of patients with an ACL injury can include a non-surgical (rehabilitation) or surgical (reconstruction) approach. Rehabilitation involves specialised physiotherapy exercises whereas the surgery involves reconstructing the ligament, usually with tissue taken from the injured person's own body (autograft).

In England, an estimated 30 000 primary ACL reconstruction surgeries are done each year[4,5] and Swedish ACL registry data suggest an incidence of 71 surgeries per 100 000 population per year.[6] The age-standardised rate of ACL reconstruction in the UK increased by 12 times from 1997 to 2017 to 24·2 surgeries per 100 000 population.[5] Based on the conservative estimate, the annual cost of ACL reconstruction to the UK National Health Service (NHS) in 2015 was £63–85 million. Rehabilitation management can be much cheaper than surgery but still has a cost burden for health-care services. Despite there being many studies in ACL injury, there remains insufficient and

Correspondence to:
Prof David Beard, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford OX3 7LD, UK
david.beard@ndorms.ox.ac.uk

Research in context

Evidence before this study

Despite being a common injury, existing management for anterior cruciate ligament (ACL) injury is based on insufficient evidence, which has led to a highly varied approach to management. The condition can be treated surgically or non-surgically, often with a preference from patients and surgeons for surgical reconstruction. A Cochrane systematic review examined whether surgery or non-surgical (conservative) management was superior for ACL injury. The study concluded that no high-quality evidence existed on which to base practice. Surgical stabilisation of the knee joint is common, but uncertainties remain over whether surgery is any more beneficial than non-surgical intervention, particularly in patients with ongoing instability and longer-term injuries. The 2013 KANON study showed that an operation was unnecessary for some patients with acute ACL injury and that previous rehabilitation before considering surgery reduced the need for ACL surgery by up to 50%. Although this study provided good evidence for recently injured individuals, the findings could not be applied to a population of symptomatic patients with longer-term injury typically seen in some health-care settings (such as the National Health Service in the UK).

The COMPARE trial in the Netherlands provided contrasting conclusions to the KANON trial. 167 patients with acute ACL rupture from six hospitals had improved symptoms, function, and sport levels at 2-year follow-up after early surgical reconstruction compared with initial rehabilitation and subsequent surgery. The inference is that surgery is superior but the clinical recommendation is complicated by the frequency of observed conversion to surgical reconstruction. Despite poorer outcomes in the rehabilitation group, 50% of these patients did not require (or select) subsequent surgery, similar to results of the KANON trial.

The contrasting findings from the few clinically relevant studies, and the need to account for less specific populations, highlighted the need for a robust randomised trial of ACL management comparing surgical and non-surgical management in individuals with longer-term ACL injury.

Added value of this study

This study showed that, in patients with non-acute ACL injuries with persistent symptoms of instability and giving way, surgical reconstruction was a superior clinical management option, in terms of outcome after 18 months, compared with management with rehabilitation therapy. The risks associated with surgery are minimal. The study adds value by providing new evidence for a specific population of patients with ACL injury (more long standing and less acute than in existing studies) and by being a pragmatic investigation in several centres. These findings can be used to guide treatment options for this specific patient group.

Implications of all the available evidence

For unstable symptomatic patients with a non-acute presentation, surgical reconstruction should be the treatment of choice. Patients can still undergo non-surgical treatment and obtain benefit, but the superior benefit of reconstruction in this particular population should be explained during any shared decision-making process, along with the risks.

conflicting evidence to show which management strategy is best to guide decision making in long-standing injured but symptomatic patients.[7–10]

High-quality trials have been done in the management of patients with (mostly acute) ACL injury with conflicting findings. The Swedish KANON trial by Frobell and colleagues[11] suggested that rehabilitation should always be attempted in the first place for acute cases and that a period of rehabilitation before considering surgery can reduce the need for ACL surgery by up to 50%. By contrast, the Dutch COMPARE trial by Reijman and colleagues[12] suggested that early ACL reconstruction might give better results for acute patients compared with receiving rehabilitation first. This study examined clinical effectiveness and cost-effectiveness of two treatment strategies (surgery or rehabilitation) for 167 patients with ACL injury and showed better self-reported outcomes in the surgery group compared with in the non-surgical group. However, the conversion from rehabilitation to reconstruction was also around 50% in this study.[12]

Although both previous trials have generated high-quality evidence, their contrasting findings and lack of applicability to managing less acute ACL injuries (such as in the NHS[13–15]) provides strong justification for this trial. Patients with ACL rupture often present as non-acute, sometimes having sustained injury sometime earlier (≤12 months can have passed since initial injury[16]). The optimum management for these patients with ACL injury remains without evidence. Arguments exist for both options. Surgery is often the default management but is expensive and might also lead to complications.[4,17] Routine prescription of formal rehabilitation, if it is not as good as surgery at stabilising the knee, could be considered wasteful. Moreover, prescription of rehabilitation might disadvantage individuals with ACL injuries by delaying optimum treatment, leading to secondary problems.

We aimed to investigate, in patients with non-acute ACL deficiency, whether a strategy of non-surgical management with the option for later ACL reconstruction if required, was more clinically effective and cost-effective than a strategy of immediate surgical reconstruction.

Methods

Study design and participants

The detailed study protocol has been published previously[18] and all information on the design and

methodology is contained within the publication. In summary, the ACL Surgery Necessity in Non-Acute Patients (ACL SNNAP) trial was a pragmatic, multicentre, superiority, randomised controlled trial done in 29 NHS secondary care hospitals across the UK (appendix p 2). The trial was designed as a pragmatic management assessment in which specific events were expected and permitted. This design included the option for later surgical intervention (ACL reconstruction) in the non-surgical group, only if required (appendix p 3). A two-stage internal pilot was included.

Patients with symptomatic knee problems (instability) consistent with an ACL injury (see inclusion and exclusion criteria in the published protocol) were eligible. Partial or complete tears were confirmed at routine outpatient appointment using MRI (and occasionally by clinical assessment). Symptomatic instability included episodes of the knee giving way or a feeling of instability with movement or activity. We excluded patients with meniscal pathology with characteristics that indicate immediate surgery—ie, locked knee or large bucket handle tear or complex cartilage tear. We also excluded any patients with evidence of later stage osteoarthritis (grade 3 or 4 on the Kellgren and Lawrence scale[19]), as well as patients with multi-plane, multi-ligament instability. We included patients with partial tears with gross instability symptoms, in line with normal clinical practice—management for such patients will be identical to that for patients with complete ACL rupture. All patients had to be potential candidates for both management options of ACL reconstruction and rehabilitation.

Potential patients were identified in routine orthopaedic outpatient and pre-assessment clinics by the local clinical team. Written consent was obtained for all patients. Patients who wished to participate completed an informed consent form and baseline questionnaire (see published protocol for detail). Ethics approval was given by the National Research Ethics Service, Oxfordshire Research Ethics Committee in October, 2016 (16/SC/0502).

Patients contributed to the design of the study and supported the development of the funding proposal and conduct of the study. Early in the project the patient and public involvement (PPI) group helped ensure that patient information sheets and report forms were accessible and user friendly. A patient representative was an active member of the trial steering committee and, as part of this role, contributed to the monitoring and supervision of trial progress.

