Pilot and Feasibility Studies

RESEARCH

Open Access

The feasibility of conducting a randomized controlled trial that compares immediate versus optional delayed surgical repair for treatment of acute Anterior cruciate ligament injury—results of the IODA pilot trial

Feryal Ghafelzadeh Ahwaz[2*†], Annemie Smeets[2,3†], Stijn Bogaerts[1,2], Pieter Berger[4] and Koen Peers[1,2]

Abstract

Background Standard care for anterior cruciate ligament (ACL) injuries often includes surgical reconstruction of the ACL. However, two randomized controlled trials (RCT) concluded that conservative treatment does not result in inferior clinical outcomes compared to immediate ACL reconstruction. More research is needed to verify these results and to assess whether patient-specific parameters can predict whether a patient would benefit from immediate surgery or conservative treatment. However, before running such an RCT, we performed this pilot study to assess the feasibility of recruiting patients for such an RCT.

Methods This is a pragmatic, multicenter, randomized, controlled pilot trial with two parallel groups funded by the Belgian Health Care Knowledge Centre (KCE trials). Patients with an acute ACL injury were recruited from two Belgian hospitals. They were randomized to either conservative treatment (e.g., rehabilitation with optional delayed surgery in case of persistent instability) or immediate surgery (< 12 weeks post-injury). The primary aim of this pilot study was to assess the feasibility of participant recruitment. Furthermore, we evaluated adherence to the protocol and the allocated treatment arm and the feasibility of recruiting a representative sample of ACL patients.

Results Out of the initial 70 screened patients, 29 were included in the pilot study, 15 were randomized in the conservative treatment group, and 14 were in the surgical treatment group. This yielded a recruitment rate of 41%. However, the investigators could not screen many potential patients due to inadequate referrals within the recruiting hospitals. Seven cross-overs were observed between the treatment arms: 3 patients who were assigned to the conservative treatment group insisted on immediate surgery, while four patients allocated to immediate surgery chose not to undergo surgery. Of the initial 29 patients, 5 dropped out after randomization. The recruited sample confirmed the typically young and physically active sample of ACL patients.

Conclusions This pilot study confirmed the challenging recruitment process for an RCT that compares a surgical and a non-surgical treatment option. While encountering substantial recruitment challenges, our pilot study revealed

†Feryal Ghafelzadeh Ahwaz and Annemie Smeets shared first authorship.

*Correspondence:
Feryal Ghafelzadeh Ahwaz
feryal.ghafelzadehahwaz@kuleuven.be
Full list of author information is available at the end of the article

that transitioning to a full-scale RCT is feasible, with some essential modifications. Key adjustments encompassed augmenting the number of participating sites, optimizing patient recruitment processes, and extending the recruitment period. Furthermore, this study showed a high completion rate, affirming the feasibility of the study protocol. However, there was a high cross-over rate (7/29 patients) between treatment arms. This should be avoided when progressing to the full trial. The recruited sample reflects a young and active population, which represents the ACL population well.

Trial registration ClinicalTrials.gov (NCT04408690) on 25/05/2020.

Keywords Anterior cruciate ligament injury, RCT, Conservative therapy, ACL reconstruction

Key messages

- Clear and comprehensive patient education about the clinical equipoise, randomization, the study's purpose and potential risks and benefits empowers patients to make well-informed decisions about participation.
- To enhance recruitment feasibility, the initiation of this study is only recommended in centers where there is no bias towards any specific treatment strategy.
- Furthermore, good collaboration between the emergency care unit, department of orthopedics, and physical and rehabilitation medicine improved the recruitment rate.

Background

It was long believed that surgical repair of the ACL is necessary to restore mechanical knee stability so that patients can safely return to sports [1], but also to avoid long-term disadvantages such as persistent knee instability, re-injury [2], and posttraumatic osteoarthritis (PTOA) [3, 4]. However, evidence on outcomes after ACL surgery does not support these beliefs. For example, Ardern et al. [5] showed that only 55% of athletes who have undergone ACL reconstruction manage to regain their pre-injury sport level. For those who do return to sport (RTS), reinjury rates are high, with up to 23% suffering a new ACL injury (ipsilateral or contralateral) within 2 years after RTS [6]. Furthermore, the risk for early cartilage degeneration is high. A recent meta-analysis showed that approximately 50% of the patients end up with PTOA even two decades after ACL surgery [7]. These findings cast doubt on the notion that ACL reconstruction restores normal knee function and prevents long-term consequences. Moreover, there remains uncertainty regarding whether ACL reconstruction offers advantages compared to conservative treatment.

A recent systematic review and meta-analysis conducted by Saueressig et al., showed that immediate surgery and conservative treatment resulted in similar patient-reported outcomes 2 years post-injury [8]. Important to mention is that this review could only use limited data as, so far only two RCTs have been performed, namely the KANON and COMPARE trial [8]. Based on these results, one can conclude that conservative management with optional delayed surgery does not result in inferior clinical outcomes compared to immediate ACL reconstruction on a population level [9].

Though, on the level of the individual patient, not all patients are successful with non-surgical treatment. In the KANON trial, 39% of the ACL patients randomized to the conservative treatment group underwent delayed surgery for persistent knee instability during the 2-year follow-up, this percentage has grown to 51% at the 5-years follow up [10, 11]. The COMPARE trial reported that 50% of the ACL patients in the conservative group required delayed surgery in the 2-year follow-up [12]. In this group of patients, time to return-to-sport is extended, and longer sick leave times are observed because surgery is delayed compared to patients undergoing immediate ACL reconstruction [13]. Hence, early identification of patients who would benefit from early ACL reconstruction, or on the contrary, from rehabilitation alone, is crucial to reduce resource consumption and decrease irrelevant overtreatment. It is hypothesized that treatment success may rely on clinical factors (such as knee function and MRI features [14] as well as the quality of rehabilitation [15], and psychological factors such as expectations [16], fear of re-injury [17, 18], and locus of control [19].

To address the lack of RCTs comparing conservative treatment and immediate surgery and to identify patient predictors for treatment success, a new RCT is needed to (1) comprehensively evaluate and compare the clinical effectiveness of both treatment options, thereby providing substantial validation and enhancement to the current scientific literature, and (2) to investigate which patient-specific factors may function as predictive factors for favourable outcomes in the context of conservative treatment for ACL injuries. Before commencing a sufficiently powered RCT to address these research questions, we conducted a pilot study. This step seemed

necessary, as many patients prefer a specific treatment [1]. Consequently, the pilot study was designed to ascertain the feasibility of conducting a large-scale RCT in terms of (1) participant recruitment, (2) adherence to the protocol and assigned treatment arms, and (3) the feasibility of recruiting a study group that accurately reflects the ACL population (young and active patients).