Randomisation and masking

Randomisation was to one of two management options: non-surgical management (rehabilitation) or surgical management (1:1) by computer allocation using a centrally managed web-based automated system (provided by Fr3dom, Brighton, UK). The allocation was generated using permuted block randomisation with varying block sizes stratified by baseline Knee Injury and Osteoarthritis Outcome score—4 domain version (KOOS4; <30 or ≥30) and recruitment site. Randomisation took place following the baseline assessment visit. Because of the nature of the interventions, neither participants nor health-care practitioners (surgeons and physiotherapists) were masked to the intervention.

Procedures

The study interventions are well described in the published protocol and used a pragmatic approach in which content was based on a minimal set of pre-established criteria. This method ensured the integrity of the comparison while allowing for usual variation in practice.

See Online for appendix

Patients who were randomly assigned to rehabilitation were referred to their nearest physiotherapy department to undergo physiotherapy delivered (or closely supervised) by a senior physiotherapist with experience of ACL injury. Routine ACL rehabilitation protocols (with documentary evidence) were followed at individual sites. Mandatory aims included the provision of a minimum of six rehabilitation sessions delivered over at least a 3-month period (appendix pp 14–16). The rehabilitation protocol had to include the following components: control of pain and swelling; regaining range of movement; improving neuromuscular control; regaining muscle strength; achieving normal gait pattern; and returning to function, activity, or sport. Sites were required to have clearly identified progression milestones and return-to-sport criteria with identification criteria for poor progression or non-progression.[20]

The progress of patients randomly assigned to non-surgical management was monitored regularly by their physiotherapist or surgeon. If, after a minimum period of at least 3 months of rehabilitation (or before, if instability or symptoms occurred before completion of the 3-month period), the participant continued with symptomatic knee instability or symptoms related to associated pathology (ie, pain or locking), the non-surgical management was considered to have been unsuccessful. This intermediate outcome was confirmed at a review clinical appointment and the following criteria were confirmed: continued feeling of knee instability or symptoms (ie, pain or locking) related to the associated pathology, at least two episodes of giving way of the knee, and unable to return to a Tegner activity level 2 points below that of their pre-injury status.

Following a policy of shared decision making, the patient and surgical team then decided whether to proceed with ACL reconstruction surgery to address continued symptoms or instability. If appropriate, the participant was listed for surgery, as per usual practice. These management conversions were within protocol and not considered crossovers.

Patients randomly assigned to reconstructive surgery were placed on a surgical waiting list to undergo a standard ACL reconstruction procedure. Operations were

carried out according to the discretion of the participating surgeon. Two types of commonplace ACL reconstruction were acceptable: one using a patella tendon graft and the other using a hamstring graft. Any physiotherapy advice and any treatment aimed at the acute presentation (ie, swelling, regaining range of motion, etc) before surgery was permitted, but no formal ACL rehabilitation programme or specific prescription for ACL remedial exercise beyond basic maintenance exercises were permitted. All other care was routine, including immediate postoperative care. Patients were engaged in a postoperative rehabilitation programme as per standard care at the participating hospital. Surgery was performed or supervised in theatre by a specialist consultant knee surgeon with recognised expertise in ACL reconstruction (having done ≥50 previous ACL reconstructions).

A surgical case report form was used to document the operation and monitor compliance with the intervention guidelines. The content of, and adherence to, the postoperative rehabilitation was also recorded for any patient undergoing surgery.

Baseline data were collected in clinic (using a web-based data collection system) just before randomisation.

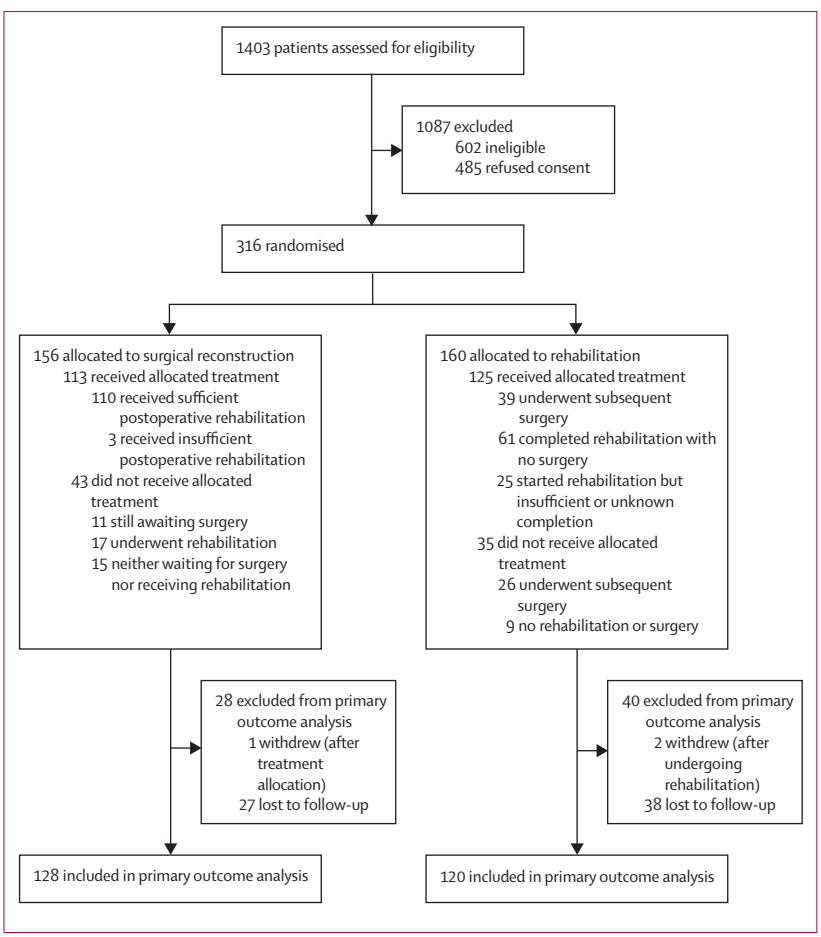

Figure 1: **Trial profile**

The KOOS4 and details of the baseline level of ACL injury with associated knee pathology from the MRI report were also collected. Follow-up outcome data were collected by self-reported questionnaire completed by participants using a web-based data collection system for the primary endpoint at 18 months. A shortened version of the follow-up questionnaire was sent out at 6 and 12 months. Follow-up questionnaires could also be completed as a paper hardcopy and returned via post or telephone. Clinical outcome and adherence data were collected throughout the trial by research teams at the local sites and triangulated between clinical sites and the research office.

Outcomes

The primary outcome was KOOS4 at 18 months after randomisation (see published protocol for details)[21] with scores ranging from 0 to 100, and a higher score indicating better health. 18 months after randomisation is when most patients will have engaged in sufficient activity to allow functional knee stability to be assessed (taking into account any delay in surgery or rehabilitation). The follow-up time was selected on the basis of clinician input, and PPI.