Methods/design

Aims

This pilot study aimed to assess (1) the feasibility of participant recruitment, (2) the adherence to the protocol and the allocated treatment arm, and (3) the feasibility of recruiting a representative sample of ACL patients that reflect a young and active population.

Study design

This is a pragmatic, multi-center, randomized controlled pilot trial with two parallel groups: (1) conservative treatment (consisting of rehabilitation + optional delayed surgery) and (2) immediate ACL reconstruction in patients with an acute ACL injury. The protocol conforms the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [20] (the SPIRIT checklist is provided as Additional file 1) and is published [21].

Study setting

This study was performed in two Belgian hospitals: the University Hospital of Leuven and the University Hospital of Liège. Patients were recruited at the Department of Orthopedics and the Department of Physical Medicine and Rehabilitation of the participating sites.

Participants

Patients aged 18 years and older visiting the two hospitals were screened for eligibility for this study. Inclusion criteria were a rotational trauma to a previously non-injured knee, a proven acute ACL rupture (< 4 weeks) confirmed using physical examination and an MRI. Exclusion criteria were a history of a previous ACL injury or knee surgery to the index knee. Additionally, patients presenting concomitant knee injuries necessitating immediate surgery were ineligible, as were females who were either pregnant or had intentions of becoming pregnant within the initial 4 months of the study, as MRI assessments during this period were not feasible.

There was no predefined sample size for this pilot trial. Instead, the primary aim was to evaluate patient recruitment feasibility over a recruitment period of minimum 6 months (Note: Leuven experienced an extended recruitment timeline due to delayed initiation at the secondary hospital in Liège).

Predefined progression criteria for advancing to a fully powered RCT were established a priori and are described in our protocol publication [21].

- ≥ 75% of expected recruitment rate: proceed unchanged
- 50–75% of expected rate: implement protocol modifications to enhance recruitment
- < 50% of expected rate: terminate trial due to insufficient feasibility

The expected recruitment rate was based on data from the KANON trial suggesting that 50% of eligible patients with acute ACL injuries are likely to participate [22].

Screening

In Leuven, patient recruitment followed three primary pathways: patients who arrived at the Emergency Department, patients who had a consultation at the orthopedic department, and.

patients presenting themselves at the Department of Physical Medicine and Rehabilitation. Patient recruitment was centralized on the bi-weekly multidisciplinary consultation attended by our orthopedic surgeon, physicians, and clinical trial assistant (physiotherapist). A good referral from the three departments (emergency care unit, orthopedics, and physical and rehabilitation medicine) was necessary to ensure comprehensive patient coverage. Therefore, we maintained regular contact with the Emergency Department every Friday during the initial 8 weeks as we noticed that many ACL injuries occurred during the weekend. Additionally, we worked on a practical workflow that made it very easy for them to schedule potential study patients for the bi-weekly multidisciplinary consultation where the recruitment took place. An additional challenge stemmed from the high turnover of medical trainees at UZ Leuven, a University hospital. To address this, we implemented periodic email updates every 3 to 6 months for incoming trainees within the involved departments.

Initially, we faced challenges providing a consistent study explanation by the different caregivers. To address this, we asked caregivers not actively involved in the study (e.g., doctors and interns at the emergency care unit) to briefly introduce the trial without delving into the full study protocol. Only during the multidisciplinary consultation, where recruitment took place, was comprehensive information provided by the investigators to interested and eligible patients.

In Liege, patients were only recruited at the Department of Physical and Rehabilitation Medicine. The orthopedic department was not interested in participating in the study. At the start of the study, there was no

standardized referral of patients to the Department of Physical and Rehabilitation Medicine. In a later phase of the study, the local investigators worked on a better patient flow to improve the screening rate.

Randomization and blinding

Once a patient signed the informed consent, he/she was randomized into one of the two treatment arms by the randomization tool integrated into the electronic case report form (REDCap). A randomization list (stratified by center) was prepared by the statistician who was not involved in the recruitment and follow-up of the patients. Random sequence generation was conducted using a computer-generated approach with variable block randomization, and allocation was concealed until the investigator performed the actual randomization. A 1:1 allocation ratio was used: 50% of the patients were allocated to the immediate surgery treatment arm and 50% to the conservative treatment arm.

Due to the nature of the interventions, it was not feasible to blind participants and care providers. However, steps were taken to ensure consistent delivery of uniform information, including the acknowledgment of clinical equipoise, across all participating centers. Data collectors and analysts were blinded to the extent possible, with outcomes collected consistently for both groups. Electronic questionnaires were employed for data collection, allowing assessors and collectors to maintain blinding. However, it is important to note that due to the subjective and self-reported nature of the assessed outcomes, there remained a potential risk of bias.

Interventions

Because of the pragmatic character of this trial, the study did not impose strict treatment guidelines. Patients received rehabilitation from their physiotherapist, and the treating surgery decided the type of surgery to reflect current practice in Belgium.

Conservative treatment consisting of rehabilitation and optional delayed ACL reconstruction

Rehabilitation

Patients completed rehabilitation under the guidance of their physiotherapist, who received general guidelines for ACL rehabilitation (see Appendix 1) [23–25]. The guidelines were broad and provided enough flexibility to the physiotherapist to implement them in clinical practice. This approach reflects current practice, which we aimed to achieve in the pragmatic trial.

Indications for delayed surgery

If a patient from the conservative treatment group reported persistent symptomatic knee instability obstructing rehabilitation progress, the option of delayed surgery was considered. To confirm the underlying cause of instability, an additional MRI was performed. The medical team, together with the patient decided to perform a surgery. Delayed surgery was not performed within the initial 12 weeks following the injury to keep a strict distinction from the treatment arm "immediate surgery".

Immediate ACL reconstruction and rehabilitation

ACL reconstructive surgery

To maintain the pragmatism of the trial, no specific guidelines were imposed regarding the choice of ACL reconstruction method. The decision concerning graft type and surgical technique was left to the clinical judgment of the orthopedic surgeon, who recorded all surgical details in the patient register. While the study did not predefine the type of surgery, strict criteria were applied regarding the timing of the procedure. Immediate ACL reconstruction had to occur within a 12-week window following the ACL injury. This condition was in place to ensure that patients in the immediate ACL reconstruction group did not undergo extensive pre-operative physiotherapy sessions, thus preserving a clear distinction between the two treatment arms.

Rehabilitation

A goal-based rehabilitation protocol was employed, mirroring that of the intervention group (see Appendix 1). However, depending on the type of surgery, the surgeon could impose restrictions regarding range of motion and weight-bearing. Rehabilitation was initiated within the first few days after surgery.

Outcomes

Primary outcomes

The primary objective was to assess the recruitment rate. This is the ratio of the recruited patients to the total number of ACL patients screened in both hospitals. The primary reason for both ineligibility and refusal to participate was also investigated.