Secondary outcomes were knee-specific quality of life (ACL QoL),[22] return to activity and level of sport participation (Tegner or modified Tegner score), health-related quality of life (EQ-5D-5L), resource use, intervention-related complications, and patient satisfaction at least 18 months after randomisation. The outcomes reflected consensus opinion in a PPI group and the reference standard for assessing ACL injury and reconstruction.[23]

Statistical analysis

The final protocol[18] and statistical analysis plan[24] for this trial have been published elsewhere. The sample size was calculated using the KOOS4 and a conservative minimal clinically important change of 8 points with an SD of 19.[24,25] Given these assumptions, 120 participants per group were required (240 in total) to achieve 90% power at a two-sided significance level of 5% in the absence of any clustering of outcome. To allow for just over 15% missing data (as in a similar trial[26]), 320 participants were needed. Further details on the justification for the sample size calculation are provided in the protocol.[18]

All principal analyses were based on the intention-to-treat (ITT) principle, analysing participants in the groups to which they were randomly assigned irrespective of compliance with treatment allocation. Statistical significance was at the two-sided 5% level, with corresponding 95% CIs derived. Baseline and follow-up data were summarised using the appropriate descriptive statistics. The analyses were done once the 18-month timepoint had been reached by the last participant.

We anticipated that the ACL SNNAP trial would involve several potential treatment pathways because of the

complex nature of the interventions and several potential pathway profiles were described and accounted for to inform the per protocol analyses.[24] Item-level missing data were dealt with according to the KOOS manual to generate KOOS subscale scores.[24] However, participant-level missing data were not imputed in the principal analyses of the primary and secondary outcomes.

The principal analysis of the primary outcome measure (KOOS4) was made using a linear regression model including treatment group, with adjustment for the stratification by site and baseline KOOS4. The model included KOOS4 at baseline as a continuous variable and adjusted for stratification by site using cluster robust SEs. Unadjusted analyses included only the treatment variable in the analysis models, with adjusted analyses further adjusting for baseline KOOS4 and allowing for intra-cluster correlation between recruitment sites. We did further analyses of the primary outcome to assess compliance, missing data, comparing area under the curve (AUC) and subgroups (appendix p 1).

For the secondary outcomes, KOOS subscales, ACL QoL, and EQ-5D-5L were analysed using linear regression models with adjustment for randomisation and baseline variables as described in the analysis of the primary outcome. Modified Tegner activity scores were analysed using a Mann-Whitney U test, with 95% CIs for proportions calculated for patient satisfaction and return to pre-injury activity level. We calculated a 95% CI for the difference in proportions of participants who reported that their knee was better at 18 months than it was before their treatment (but after their injury) using Newcombe's method 10 (also referred to as the score method). We summarised numbers of complications by treatment group and compared differences in withdrawals between treatment groups.

We also estimated the probability that surgical management was the most cost-effective option at different threshold values per quality-adjusted life-year (QALY) gained.[27] We estimated health-care costs and QALYs for all participants from the date of recruitment until withdrawal from study or end of follow-up at 18 months. Health-care costs and QALYs were discounted at 3·5% per year and missing data were imputed with multiple imputation by chained equations (30 imputed datasets) after assessing missing at random to be a plausible assumption. We estimated the joint uncertainty around incremental healthcare costs and QALYs (ie, the difference between surgical and non-surgical management), and calculated the probability that surgical management is more cost-effective than non-surgical management at £30 000 per QALY. Analyses were done in Stata (version 17.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 1, 2017, and April 12, 2020, we assessed 1403 patients for eligibility. Of these, we recruited 316 (22·5%) participants (figure 1). 602 (42·9%) screened patients were ineligible. The main reasons included other study knee-related pathology such as medial or lateral collateral ligament injury (n=55 [9%]) or meniscal pathology (n=148 [25%]), having undergone previous knee surgery (n=91 [15%]), or having an acute injury (n=81 [13%]). 485 (34·6%) of 1403 screened patients were eligible, 276 (57%) of whom declined to participate in the trial because of preference for surgery, whereas 115 (24%) eligible patients declined because of preference for rehabilitation (appendix p 4).

156 (49%) participants were randomly assigned to the surgical management group and 160 (51%) to the rehabilitation group. Groups were similar in terms of baseline characteristics, with a mean age of 32·9 years (SD 9.8; table 1). Three patients withdrew from ACL SNNAP (figure 1), one of whom did not confirm their data that were collected up to the point of withdrawal could be used and therefore their outcome data are not presented here. The proportion of male patients was slightly higher in the surgical group than in the rehabilitation group (table 1). 108 patients (34%) had sustained their injury within the past 4 months and 207 (66%) patients had sustained injury more than 4 months ago. 68 (22%) patients had sustained their

	Surgical reconstruction (n=156)	Rehabilitation (n=159)	Total (n=315)
Sex			
Male	110 (71%)	98 (62%)	208 (66%)
Female	46 (29%)	61 (38%)	107 (34%)
Age at randomisation	32·9 (10·0)	32·9 (9·6)	32·9 (9·8)
Time since injury, months			
<4	58 (37%)	50 (31%)	108 (34%)
4–5	34 (22%)	37 (23%)	71 (23%)
6–8	23 (15%)	25 (16%)	48 (15%)
9–11	6 (4%)	14 (9%)	20 (6%)
12–23	11 (7%)	16 (10%)	27 (9%)
≥24	24 (15%)	17 (11%)	41 (13%)
KOOS4 at baseline	45·7 (19·6)	43·3 (18·1)	44·5 (18·9)
Tegner activity score at baseline			
0–3	119 (76%)	127 (80%)	246 (78%)
4–6	32 (21%)	28 (18%)	60 (19%)
7–10	5 (3%)	4 (3%)	9 (3%)
ACL QoL at baseline	26·1 (17·4); n=156	23·2 (14·6); n=157	24·6 (16·1); n=313
EQ-5D-5L VAS	64·2 (20·8); n=154	68·4 (20·6); n=156	66·3 (20·8); n=310
EQ-5D-5L index	0·56 (0·25); n=156	0·57 (0·26); n=158	0·56 (0·26); n=314

Data are n (%) or mean (SD). One patient who was randomly assigned to the rehabilitation group withdrew and their outcome data were not used for the trial and are not reported in the tables. ACL=anterior cruciate ligament. KOOS4=Knee Injury and Osteoarthritis Outcome Score—4 domain version. QoL=quality of life. VAS=visual analogue scale.

Table 1: **Baseline characteristics**

	Surgical reconstruction, KOOS4	Rehabilitation, KOOS4	Surgical reconstruction *vs* rehabilitation	
			Mean difference (95% CI)	p value
Intention to treat				
Adjusted*	73·0 (18·3); n=128	64·6 (21·6); n=120	7·9 (2·5–13·2)	0·0053
Unadjusted	73·0 (18·3)	64·6 (21·6)	8·3 (3·3–13·3)	0·0012
Per protocol conservative				
Adjusted	75·9 (16·1); n=94	69·1 (18·7); n=73	7·3 (0·8–13·8)	0·030
Unadjusted	75·9 (16·1)	69·1 (18·7)	6·8 (1·5–12·2)	0·012
Per protocol pragmatic				
Adjusted	75·7 (16·2); n=95	64·8 (21·5); n=100	11·2 (5·7–16·8)	0·0003
Unadjusted	75·7 (16·2)	64·8 (21·5)	10·9 (5·5–16·3)	0·0001

Data are mean (SD), unless otherwise indicated. KOOS4=knee injury and osteoarthritis outcome score—4 domain version. *Main result for primary outcome.

Table 2: **Primary outcome analysis**

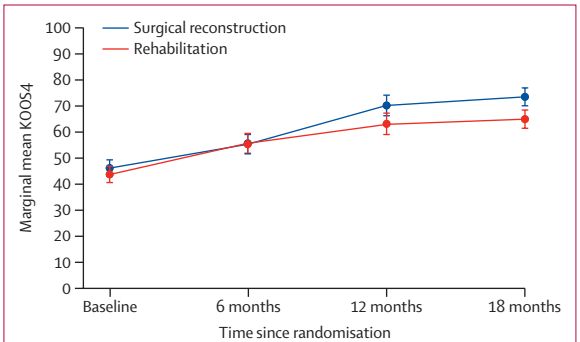

Figure 2: **Marginal mean KOOS4 at each timepoint in the intention-to-treat population**
Wings represent 95% CIs. KOOS4=Knee Injury and Osteoarthritis Outcome Score—4 domain version.

injury 1 year or more before recruitment and some up to 10 years previously. Baseline patient-reported outcome measures were well balanced between the two treatment groups (mean KOOS4 at baseline was 45·7 [SD 19·6] for surgical management and 43·3 [SD 18·1] for those allocated to rehabilitation). Complete baseline data are provided in the appendix (p 7).

119 (38%) injuries were sustained playing football. Other sports (including netball, rugby, skiing, snowboarding, and non-specific sports) made up a substantial proportion of other injuries (appendix p 6). 19 (6%) of 299 patients had partial tears. 125 (78%) of 160 participants in the rehabilitation group received initial rehabilitation treatment within the trial. Of these, 61 (49%) patients

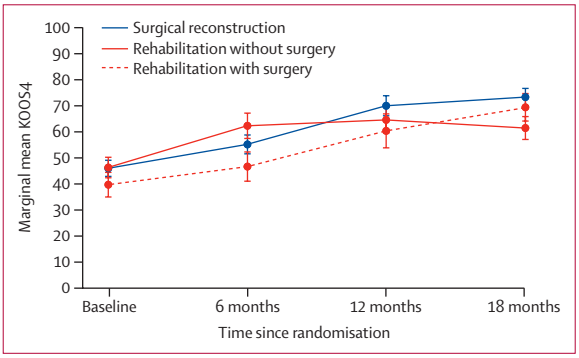

Figure 3: **Marginal mean KOOS4 scores at each timepoint by receipt of surgery in the rehabilitation group**
Wings represent 95% CIs. KOOS4=Knee Injury and Osteoarthritis Outcome Score—4 domain version.

completed rehabilitation treatment with no subsequent surgery, 39 (31%) had subsequent reconstruction for continued symptoms, and 25 (20%) started rehabilitation but did not complete the treatment (figure 1). 35 (22%) of 160 patients in the rehabilitation group did not undergo the allocated rehabilitation treatment, of whom 26 (74%) had subsequent reconstruction. 65 (41%) patients allocated to rehabilitation had subsequent reconstruction for ongoing symptoms in line with the protocol.

113 (72%) of 156 patients allocated to surgical reconstruction underwent surgical reconstruction (figure 1). 43 (28%) patients did not undergo reconstruction, of whom 11 (26%) were still awaiting surgery and 17 (40%) elected for rehabilitation despite surgical allocation (figure 1). These 17 patients were considered outside the expected management protocols. The median time to surgery was 113 days (IQR 66–158) in the surgical management group and 237 days (156–241) for those who underwent surgery in the rehabilitation group (appendix p 8).

Of the 313 forms sent out at 18 months, 248 (79%) were completed. KOOS4 analyses (primary outcome) for all analysis populations are shown in table 2 and figure 2. For the ITT analysis of KOOS4 at 18 months, 128 (82%) participants in the surgical management group had scores available for analysis, compared with 120 (75%) participants in the rehabilitation group (table 2). Mean KOOS4 at 18 months after randomisation increased to 73·0 in the surgical management group and to 64·6 in the rehabilitation group. The adjusted mean difference was 7·9 (95% CI 2·5–13.2; p=0·0053), in favour of surgical management (table 2). A similar number of patients in the surgical management and the rehabilitation groups had an increase in KOOS4 from baseline to 18 months of 8 or more (100 [78%] *vs* 87 [73%]). The per protocol pragmatic and per protocol conservative analyses supported the ITT results, with all treatment effects significantly favouring surgical management (table 2). Findings from complier average causal effect analyses similarly favoured surgical management

(appendix p 8). Assessment of influence of missing data (pattern-mixture model) showed the results were robust up to a 5-point difference in KOOS4 (in favour or against surgical reconstruction group; appendix pp 1, 9). We found no differences in treatment effect for any of the subgroup factors (sex, baseline KOOS4, age, and baseline Tegner activity scores; appendix p 9).

We did a secondary AUC analysis on the ITT population using KOOS4 at baseline, 6, 12, and 18 months (appendix p 10). The difference in AUC values was 4·1 (95% CI 0·4–7·7; p=0·028), which was also in favour of surgical management. Figure 3 shows the marginal mean KOOS4 but with the rehabilitation treatment group split into those who received surgery and those who did not. These two subgroups had different profiles.

KOOS subscales (pain, symptoms, activities of daily living, sports and recreation, and knee-related QOL) were analysed separately as secondary outcomes (table 3). All subscales showed statistically significant differences in favour of surgical management (table 3).

One intraoperative complication was recorded in the surgical management group and two in the rehabilitation group. 11 clinical events in which a medical professional was encountered were recorded in the surgical management group (in 10 patients), compared with 12 in the rehabilitation group (in 11 patients; appendix pp 10–11). Three graft failures were reported (two in the surgical group and one in the rehabilitation group). The most common complication was newly acquired meniscal pathology (one in surgical management and three in rehabilitation; appendix pp 10–11).

115 participants in the surgical reconstruction group and 116 in the rehabilitation group had EQ-5D-5L scores available at 18 months. The mean index score for generic quality of life (EQ-5D-5L) was 0·77 in the surgical group and 0·72 in the rehabilitation group (appendix p 12). The adjusted mean difference was 0·04 (95% CI –0·02 to 0·10; p=0·22; appendix p 12).

89 (57%) of 156 participants had ACL QoL scores at 18 months available in the surgical management group, compared with 82 (51%) of 160 in the rehabilitation group (appendix p 12). Mean ACL QoL scores were 59·7 in the surgical group and 48·2 in the rehabilitation group (appendix p 12). The adjusted mean difference was 11·6 (95% CI 4·4–18·8; p=0·0028), in favour of surgical management (appendix p 12).