We noticed that not all ACL patients were screened by one of the investigators due to a lack of referral to the recruiting department/consultation. To estimate how many potential patients were missed, we also calculated the ratio between the recruited patients and the number of ACL surgeries performed in both hospitals (based on recorded registrations). We are aware that this is still an underestimation of the total number of ACL patients seen by the hospital because some of the patients undergo non-operative treatment, with has no specific medical registration number in Belgium.

Secondary outcomes

The secondary objective of this pilot study was to assess (1) adherence to the protocol and the assigned treatment arm and to assess (2) the feasibility to recruit a sample that reflect a young and active population.

(1) To calculate adherence we calculated the proportion of who discontinued the assigned treatment arm and documented the primary reasons for non-adherence. Furthermore, the proportion of patients who did not complete specific assessments was determined. For each functional test and questionnaire, the percentage of patients who successfully completed the assessment was calculated. Furthermore, any underlying reasons for uncompleted assessments were explored as necessary. These findings were utilized to investigate the potential need for additional strategies aimed at optimizing adherence to the study protocol and assigned treatments.
(2) To assess the feasibility to recruit a sample that reflect a young and active population, we describe the patient demographics of the recruited sample.

Patients experience

After the first six patients completed the 7-month follow-up visit, we conducted an intermediate assessment to gain insights into their experiences and perspectives regarding their participation in the study. This assessment aimed to gather valuable feedback and information that could help refine and enhance the overall study process. We assessed this by using the SPFQ questionnaire (Study Participant Feedback Questionnaire) [26].

Experiences of the investigators

To evaluate the experience of investigators involved in the trial, we administered a survey to the research teams at CHU Liège and UZ Leuven. The survey served as a valuable tool for gathering feedback and identifying areas of improvement in the study's implementation, facilitating the ongoing refinement of the trial.

Outcomes collected for the full RCT

All patients of this pilot trial were asked to continue with the full trial that investigated the clinical effectiveness of both treatments. To allow the transfer of data of patients participating in the pilot trial, we already collected the variables that are considered necessary for this full RCT. Since these outcomes are outside the scope of this pilot study, we refer to our previously published protocol paper for a detailed description of these outcomes (mainly patient-reported outcome measures) [21].

Timeline

Besides the baseline visit (time of randomization), there were 3 follow-up visits: 4, 7, and 12 months after randomization (see Fig. 1). Table 1 comprehensively

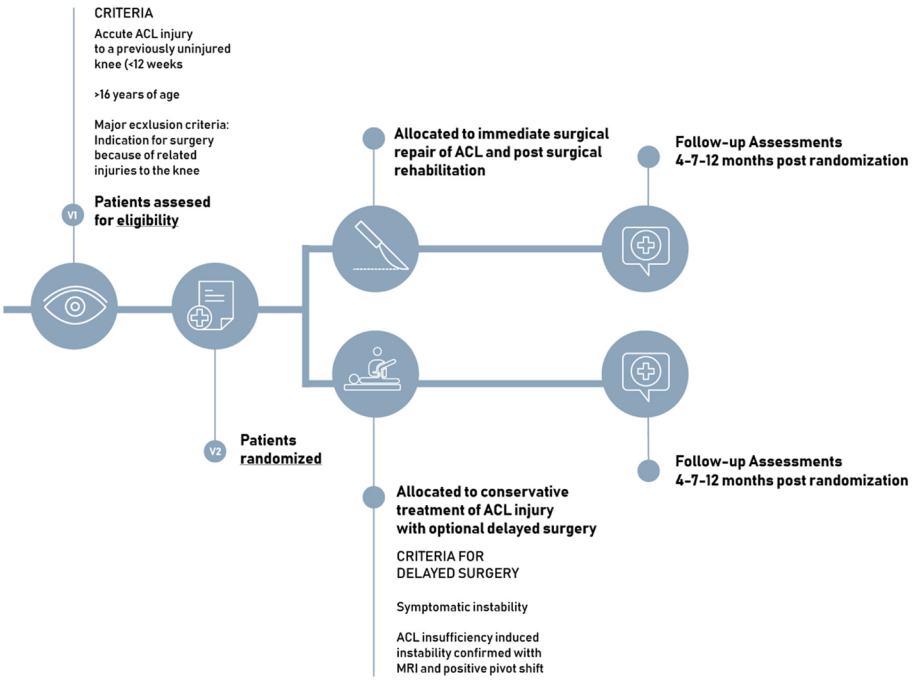

Fig. 1 Trial flow chart

Table 1 Overview trial procedures

Procedures/assessment	Screening	Randomization + baseline assessment	Intervention	Follow-up visits		
Visits	V1	V2		V3	V4	V5
Timing (months)	< 8 weeks after injury	Baseline < 8 weeks after injury		4 months post-injury ± 14 days	7 months post-injury ± 14 days	12 months post-injury ± 14 days
Enrolment						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
Intervention						
1. Rehabilitation + optional delayed surgery			(X)[1]	(X)[1]	(X)[1]	(X)[1]
2. Immediate ACL reconstruction			X[2]			
Assessments*						
MRI	(retrieved from patient record)			X		
PROMS[#]		X		X	X	X
Adverse events				X	X	X
Isokinetic strength				X	X	X
Single leg hop for distance					X	X

The following patient reported outcome measures (PROMS) will be assessed at V2–V5: KOOS return-to-sport, return-to-work, IPQ-R, TSK, EARS, and quality of rehabilitation

[1] Optional delayed surgery can occur after randomization

[2] Immediate ACL reconstruction has to be performed within 12 weeks after injury

summarizes all the assessments conducted during each patient's visit. It is important to note that this pilot trial collected more outcomes than necessary to address the objectives of this pilot trial; these additional data were solely collected for potential use in the full RCT trial.

Statistical analyses

Feasibility and adherence outcomes were reported in a descriptive and narrative manner. In this pilot trial, none of the other outcomes collected for the full RCT (e.g., patient-reported outcome measures, functional tests, and MRI data) were yet analyzed, as the aim of this pilot trial was not to compare the clinical effectiveness of both interventions.

Results

Process feasibility

Recruitment and recruitment rate

Between September 2020 and March 2022, 70 patients were screened for eligibility in both hospitals Among these patients, 25 were excluded from the study as they did not meet the eligibility criteria. The primary reasons for their ineligibility were not 18 years or older ($n=4$), non-acute ACL injuries ($n=10$), prior ACL injuries or knee surgery to the index knee ($n=5$), and the necessity of immediate surgery due to concomitant severe knee injuries that required surgery ($n=6$) (Fig. 2).