Patient satisfaction was assessed by asking patients the nature of their problems at 18 months compared with before their treatment, as well as if they would still choose to have the same treatment if they were able to go back in time. 102 (83%) participants in the surgical reconstruction group said their knee was better than it was before treatment at 18 months, compared with 79 (68%) in the rehabilitation group, with a difference of 15% (95% CI 4–25) in favour of surgical management (appendix p 12). 98 (80%) participants in the surgical management group said that they would choose the same treatment again compared with 71 (61%) in the rehabilitation group (appendix pp 12–13). 21 (18%) patients in the rehabilitation group said that they would not choose the same treatment again, compared with six (5%) in the surgical management group (appendix pp 12–13).

	Surgery (n=128)	Rehabilitation (n=120)	Mean difference	p value
Pain	85·3 (15·5)	79·3 (19·2)	5·4 (0·9–9·9)	0·020
Symptoms	79·4 (15·7)	71·9 (20·8); n=119	6·8 (2·7–10·9)	0·0020
Activities of daily living	91·2 (14·5); n=105	85·0 (20·3); n=88	8·1 (3·2–13·0)	0·0022
Sports and recreation	68·9 (24·9)	59·2 (29·8)	9·3 (0·3–18·3)	0·043
Knee-related QoL	58·1 (25·0)	48·1 (26·6)	9·7 (2·9–16·4)	0·0065

Data are mean (SD) or mean (95% CI), unless otherwise indicated. Data collection of the four domains used in the primary outcome was prioritised. For all five domains, missing data were because of withdrawal or participant non-response. KOOS4=Knee Injury and Osteoarthritis Outcome Score—4 domain version. QoL=quality of life.

Table 3: **Analysis of KOOS subscales (secondary outcomes) at 18 months**

Median Tegner activity scores at 18 months were 5 in the surgical reconstruction group and 4 in the rehabilitation group, with the difference in favour of surgical reconstruction (p=0·0065 Mann-Whitney U test; appendix p 13). At 18 months, 27 (28%) participants in the surgical group had returned to their pre-injury activity level, compared with 21 (24%) in the rehabilitation group (appendix p 13). 65 (68%) of 95 participants with available scores in the surgical group did not reach the activity level that they expected to return to after treatment, compared with 63 (73%) of 86 patients with scores available in the rehabilitation group (appendix p 13).

No ethics-reportable adverse events or serious adverse events were reported in the ACL SNNAP trial. Figure 4 shows the cost-effectiveness acceptability curve capturing the probability that surgical reconstruction is cost-effective compared with rehabilitation at different threshold values. Surgical reconstruction was the most cost-effective option at £30 000 (72% probability) per QALY gained (figure 4). This finding was a result of better outcomes (1·03 QALYs per participant compared with 0·98 QALYs per participant; p=0·17) despite higher health-care costs (£3186 compared with £2169 per participant; difference £1017 [95% CI 557–1476]; p<0·001) of surgical reconstruction compared with rehabilitation (figure 4).

Discussion

We found that both groups improved over time but patients with non-acute anterior cruciate ligament injury undergoing immediate surgical reconstruction without any further intervention had substantially better

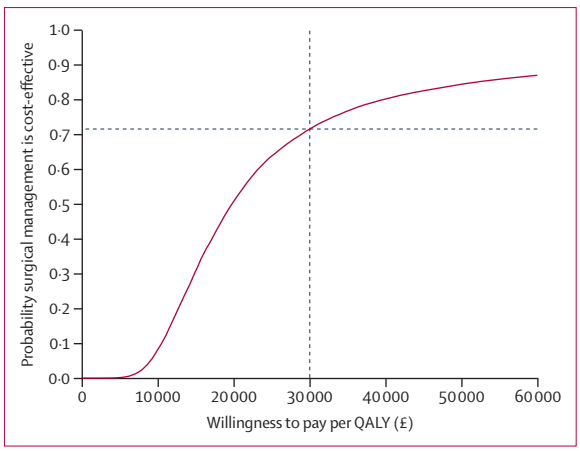

Figure 4: **Cost-effectiveness acceptability curve**
Figure plots the probability (y-axis) that surgical management is cost-effective compared with non-surgical management for different willingness-to-pay thresholds per QALY gain (x-axis). Probability captures the joint uncertainty in incremental costs and QALYs of surgical management compared with rehabilitation. Given a willingness-to-pay threshold of £30 000 per QALY gained, the probability that surgical management is cost-effective compared with rehabilitation is 0·72. QALY=quality-adjusted life-year.

outcomes at 18 months after randomisation than did those undergoing non-surgical management (and any subsequent necessary surgery). The secondary outcome measures also favoured surgical reconstruction over non-surgical management.

A substantial proportion of patients allocated to the rehabilitation group underwent surgery following failure to stabilise the knee by rehabilitation alone. This effect was expected and in line with the protocol, although slightly smaller than was expected for non-acute patients and compared with more acute populations.[11,23] Further understanding of management efficacy and profile was achieved by examining the subgroups within the rehabilitation group, namely those who completed the rehabilitation management in full and did not require surgery, and those in the rehabilitation group who required subsequent surgery because of continued persistent symptoms. Patients who did not require surgery in the rehabilitation group improved more quickly (as per KOOS4 score) but then rapidly plateaued with a final KOOS4 at 18 months around 12 points below that of the surgical group. By contrast, patients who had subsequent reconstruction surgery after unsuccessful rehabilitation were slow to progress initially (presumably because of continued knee instability) but at 18 months had KOOS4 results similar to those in the surgery group.

The study gave some insight into the effect of ACL injury in general. The overall mean baseline KOOS4 was 44·5. Patients were predominantly active before injury, with most patients having a Tegner activity score above 4 before injury, compared with less than a quarter at recruitment. These results show the remarkable reduction in activity and consequence of ACL injury, regardless of treatment type (appendix pp 7, 13).

Although not necessarily limitations, the study revealed several interesting characteristics and methodological nuances, particularly with regard to trial conduct and recruitment. The slow recruitment in the early part of the study necessitated adjustments to inclusion criteria based on the screening data. This adjustment would not have been possible without detailed and accurate screening data. Early in recruitment we found that comorbidity resulted in substantial patient exclusions, specifically, meniscal pathology (148 [25%] of 602 patients were deemed ineligible) and medial collateral ligament injury pathology (55 [9%] of 602 patients deemed ineligible; appendix p 4). Thus, after consensus meetings the criteria were relaxed to include patients who had meniscal injury or medial collateral ligament injury not requiring urgent surgery. Consideration was given to constructing comprehensive per protocol analyses to enable fair comparisons and interpretations in the event of poor compliance, but ultimately these were only needed for reassurance in view of the ITT findings.

The acuteness of injury was also found to be a reason for non-eligibility and under-recruitment. To address this issue, the 4-month acuteness boundary was relaxed. The guidance provided to recruiting centres was to exclude patients only if their acute episode had not settled, which improved recruitment and few patients were deemed ineligible under an acute injury category. Importantly, the study findings only apply to patients with non-acute injury.