In addition to the ineligible patients, 16 patients declined to participate. Their reasons for declining included preference for surgery in 11 cases, preference for conservative treatment in 3 cases, a lack of.

interest in 1 case, and too large travel distance to the hospital in 1 case. Consequently, a total of 29 patients out of the initial 70 screened patients were recruited, resulting in a recruitment rate of 41%.

We noticed that not all ACL patients were screened by one of the investigators due to a lack of referral to the recruiting department/consultation. To estimate the number of potential patients we missed, we requested how many ACL surgeries were performed during the recruitment period.

We noticed that not all ACL patients were screened by one of the investigators due to a lack of referral to the recruiting department/consultation. We requested how many ACL surgeries were performed during recruitment to estimate the number of potential patients we missed.

Based on this information, we estimated the percentage of recruited patients per month for both hospitals (Figs. 3 and 4), starting from the first month after the site initiation visit (SIV). In UZ Leuven, the average recruitment rate was 32%. In CHU Liège, the average recruitment rate

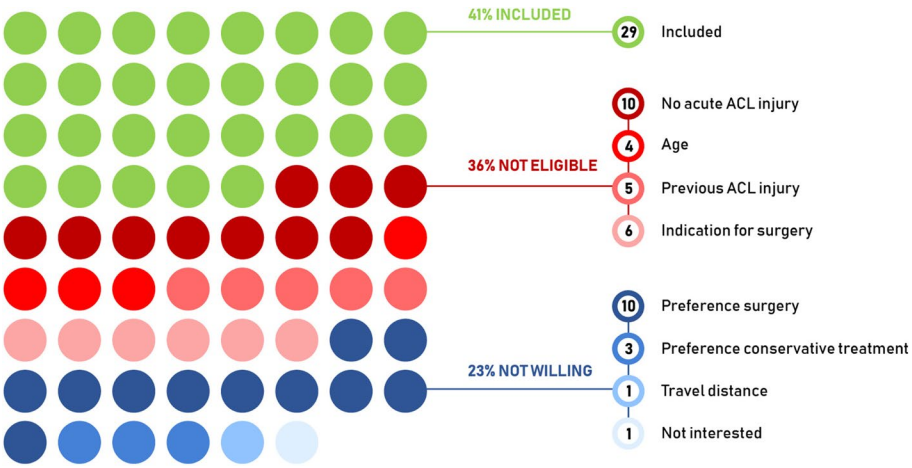

Fig. 2 Overview of screening data

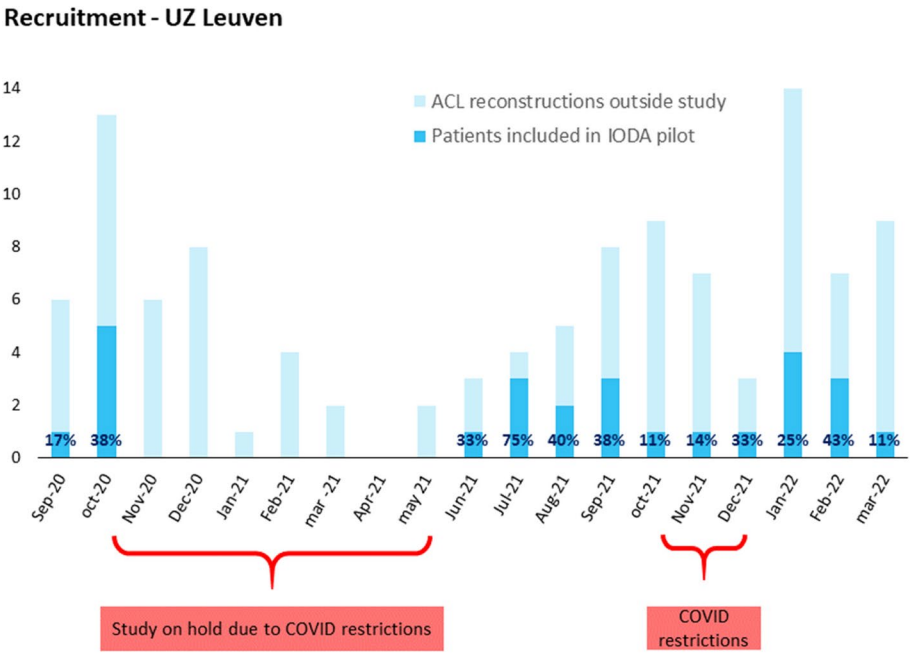

Fig. 3 Recruitment in UZ Leuven

was 17%. The recruitment period was shorter because the SIV was delayed (first because of COVID-19, later due to the absence of the PI).

The recruitment percentage provided is an approximate estimation. This number is based on all ACL *reconstructions* performed in the hospital, which may not accurately reflect the number of eligible patients for the study due to several factors. Some patients opted for conservative treatment, which is not included in this number of ACL reconstructions due to the lack of a specific registration code for conservative ACL treatment. Additionally, not all ACL patients were eligible for the study. Some required immediate surgery due to additional joint damage, and some were non-acute ACL injuries. As a result, the number of eligible patients is probably smaller than those in Figs. 3 and 4.

Adherence to allocated treatment arm and protocol

The secondary objective of this pilot trial was to investigate the adherence of patients to the treatment arm to which they were assigned, and secondly, to evaluate the feasibility of the study protocol.