The initial lack of equipoise in both clinicians and patients was also problematic—276 (57%) of 485 patients who did not consent declined to participate in the trial because of a preference for surgery. Conversely, 115 (24%) patients of those who were eligible but declined preferred rehabilitation. Site visits and extra consideration in trial presentation for patients, by clarifying the uncertainty that exists around the benefit for both treatment options, helped alleviate this issue. In terms of surgeon and clinician equipoise, these individuals were allowed to recognise their own lack of equipoise and therefore deem themselves unsuitable as a recruiting surgeon or site. Among clinical staff who expressed equipoise, continual reinforcement of this position and the importance of upholding this position for the benefit of the trial was required. A final challenge to trial conduct was the patient pathway and previous treatment. Several potential patients at screening had already undertaken a comprehensive rehabilitation programme, but without success (therefore being deemed ineligible).

Our study had several limitations. The early changes to the protocol to accommodate patients with a shorter injury history (but still not acute) to improve recruitment altered the characteristics of the study population. Overall, patients had less long-standing injury than was originally planned. Moreover, the study addressed a deliberately specific population of patients who continued to have ACL injury-related symptoms of

instability and had not undergone any previous formal treatment.

Another potential limitation is the proportion of patients who did not undergo surgical reconstruction, despite allocation to that group. The true benefit of surgical reconstruction could be somewhat greater than the ITT analysis suggests. The 18-month follow-up period ideally could have been longer but was constrained by various factors including funding. Notwithstanding, most patients had established their level of instability at this timepoint since being included in the trial. The trial design and analysis accounted for delayed surgery in both groups.

The choice of a 3-month period for rehabilitation (before review) was somewhat arbitrary but in line with normal clinical practice. No evidence supports a particular timeframe that is appropriate for rehabilitation intervention. Furthermore, the trial cannot guarantee best practice rehabilitation (nor was it designed to). The results cannot be extrapolated to high-level sports institutions where the frequency, content, and application of rehabilitation techniques might be different to that investigated for SNNAP (in the NHS). We had some concern that the trial might disadvantage patients in the non-surgical group, while exercising on an unstable knee. Patients might have had episodes of instability or giving way and sustain secondary damage to their menisci (thereby compromising longer-term outcomes). However, only four patients acquired meniscal damage, three in the rehabilitation group and one in the surgical group. A potential further limitation is that we were unable to explore reasons for the low rate of return to sports.

Over 18 months of follow-up in the ACL-SNNAP trial, we found that surgical reconstruction led to improved health-related QoL compared with non-surgical management, albeit non-significantly, but with higher health-care costs. Using £20 000–30 000 per QALY thresholds, we found surgical reconstruction to be cost-effective in the UK setting. This is the first study estimating the effectiveness and cost-effectiveness of two common interventions for patients with non-acute ACL deficient knees. Our cost-effectiveness analysis is based on the largest randomised trial comparison of surgical and non-surgical management of patients with non-acute ACL injury. The health economics analysis also had some limitations, including the many missing data on use of health-care resources and EQ-5D-5L. We accounted for this limitation using multiple imputation.[28]

As the trial was embedded in routine NHS care it was intended to be inclusive (all patients who met the selection criteria at participating sites were candidates). We maximised methods of follow-up—ie, online, postal, and telephone calls to be inclusive of patients' preferences for completion. In addition to study participants, we included a representative sample of clinicians and trial personnel at recruiting sites. The trial was promoted at national conferences to increase awareness of the project and encourage interest and geographical diversity of trial sites. Patients contributed to the design of the study and supported the development of the funding proposal and conduct of the study. Early in the project the PPI group helped ensure that patient information sheets and report forms were accessible and user-friendly. A patient representative was an active member of the trial steering committee and, as part of this role, contributed to the monitoring and supervision of the trial progress.

The ACL SNNAP trial showed that, although benefit can still be obtained from initial non-surgical treatment, immediate surgical reconstruction of the ACL in patients with symptomatic non-acute injury is a superior management strategy when compared with rehabilitation. The superiority of surgical reconstruction was shown in self-reported outcomes of function and pain, complication rate, and several secondary outcomes, including activity level and patient satisfaction. Interestingly, neither group had good evidence of returning to their pre-injury level of sport or activity. Immediate ACL reconstruction, despite attracting higher costs than rehabilitation, was shown to be cost-effective.

In shared decision making with patients with longer-term ACL injuries (which are no longer acute), ACL reconstruction is likely to give superior results over a non-operative strategy. Patients who do not want surgery (for any reason) should be reassured that their injury can still improve with non-operative care and the option for later surgical reconstruction remains open.

ACL SNNAP Study Group

Independent members of the Data Monitoring Committee: Richard Emsley (Chair; King's College London, London, UK), George Peat (Keele University, Keele, UK), and Martyn Snow (Royal Orthopaedic Hospital, Birmingham, UK). Independent members of the trial steering committee: Marion Campbell (Chair; University of Aberdeen, Aberdeen, UK), Tessa Howell (Patient Representative), Hilary Johnson (Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK), Stephen McDonnell (Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK), Thomas Pinkney (University of Birmingham, Birmingham, UK), and Mark Williams (Oxford Brookes University, Oxford, UK). Trial co-investigators: Helen Campbell, Andrew Carr, Jonathan Cook, Loretta Davies, Jose Leal, Paul Monk, and Andrew Price (University of Oxford, Oxford, UK); Sarah Lamb (University of Exeter, Exeter, UK); Fares Haddad (University College London Hospitals NHS Foundation Trust, London, UK); Karen Barker and William Jackson (Oxford University Hospitals NHS Foundation Trust, Oxford, UK); Sean O'Leary (Royal Berkshire NHS Foundation Trust, Reading, UK); and Chris Wilson (Cardiff and Vale University Health Board). Research fellows: Simon Abram and Arsenio Páez (University of Oxford). Trial management: Loretta Davies, Carlos Morgado Areia (until October, 2018) and Jackie Davies (until June, 2016). Trial administration: Katie Chegwin and Jiyang Li (until February, 2018). Data management: Heidi Fletcher and Akiko Greshon (University of Oxford). Database and programming management: Christina Bagg, Mark Brown, and Michael Phillips (Fr3dom). Trial statisticians: Jamie Stokes, and Beverly Shirkey (until April, 2020). Health economists: Jose Leal, Vanessa Lythe, and Burhan Mirza (University of Oxford). All principal investigators (PIs) and research teams: Laura Haywood, Anne Nicholson, Joanne Riches, Sean Symons (PI), and Mark Vertue (Basildon and Thurrock University Hospitals NHS Foundation Trust, Basildon, UK); Louay Al Mouazzen, Rachel Bray, Damian Clark, James Coulthard, Tim Holland, Nick Howells,