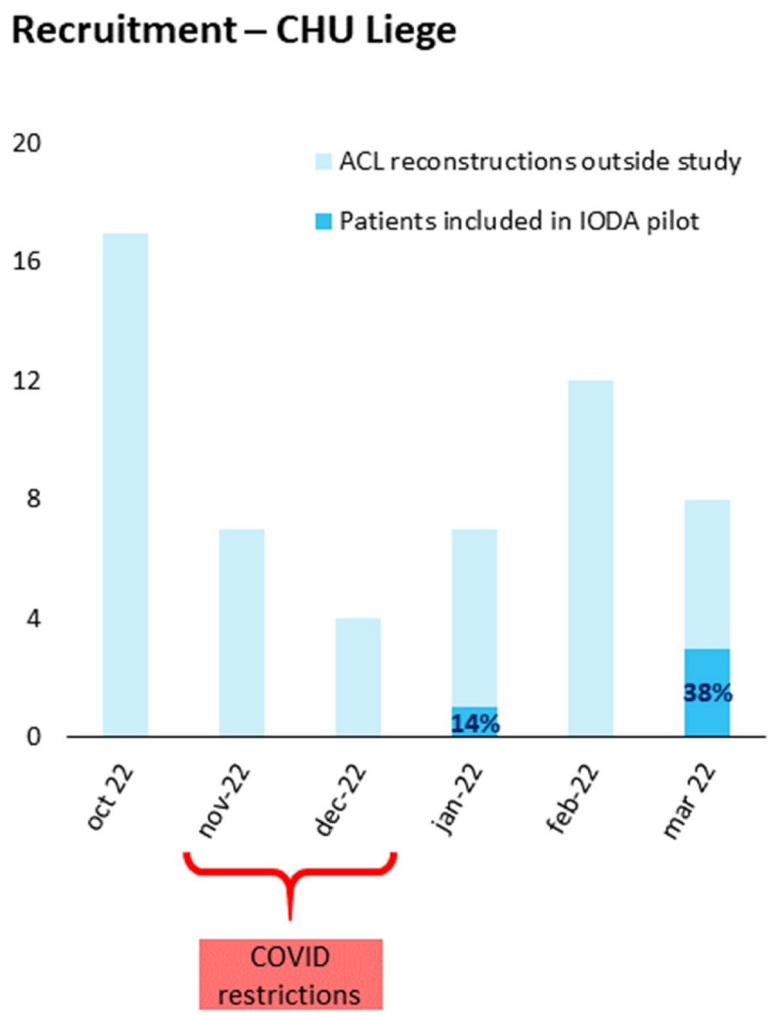

Fig. 4 Recruitment in CHU Liège

Adherence to allocated treatment arm

The trial flowchart (Fig. 5) provides an overview of the patients who-crossed over between treatment arms.

Immediate surgery

Ten of the 14 patients randomized to "immediate surgery" underwent ACL reconstruction within the prescribed 12-week timeframe. Two patients chose conservative treatment and withdrew from the study. One patient postponed his surgery due to a busy work schedule and underwent the procedure later than 12 weeks after the injury. Additionally, in one case, the surgeon deemed immediate surgery medically inadvisable, and consequently, this patient did not undergo surgery at all.

Conservative treatment

Three out of the 15 patients randomized to 'conservative treatment' underwent ACL reconstruction within the 12-week timeframe. These three patients had a strong preference for surgery and chose to undergo immediate surgery. These patients agreed to continue their participation in the study.

Drop out

In total five participants dropped out during the follow-up of 12 months. Among them, two patients discontinued their participation immediately after randomization, as they were not randomized to their preferred treatment arm (e.g., preference for conservative treatment but had been assigned to the immediate surgery group). Two other patients dropped out after the baseline visit due to time constraints and a long travel distance to the hospital. The fifth patient did not complete the final visit because of time constraints.

Protocol feasibility

The protocol primarily incorporated questionnaires along with strength testing (isokinetic strength) and

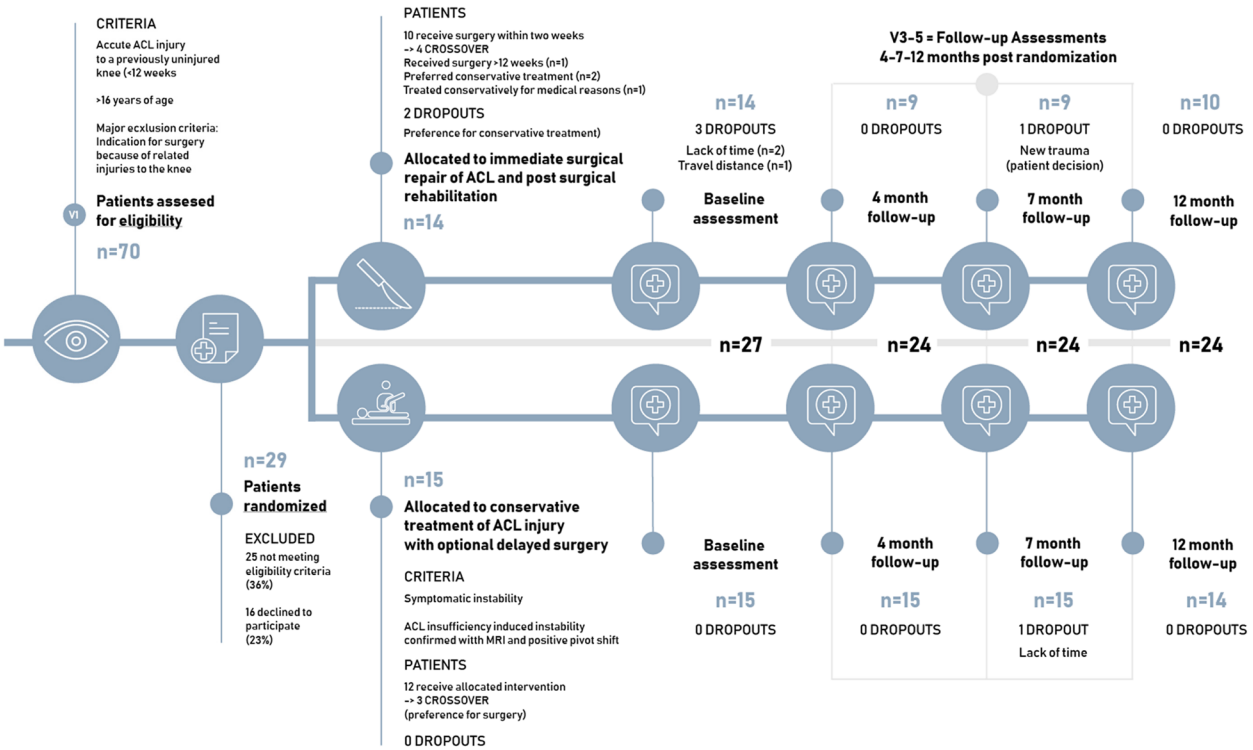

Fig. 5 Screening flowchart + results recruitment

a knee function test (single leg hop for distance). The completeness rate for these assessments was very high. The questionnaires administered electronically via REDCap achieved a 100% completion rate. Occasionally, reminders were sent to the patients, but their timely dispatch contributed to this high rate of completion. The isokinetic strength test, was successfully administered to all participants except for one patient during the 4-month follow-up visit. This exceptional circumstance was attributed to an administrative error.

Patients experience

All six patients had a positive experience with study enrollment and participation (see Appendix 2 with the results of the SPFQ). They reported that the information was clear and they were comfortable asking questions. While most were satisfied with the organization of trial visits, three patients found that the timing of the follow-up visits (at our bi-weekly multidisciplinary consultation) could have been more flexible. Most patient reported that study commitment was similar to what they expected. However, two patients reported that it took more commitment than expected.

Experiences of the investigators

A survey was sent to the investigators of CHU Liège and UZ Leuven to evaluate their experience of participating in the trial. In summary, the survey revealed the following for CHU Liège: The Department of Physical Medicine and Rehabilitation saw limited patient engagement, as most individuals sought care directly from the Department of Orthopedics. Therefore, not all potential patients were screened for study participation. Additionally, the team faces logistical difficulties in securing timely MRI appointments for patients, primarily due to the constrained availability of the MRI scanner. The challenges in UZ Leuven were related to inconsistent study explanations due to patients seeking care through different hospital departments, limited awareness of the IODA study among medical trainees due to frequent rotations, and the complexity of coordinating assessments at mutually convenient times for patients.

Description of recruited sample

Table 2 presents the demographics of the total sample (= all patients who completed at least the baseline visit).

Table 2 Patient demographics of total sample

	Total sample (mean±SD)
Number	29
Gender	6 females / 23 males
Age	27,25 ± 8,26 years
Height	176,89 ± 7,59 cm
Weight	75,57 ± 14,74 kg
Education	9 secondary school 14 bachelor degree 6 master degree
Randomization	14 immediate surgery 15 conservative treatment
Sport participation	24 competitive level 4 recreational level 1 no regular sport participation
concomitant lesions	5 meniscal injuries (4 lateral and 1 medial) 10 collateral ligaments (9 MCL and 1 LCL) 3 cartilage damage

Discussion

The main aim of this pilot study was to assess the feasibility of recruiting patients with an acute ACL injury for an RCT that compares immediate surgery with conservative treatment. In total, 41% of the screened patients could be recruited, which indicates that recruitment is feasible. Based on this outcome, this pilot study progressed to a full RCT (the IODA trial–ClinicalTrials.gov NCT04408690). The IODA trial is the third RCT (besides the KANON and COMPARE trial), comparing immediate surgery and conservative treatment after acute ACL rupture. However, it is the first trial that will be sampled to investigate whether patient-specific parameters measured at the time of diagnosis can predict treatment success. Accurate predictions are needed for early patient stratification, as timely administration of the most suitable treatment leads to optimal clinical results while minimizing unnecessary medical costs.

Recruitment feasibility

The primary objective of this feasibility study was to assess the recruitment rate. Before the start of the study, clear progression criteria were defined together with the funder of the trial [21]. We defined that a recruitment rate of at least 75% of the expected rate was necessary. The expected recruitment rate was based on the recruitment numbers of the KANON trial, in which the investigators could recruit 22% of all screened patients (141 out of 642 screened patients) and 72% of all eligible patients (141 out of 196 eligible patients) [10]. In our pilot study, 41% of all screened patients were recruited (29 out of 70 patients), and 64% of the eligible patients were recruited (29/45).

However, one of the challenges that became evident throughout this pilot study was the limited number of patients screened for inclusion. For example, despite a substantial volume of ACL surgeries performed at CHU Liège (52 cases during 6 months), only 7 patients were screened. This big contrast between the surgeries performed and the limited number of patients recruited for the study underscores the importance of carefully evaluating the factors influencing patient recruitment in a healthcare institution. This low screening rate primarily resulted from bad patient referrals within the hospital setting. Not only is a very close collaboration between different departments (Emergency care, orthopedics and physical and rehabilitation medicine) necessary, but also all caregivers need to be willing to recruit patients. So, to optimize the feasibility and effectiveness of future studies of this nature, it is advisable to consider initiating such research in medical centers where there is a good

multidisciplinary collaboration with no bias favoring any specific treatment strategy.

These insights helped us to define which essential modifications were necessary to transition to a full-scale RCT. These adjustments included increasing the number of participating sites, searching for sites with strong collaboration between departments (or they are open for this), streamlining patient recruitment procedures, and prolonging the recruitment period.

This feasibility study also investigated the primary reasons behind patient ineligibility, a crucial exploration that could guide potential revisions to the eligibility criteria when progressing to the full trial. Among the factors leading to exclusion, the predominant one was the presence of a non-acute ACL injury (9/25 ineligible patients). These patients (who visited the emergency department and/or doctor more than 4 weeks after their injury) were excluded to prevent that they already had an extensive rehabilitation program before randomization. This allowed us to make a clear distinction between immediate (< 12 weeks post-injury) and delayed surgery (> 12 weeks post-injury). Consequently, this exclusion criterion is thus not adapted for the full trial.

In contrast, a criterion adapted for the full trial is the minimum age. Four patients were excluded from the pilot trial as they had yet to reach the age of 18. For the full trial, the minimum age has been set at 16 years old, as skeletal maturity can reasonably be assumed at this stage of development.

This study also administered why patients refused to participate, with the predominant factor being a preference for surgery, as indicated by 11 out of the 16 patients who declined to participate. This aligns with our initial expectations and underscores the prevalent belief that surgery is necessary for successful outcomes. In contrast, a smaller proportion of patients (3 out of 16) refused participation due to a preference for conservative treatment. This observation mirrors findings from the KANON and COMPARE trials, where a strong treatment preference was a primary driver of patients unwilling to participate. However, it is important to note that while some patients declined participation in this RCT due to treatment preference, this represented only a third of the eligible patients. Hence, the feasibility of conducting this RCT in Belgium remains possible.

Adherence

This pilot study showed a very high completion rate of the assessments described in the study protocol, affirming the feasibility of the protocol. Therefore, no assessment adjustments are deemed necessary for the full RCT. The major part of the assessments consisted of surveys, which were sent by mail to the patients. The completion rate was 100% for these surveys. Sometimes, reminders were necessary to achieve timely completion of the surveys. The other assessments were isokinetic strength tests of the thigh muscles and a functional test (single leg hop for distance) performed at the follow-up visits. One patient missed his strength test because of an administrative error.

In addition to the completion rate of the assessments, we also examined adherence to the assigned treatment arms—notably, seven of the 29 patients crossed to the alternative treatment arm. The main reason was a strong preference for the treatment arm they had not been randomized initially to. In total, three patients insisted on having immediate surgery despite being randomized to conservative treatment, and two patients did not want immediate surgery even though they were randomized to that treatment arm. The investigators thoroughly communicated the methodological importance of adhering to their assigned treatment, but these patients remained persistent in their preferences.

The study protocol did not specify the exclusion of these patients; therefore, they were allowed to continue the study if they agreed. Ultimately, two patients opted to withdraw from the study, while the other five patients were followed until the 12-month post-injury.

The observed cross-over rate of 24% is high and raises concerns, necessitating precautionary measures to mitigate cross-overs in the full RCT. A significant number of cross-overs could substantially compromise the RCT's quality. In the KANON and COMPARE trial, cross-overs between treatment arms were relatively limited, typically involving only 1–3 patients per treatment arm on a larger sample size. To address this issue in the full trial, investigators will emphasize the importance of patients adhering to their allocated treatment arm. Additionally, sensitivity analyses will be conducted to explore the impact of these cross-overs on the study's outcomes.