Andrew Jones, Richard Kapur, Alastair Kiszely, Harry Krishnan, Karen MacDonald-Taylor, Jon Manara, James Murray (PI), Corina Negrut, Vishai Pai, Andrew Porteous, Sven Putnis, James Robinson, Shav Rupasinghe, Veenesh Selvaratnam, James Smith, Nick Smith, Jarrad Stevens, Clare Taylor, Anthony Theodorides, Niraj Vetharajan, Helen Vint, and Lucy Young (North Bristol NHS Trust, Bristol, UK); Susan Bullock, Rebecca Cook, Alexander Dodds (PI), Amanda Freeman-Hicks, and Paula Hillout (Gloucestershire Hospitals NHS Foundation Trust); Thomas Cornell, Abbie Coutts, Suzy Dean, Nicki Devooght-Johnson, Emma Ferrell, Eve Fletcher, Chrissie Hall, Benjamin Kent, Sandra Kessly, Robin Kincaid (PI), Mohamed Lazizi, Ahmed Mostafa, Toby Nisbett, Tim Powell, Peter Riddlestone, Andrew Roberton, Jessica Summers, Lucy Whitbread, and Belinda Wroath (Royal Cornwall Hospitals NHS Trust, Truro, UK); Emma Fenlon, Andrew Hall, Helen Jeffrey, and Raghuram Thonse (PI; Countess of Chester Hospital NHS Foundation Trust, Chester, UK); Debra Dunne, Andy Metcalfe (PI), Kerri McGowan, Simon Middleton, Feisal Shah, Tim Spalding, Charlie-Marie Suddens, Tamar Sweed, Joanna Teuke, Peter Thompson, and David Wright (University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK); Justine Amero, Emma Brown, Hugh Chissell, Andrea Croucher, Gareth Dickinson, Catherine Hawkes-Blackburn, Alice Peacocke, Graham Smith (PI), and Carol Snipe (Frimley Health NHS Foundation Trust, Frimley, UK); Kim Dearnley, and Reza Mayahi (PI; Hull and East Yorkshire Hospitals NHS Trust, Hull, UK); Barry Andrews (PI), Massimo Barcelona (PI), Hazel Giles, Abdulkerim Gokturk, Paul Harnett, Katie Jeeves, Joyce Kadunyi, Sheena Mendoza, Ines Reichert, Marta Santamaria, and Harshinder Virdee (Kings College Hospital NHS Foundation Trust, London, UK); Sanjeev Anand (PI), Nayef Aslam-Pervez, Stephen Draycott, Faye Howarth, Irfan Jina, Niall Maher, Denise Ross (PI), and Lindsey Worstenholme (Leeds Teaching Hospitals NHS Trust, Leeds, UK); Abdul Baig, Arun Bhaskaran, Daniel Banks, Tracy Brear, Carla Christie, Laura Cowen, Jack Davis, Ross Dixey, Colin Esler (PI), Amirah Essop-Adam, Christina Haines, Linzy Houchen-Wolloff, Husein Varachia, and Richard Wood (University Hospitals of Leicester, Leicester, UK); Glaxy Gray, Jessica Nichols, Alice Panes, Susan Partridge, Lawrie Rogerson, Pankaj Sharma (PI), David Triggs, Ian Venables, and Danielle Wilcock (Manchester University NHS Foundation Trust, Manchester, UK); Sarah Buckley, Thelma Darian, Elizabeth Denis, Jo Duncan, Charlotte Hirst, James Newman, Fern Richardson, and Jon Smith (PI; The Mid Yorkshire Hospitals NHS Trust, Wakefield, UK); Megan Adcode, Megan Cottingham, Eliza Foster, Andrew Kelly (PI), Niamh McKay, Jane Rewbury, Alison Whitcher, James Williams, and Esther Zebracki (Taunton and Somerset NHS Foundation Trust, Musgrove, UK); Llinos Davies, Jayadeep Jayachandran (PI), Alison Tardivel, and Victoria Whitehead (Betsi Cadwaladr University Health Board, North Wales, Bangor, UK) Simon Abram, Carlos Areia, Martha Batting, Amy Bond, Nick Bottomley (PI), Loretta Davies, Marc Deakin, Christopher Dodd, Alison Hudak, Samantha Hynes, Will Jackson, Luke Jones, Gail Lang, David McKenna, Susan Morris, Andrew Price, Clare Scott-Dempster, Adam Sykes, Iason Vichos, and Simon Wood (Oxford University Hospitals NHS Foundation Trust); Rupert Clifton (PI), Stephanie Diaz, Craig Hendy, Nishil Modi, Brendan O'Mahony, Susan O'Sullivan, Nicola Parker, Mira Pecheva, and Rowan Rumonovic (North West Anglia NHS Foundation Trust, Peterborough, UK); Emma McLoughlin, Jeremy Rushbrook (PI), and Anna Thornhill (Solent NHS Trust, Portsmouth, UK); Emily Bannister, Chloe Brown, Debbie Burden, Terence Campbell, Emma Craig, Rashmi Easow, Julie Foxton, Alexandra Hazlerigg, Chethan Jayabev, Rosie Murdoch, Sean O'Leary (PI), and Georgie Parsons (Royal Berkshire NHS Foundation Trust); Harry Brown, Paula Carvelli, Rugaia Montaser, Ali Pepper, Sinduja Sivarajan, Oliver Templeton-Ward (PI), and Eva Wilson (Royal Surrey County Hospitals NHS Foundation Trust, Guildford, UK); Julie Cronin, Sarah Diment, Victoria King, Katharine Shean, Leonidas Vachtsevanos, Katharine Wilcocks, and Ben Wilson (Salisbury NHS Foundation Trust, Salisbury, UK); Paul McNestry, Joanna Ollerenshaw (PI), James Stoddard, and Paul Sutton (Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK); Sanjay Anand, Judith Bell, Albert Chikate, Diane Daniel, Timothy Davies, Tom Finnigan, Antonio Frasquet-Garcia, Susan Hopkins, Sharon Kerrison, Angela McGowan, David Sands Johnson (PI), Lara Smith, Philip Turner, and Helen Wilkinson (Stockport NHS Foundation Trust, Stockport, UK); Lynne Allsop, Deborah Anthony, Rebecca Boulton, Sarah Brown, Vikram Desai (PI), Mandy Gill, Cheryl Heeley, Sushrut Kulkarni, Wayne Lovegrove, Dominic Nash, Terri-Ann Sewell, Sarah Shelton, and Katie Slack (Sherwood Forest Hospitals NHS Foundation Trust, Sutton in Ashfield, UK); David Beard, James Cartwright, Lynda Connor, Andrew Davies, Caroline Davies, Matthew Dodd (PI), Glyn Gainard, Dave Graham-Woollard, Carl Murphy, Leanne Quinn, Caradog Thomas, Jenny Travers, and Marie Williams (Swansea Bay University Health Board, Swansea, UK); Amanda Bell, Sunny Deo, Katharine Francis, Tracy Jackson, Laura McCafferty, Basalingappa Navadgi, Karan Plank, Venkat Satish (PI), and Claire Thelwall (Great Western Hospitals NHS Foundation Trust, Swindon, UK); Fares Haddad (PI), Rachel Knight, Rahul Patel, and Bruce Paton (University College London Hospitals NHS Foundation Trust, London, UK); Ashutosh Acharya, Utuman Aland, Miltiades Areirobulos, Pascal de Feyter, Lisa Ditchfield, Hafiz Iqbaz, Daniel Massey, and Gareth Stables (PI; Warrington and Halton Hospitals NHS Foundation Trust, Warrington, UK); Sarah Appleby, Henry Bourke (PI), Michael Brown, Sarah Cable, Alexander Damen, Joana Da Rocha, Louise Foster, Elizabeth Hamilton, Catriona Hatton, Cassie Honeywell, Kunal Kulkarni, Lucy Markham, Haadiya Mohammed, and John O'Grady (Frimley Health NHS Foundation Trust, Wexham Park Hospital, Slough, UK); Yogesh Joshi (PI), Heather Mclintock, Tania Morgan, Jane Stockport, and Victoria Whitehead (Betsi Cadwaladr University Health Board, Wrexham, UK); Pranshu Agrawal, Jo Armstrong, Shannon Briggs, Ben Coupe (PI), Anne Evans, Rob Gilbert, Sandra Latham, Aslam Mohammed, Valerie Parkinson, Valerie Parkinson, Rafael Sales, Katja Van De Snepscheut-Jones, David Wilcock, and Daniel Wright (Wrightington, Wigan and Leigh NHS Foundation Trust, Wigan, UK); Joanna Allison, Simon Baker, Kate Beesley, Gill Ferrari, Benedict Lankester (PI), Alison Lewis, Joanne Lyons, Jamie O'Callaghan, Sarah Sutcliffe, and Dianne Wood (Yeovil District Hospital NHS Foundation Trust, Yeovil, UK).