The feedback on patients' experience (administering the SPF questionnaires in the first six patients) obtained valuable insights on improving patient participation. This showed, for example, that some patients asked for more flexibility to schedule study visits. Consequently, efforts were made to accommodate alternative visit times to minimize drop-outs. Furthermore, this survey revealed that providing clear and comprehensive information fosters a deeper understanding of the study's objectives, potential advantages, and associated risks and empowers patients to make informed decisions about their participation.

Representativity of the sample

The participants of the IODA trial had an average age of 27 years, which is similar to the KANON trial (25 years)

and is in agreement with the epidemiological study of Sanders et al., who reported that the average age at the time of ACL injury is 29 years old [10, 27]. Our sample predominantly comprised males (23), with a smaller representation of females (6), and nearly all participants were actively engaged in sports prior to their injury (except one patient who had a physically demanding job). Moreover, a substantial portion of the patients 24/29 performed a cutting or pivoting sport at a competitive level (not at a professional level). Again, this agrees with epidemiological findings and is similar to the two existing RCTs (COMPARE and KANON trial) [10, 12]. Based on the demographics of this pilot sample, one can conclude that recruiting young and active patients for a full RCT that compares surgery with conservative treatment is feasible. This representative sample is highly needed if one wants to verify—in an unbiased manner—whether age and activity level are good indicators to decide whether or not a patient should undergo immediate surgery after ACL rupture. This has not yet been investigated in a randomized design.

Furthermore, there exists a prevailing belief that patients with concomitant intra-articular lesions preferably need to undergo surgery. To effectively assess the validity of this belief, the study should include such patients, not solely those with isolated ACL ruptures. Consequently, the study protocol defined that patients with concomitant lesions would only be excluded if a compelling surgical indication was present (e.g., bucket-handle tear of the meniscus that blocks the knee or tibia plateau fracture). The participating surgeons pragmatically determined this exclusion criterion. Based on the pilot study results, we can conclude that patients with concomitant meniscal and ligament lesions were also successfully recruited.

Limitations

The investigators want to emphasize transparency and clarify that the recruitment rate was based on the number of screened patients with an ACL injury. This screening process was limited to patients who consulted with one of the participating trial doctors, representing those who progressed to the screening phase. The number of patients with an ACL injury who visited the hospitals was higher in both hospitals but cannot be retrieved as only ACL surgeries have a specific registration number (no registration number for conservative treatment). Some patients went to another hospital and/or a doctor outside the hospital after visiting the emergency department. Despite substantial efforts to optimize the referral process from the emergency care unit to the study investigators, some patients were still missed. Additionally, the COVID-19 pandemic had a significant impact on our study. It led to two distinct periods of disruption due to government restrictions on non-essential surgeries and reduced availability for scheduling surgeries. It is important to acknowledge that this disruption affected the representativeness of our recruitment process during those periods.

Although, RCTs are considered the gold standard for evaluating the effectiveness of medical interventions, RCTs have notable limitations. Including high costs, a high failure rate, difficulties in meeting recruitment goals, and limited external validity, which complicates the application of findings to real-world patient populations. These challenges are confirmed in our pilot trial.

A promising alternative is the registry-based randomized controlled trial (RRCT), which utilizes existing registries to prospectively collect treatment and outcome data. RRCTs have the potential to significantly influence clinical practice and health policy. However, several challenges must be addressed to fully realize their potential, including the need for universally accepted criteria to define RRCTs (28). Due to the absence of such registries in Belgium, implementing RRCTs in the IODA trial is not feasible.

Conclusion

This pilot study confirmed the challenges encountered in recruiting participants for an RCT comparing surgical and non-surgical treatment options for ACL injuries. Despite these substantial recruitment challenges, our findings demonstrate that transitioning to a full-scale RCT is feasible, contingent upon implementing some essential modifications. These adjustments include increasing the number of participating sites, searching for sites with strong collaboration between departments (or they are open to this), optimizing patient recruitment procedures, and prolonging the recruitment period. The recruited sample consisted of young patients who participated in sports activities of different levels and was not limited to patients with isolated ACL ruptures, which is a good representation of the ACL population. However, it is worth highlighting that many patients did not adhere to their randomized treatment assignments, underscoring the need for proactive measures to mitigate this challenge in the upcoming full trial.

Trial status

The full RCT is ongoing in five different hospitals in Belgium (Leuven, Liège, Brussels (2 hospitals) and Gent). To date, we have recruited 60 patients, in addition to the 29 patients from the pilot study. The full trial is registered on ClinicalTrials.gov: NCT05747079 (02/03/2023).

Abbreviations

ACL	Anterior cruciate ligament
RCT	Randomized controlled trial
MRI	Magnetic resonance imaging
KOOS	Knee Injury and Osteoarthritis Outcome Score
QOL	Quality of life
EARS	Exercise adherence rating scale
ROM	Range of motion
PROMS	Patient-reported outcome measures
ADL	Activities of daily living
SLHD	Single leg hop for distance
RTS	Return to sport
ACLOAS	Anterior cruciate ligament osteoarthritis score
TSK	Tampa Scale of Kinesiophobia
IPQ-R	Illness Perceptions Questionnaire (Revised)
AE	Adverse events
GCP	Good clinical practice
KCE	Belgian Health Care Knowledge Centre
GDPR	General data protection regulation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40814-025-01652-2.

Additional file 1. Appendix 1: Table 1. Overview of the rehabilitation guidelines per treatment arm

Additional file 2. Appendix 2: Results of the Study Participant Feedback Questionnaire (SPFQ)

Acknowledgements
Not applicable.

Status of the study
Patient recruitment is ongoing in the University Hospital of Leuven, CHU Liège, Jessa Ziekenhuis, Clinique Saint Luc Bouge and UZ Brussel and 59 patients are randomized (29 pilot study + 30 full study).

Confidentiality
Personal data recorded on all documents will be regarded as confidential. All data will be handled and stored in accordance with the General Data Protection Regulation (GDPR) and the Data Protection Act 2018. During the clinical trial and after trial closure, adequate and accurate records will be maintained to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. All essential documents will be stored to ensure that they are readily available, upon request, for the minimum period required by national legislation or for longer if needed.

Authors' contributions
PK as chief investigator. SA, BS, and BP were co-applicants on the grant application to KCE trials. PK, SA, BS, and BP were involved in the design of the study. GAF and SA were responsible for writing the manuscript. All authors read and approved the final manuscript.

Funding
Funding for this study was obtained through the Belgian Health Care Knowledge Centre Trials Programme (KCE trials) under research agreement KCE 18–1158.
The protocol has undergone a peer-review by the Trials Board according to the Standard Operating Procedures of the KCE trials programme (https://kce.fgov.be/nl/kce-trials-procedures). KCE trials has no role in the collection, analysis and interpretation of the data and in writing of the manuscripts.

Data availability
Data sharing is not applicable to this article as data collection is still ongoing.

Ethics approval and consent to participate
I confirm that all experiments in this study will be conducted in strict accordance with the relevant guidelines and regulations, or in accordance with the Declaration of Helsinki.
Ethics approval and consent to participate—The IODA study was approved by the ethical committees of the four participating centers (protocol version 2—date: 30/01/2023): de Ethische Commissie Onderzoek UZ/KU Leuven (S67021) and Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège (2020–212). If the medical doctor confirms the eligibility and the patient agrees upon participation, informed consent will be signed by both the investigator and the patient. The study will be conducted in accordance to relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Physical & Rehabilitation Medicine, University Hospitals Leuven, Leuven, Belgium. [2]Research Group of Physical & Rehabilitation Medicine, Department of Development & Regeneration, KU Leuven, Leuven, Belgium. [3]Department of Rehabilitation Sciences & Physiotherapy, Research Group of Musculoskeletal Rehabilitation, KU Leuven, Leuven, Belgium. [4]Department of Orthopedic Surgery, University Hospitals Leuven, Leuven, Belgium.

Received: 28 February 2024 Accepted: 28 April 2025
Published online: 08 May 2025

References

1. Thorstensson CA, Lohmander LS, Frobell RB, Roos EM, Gooberman-Hill R. Choosing surgery: patients' preferences within a trial of treatments for anterior cruciate ligament injury. A qualitative study. BMC Musculoskelet Disord. 2009;10:100.
2. Paterno MV, Rauh MJ, Schmitt LC, Ford KR, Hewett TE. Incidence of second ACL injuries 2 years after primary ACL reconstruction and return to sport. Am J Sports Med. 2014;42(7):1567–73.
3. Lie MM, Risberg MA, Storheim K, Engebretsen L, Oiestad BE. What's the rate of knee osteoarthritis 10 years after anterior cruciate ligament injury? An updated systematic review. Br J Sports Med. 2019;53(18):1162–7.
4. Poulsen E, Goncalves GH, Bricca A, Roos EM, Thorlund JB, Juhl CB. Knee osteoarthritis risk is increased 4–6 fold after knee injury - a systematic review and meta-analysis. Br J Sports Med. 2019;53(23):1454–63.
5. Ardern CL, Taylor NF, Feller JA, Webster KE. Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. Br J Sports Med. 2014;48(21):1543–52.
6. Wiggins AJ, Grandhi RK, Schneider DK, Stanfield D, Webster KE, Myer GD. Risk of secondary injury in younger athletes after anterior cruciate ligament reconstruction: a systematic review and meta-analysis. Am J Sports Med. 2016;44(7):1861–76.
7. Cinque ME, Dornan GJ, Chahla J, Moatshe G, LaPrade RF. High rates of osteoarthritis develop after anterior cruciate ligament surgery: an analysis of 4108 patients. Am J Sports Med. 2018;46(8):2011–9.
8. Saueressig T, Braun T, Steglich N, Diemer F, Zebisch J, Herbst M, et al. Primary surgery versus primary rehabilitation for treating anterior cruciate ligament injuries: a living systematic review and meta-analysis. Br J Sports Med. 2022;56(21):1241–51.
9. Filbay SR, Roemer FW, Lohmander LS, Turkiewicz A, Roos EM, Frobell R, et al. Evidence of ACL healing on MRI following ACL rupture treated with rehabilitation alone may be associated with better patient-reported outcomes: a secondary analysis from the KANON trial. Br J Sports Med. 2023;57(2):91–8.
10. 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(4):331–42.

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, van Arkel E, van den Brand I, van Linge J, 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. von Essen C, McCallum S, Barenius B, Eriksson K. Acute reconstruction results in less sick-leave days and as such fewer indirect costs to the individual and society compared to delayed reconstruction for ACL injuries. Knee Surg Sports Traumatol Arthrosc. 2020;28(7):2044–52.
14. van Meer BL, Oei EH, Bierma-Zeinstra SM, van Arkel ER, Verhaar JA, Reijman M, et al. Are magnetic resonance imaging recovery and laxity improvement possible after anterior cruciate ligament rupture in nonoperative treatment? Arthroscopy. 2014;30(9):1092–9.
15. Rosso F, Bonasia DE, Cottino U, Cambursano S, Dettoni F, Rossi R. Factors affecting subjective and objective outcomes and return to play in anterior cruciate ligament reconstruction: a retrospective cohort study. Joints. 2018;6(1):23–32.
16. Everhart JS, Best TM, Flanigan DC. Psychological predictors of anterior cruciate ligament reconstruction outcomes: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2015;23(3):752–62.
17. Paterno MV, Flynn K, Thomas S, Schmitt LC. Self-reported fear predicts functional performance and second ACL injury after ACL reconstruction and return to sport: a pilot study. Sports Health. 2018;10(3):228–33.
18. Kvist J, Ek A, Sporrstedt K, Good L. Fear of re-injury: a hindrance for returning to sports after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2005;13(5):393–7.
19. Thomee P, Wahrborg P, Borjesson M, Thomee R, Eriksson BI, Karlsson J. Self-efficacy of knee function as a pre-operative predictor of outcome 1 year after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2008;16(2):118–27.
20. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
21. Smeets A, Ghafelzadeh Ahwaz F, Bogaerts S, De Groef A, Berger P, Kaux JF, et al. Pilot study to investigate the feasibility of conducting a randomised controlled trial that compares Immediate versus Optional Delayed surgical repair for treatment of acute Anterior cruciate ligament injury: IODA pilot trial. BMJ Open. 2022;12(3): e055349.
22. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. New England J Med. 2010;363(4):331–42.
23. Wilk KE, Arrigo CA. Rehabilitation principles of the anterior cruciate ligament reconstructed knee: twelve steps for successful progression and return to play. Clin Sports Med. 2017;36(1):189–232.
24. van Melick N, van Cingel REH, Brooijmans F, Neeter C, van Tienen T, Hullegie W, et al. Evidence-based clinical practice update: practice guidelines for anterior cruciate ligament rehabilitation based on a systematic review and multidisciplinary consensus. British J Sports Med. 2016;50(24):1506-+.
25. Cavanaugh JT, Powers M. ACL rehabilitation progression: where are we now? Curr Rev Musculoskelet Med. 2017;10(3):289–96.
26. Nieboer AP, Cramm JM. Validation of the SPF-Q, an instrument to assess the quality of production functions to achieve well-being, among multimorbid patients. Health Qual Life Outcomes. 2020;18(1):321.
27. Sanders TL, Maradit Kremers H, Bryan AJ, Larson DR, Dahm DL, Levy BA, et al. Incidence of anterior cruciate ligament tears and reconstruction: a 21-year population-based study. Am J Sports Med. 2016;44(6):1502–7.

Publisher's Note