Contributors

All authors contributed to the design and development of the trial protocol. DJB was responsible for writing the initial draft of the manuscript with assistance from LD, JAC, JS, JL, and AP. All authors read, provided input, and approved the final manuscript. JAC and JS accessed and verified the data. All authors had access to the summarised data but not patient-specific data or group codings to maintain integrity of the trial.

Declaration of interests

We declare no competing interests.

Data sharing

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Acknowledgments

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.

References

1 Spindler KP, Wright RW. Clinical practice. Anterior cruciate ligament tear. *N Engl J Med* 2008; **359:** 2135–42.

2 Kaeding CC, Léger-St-Jean B, Magnussen RA. Epidemiology and diagnosis of anterior cruciate ligament injuries. *Clin Sports Med* 2017; **36:** 1–8.

3 Khan T, Alvand A, Prieto-Alhambra D, et al. ACL and meniscal injuries increase the risk of primary total knee replacement for osteoarthritis: a matched case-control study using the Clinical Practice Research Datalink (CPRD). *Br J Sports Med* 2019; **53:** 965–68.

4 Jameson SS, Dowen D, James P, Serrano-Pedraza I, Reed MR, Deehan D. Complications following anterior cruciate ligament reconstruction in the English NHS. *Knee* 2012; **19:** 14–19.

5 Abram SGF, Price AJ, Judge A, Beard DJ. Anterior cruciate ligament (ACL) reconstruction and meniscal repair rates have both increased in the past 20 years in England: hospital statistics from 1997 to 2017. *Br J Sports Med* 2020; **54:** 286–91.

6 Peat G, Bergknut C, Frobell R, Jöud A, Englund M. Population-wide incidence estimates for soft tissue knee injuries presenting to healthcare in southern Sweden: data from the Skåne Healthcare Register. *Arthritis Res Ther* 2014; **16:** R162.

7 Grindem H, Eitzen I, Engebretsen L, Snyder-Mackler L, Risberg MA. Nonsurgical or surgical treatment of ACL injuries: knee function, sports participation, and knee reinjury: the Delaware-Oslo ACL Cohort Study. *J Bone Joint Surg Am* 2014; **96:** 1233–41.

8 Meuffels DE, Favejee MM, Vissers MM, Heijboer MP, Reijman M, Verhaar JA. Ten year follow-up study comparing conservative versus operative treatment of anterior cruciate ligament ruptures. A matched-pair analysis of high level athletes. *Br J Sports Med* 2009; **43:** 347–51.

9 Dawson AG, Hutchison JD, Sutherland AG. Is anterior cruciate reconstruction superior to conservative treatment? *J Knee Surg* 2016; **29:** 74–79.

10 Monk AP, Davies LJ, Hopewell S, Harris K, Beard DJ, Price AJ. Surgical versus conservative interventions for treating anterior cruciate ligament injuries. *Cochrane Database Syst Rev* 2016; **4:** CD011166.

11 Frobell RB, Roos HP, Roos EM, Roemer FW, Ranstam J, Lohmander LS. Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. *BMJ* 2013; **346:** f232.

12 Reijman M, Eggerding V, van Es E, et al. Early surgical reconstruction versus rehabilitation with elective delayed reconstruction for patients with anterior cruciate ligament rupture: COMPARE randomised controlled trial. *BMJ* 2021; **372:** n375.

13 Francis A, Thomas RD, McGregor A. Anterior cruciate ligament rupture: reconstruction surgery and rehabilitation. A nation-wide survey of current practice. *Knee* 2001; **8:** 13–18.

14 Kapoor B, Clement DJ, Kirkley A, Maffulli N. Current practice in the management of anterior cruciate ligament injuries in the United Kingdom. *Br J Sports Med* 2004; **38:** 542–44.

15 Evans S, Shaginaw J, Bartolozzi A. ACL reconstruction—it's all about timing. *Int J Sports Phys Ther* 2014; **9:** 268–73.

16 Bollen SR, Scott BW. Rupture of the anterior cruciate ligament—a quiet epidemic? *Injury* 1996; **27:** 407–09.

17 Lohmander LS, Roos EM. The evidence base for orthopaedics and sports medicine. *BMJ* 2015; **350:** g7835.

18 Davies L, Cook J, Leal J, et al. Comparison of the clinical and cost effectiveness of two management strategies (rehabilitation versus surgical reconstruction) for non-acute anterior cruciate ligament (ACL) injury: study protocol for the ACL SNNAP randomised controlled trial. *Trials* 2020; **21:** 405.

19 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957; **16:** 494–502.

20 Negus J, Fransen M, Chen JS, Parker DA, March L. Exercise-based interventions for conservatively or surgically treated anterior cruciate ligament injuries in adults. *Cochrane Database Syst Rev* 2012; **10:** CD010128.

21 Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998; **28:** 88–96.

22 Mohtadi N. Development and validation of the quality of life outcome measure (questionnaire) for chronic anterior cruciate ligament deficiency. *Am J Sports Med* 1998; **26:** 350–59.

23 Lynch AD, Logerstedt DS, Grindem H et al. Consensus criteria for defining 'successful outcome' after ACL injury and reconstruction: a Delaware-Oslo ACL cohort investigation. *Br J Sports Med* 2015; **49:** 335–42.

24 Stokes JR, Beard DJ, Davies L, et al. ACL Surgery necessity in non-acute patients (ACL SNNAP): a statistical analysis plan for a randomised controlled trial. *Trials* 2022; **23:** 389.

25 Cook JA, Julious SA, Sones W, et al. DELTA^2 guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. *BMJ* 2018; **363:** k3750.

26 Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. *N Engl J Med* 2010; **363:** 331–42.

27 Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves—facts, fallacies and frequently asked questions. *Health Econ* 2004; **13:** 405–15.

28 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:** 1157–70.