


# BMJ Open 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

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## ABSTRACT

**Introduction** Standard care for anterior cruciate ligament (ACL) injuries includes surgical reconstruction of the ACL. However, two randomised controlled trials (RCTs) concluded that conservative treatment does not result in inferior clinical outcomes compared with immediate ACL reconstruction. More research is needed to in the first place verify these results, and second to assess whether patient-specific parameters determine whether a patient would benefit from one treatment option over the other. However, before running a full RCT, it seems necessary to perform a pilot study that assesses the feasibility of recruiting patients with ACL for such a RCT. This is because recruitment may be challenging as many patients have strong treatment beliefs. Therefore, this pilot study will assess whether a large RCT is feasible with regard to participant recruitment, adherence to the allocated treatment arm and protocol feasibility. These pilot findings will help deciding about progressing to a future full RCT.

**Methods and analysis** This is a pragmatic, multicentre, randomised controlled pilot trial with two parallel groups. Patients with an acute ACL injury will be recruited from two Belgian hospitals. Patients will be randomised to either conservative treatment or surgical treatment. Patients will be followed-up at 3, 6 and 12 months postrandomisation. Recruitment feasibility will be evaluated by calculating the recruitment rate 4 months after the two sites have been initiated. Clear criteria for progression to a full trial are defined. Adherence to the protocol will be assessed by calculating the proportion of patients who complete the assessments. Furthermore the proportion of patients who cross-over between treatment arms during the follow-up period will be assessed.

**Ethics and dissemination** The study was approved by the ethical committees: Ethische Commissie Onderzoek UZ/KU Leuven (S62004) and Comité d’Ethique Hospitalo-Facultaire Universitaire de Liège (2020212). Results will be made available to caregivers, researchers and funder.

## Strengths and limitations of this study

- This pilot study assesses the feasibility of recruiting patients with an acute anterior cruciate ligament injury for a randomised controlled trial comparing immediate surgery with conservative treatment.
- This feasibility study is necessary because recruitment might be challenging because of patients’ treatment preferences.
- Strict progression criteria were imposed which will allow us to make an objective decision on progression to a full adequately powered trial.
- With the insides of this pilot study we can optimise recruitment and protocol adherence.
- This study is only a pilot study, so no conclusions can be made regarding clinical effectiveness of both treatment options or patient-specific factors that predict treatment success.

**Trial registration number** This trial is registered on ClinicalTrials.gov (NCT04408690) on 29 May 2020.

## INTRODUCTION

An anterior cruciate ligament (ACL) rupture is a common injury, especially in young, physically active individuals, with an annual incidence of approximately 7/10 000 persons in the general population.<sup>1,2</sup> Frequently, additional injuries to the menisci, cartilage, collateral ligaments or subchondral bone are present.<sup>3</sup> The rupture of the ACL and damage to other knee stabilising structures often results in knee joint instability affecting daily activities and sports, leading to poor knee-related quality of life.<sup>4</sup>

The standard care for ACL injuries includes reconstructive surgery.<sup>1</sup> For years, it was believed that surgical repair of the ACL is necessary to restore mechanical knee stability in order to safely return to sport<sup>5</sup> and to avoid long-term disadvantages such as persistent knee instability, reinjury<sup>6</sup> and post-traumatic knee osteoarthritis.<sup>7,8</sup> However, evidence assessing treatment outcomes after ACL reconstruction does not support these beliefs. A recent meta-analysis showed that about 50% of the patients who underwent surgical repair of their ACL have cartilage degeneration 20 years after surgery<sup>9</sup> and up to 23% suffer a new ACL injury (ipsilateral or contralateral) within 2 years after return to sport.<sup>10</sup> Furthermore, Ardern *et al*<sup>11</sup> found that only 55% of athletes who underwent an ACL reconstruction return to their preinjury sport level. Based on these findings, one can conclude that ACL reconstruction does not guarantee restoration of normal knee function and protection to long-term disadvantages.

In 2016, Monk *et al*<sup>12</sup> performed a Cochrane systematic review to assess whether ACL surgery or conservative treatment (consisting of rehabilitation and optional delayed surgery) was superior for treating ACL injuries. They concluded that no high-quality evidence exists as there was only one randomised controlled trial (RCT) (KANON trial) available at that time.<sup>13</sup> The KANON trial found no differences in patient-reported, structural or functional outcomes at 2 and 5 years follow-up.<sup>13,14</sup> Since the publication of the systematic review of Monk *et al* in 2016,<sup>12</sup> two more RCTs have been initiated (a Dutch trial: COMPARE trial, NTR2746 and an English trial: ACL SNNAP study, NCT02980367).<sup>15</sup> The COMPARE trial<sup>16</sup> found, at 2-year follow-up, slightly better self-reported outcomes (knee symptoms, self-reported knee function and perception of the ability to participate in sports) in the immediate surgery group compared with the conservative group, but none of these findings were large enough to be clinically important. Data collection of the second RCT (ACL SNNAP trial) has not yet been finished.<sup>15</sup>

Based on the results of the KANON trial<sup>13</sup> and the COMPARE trial,<sup>17</sup> one can conclude that conservative management with optional delayed surgery does not result in inferior clinical outcomes compared with immediate ACL reconstruction, on population level. However, on patient-level, large between-subject differences were found. Both trials reported that about 50% of the patients with ACL in the conservative group showed persistent knee instability requiring a delayed surgery.<sup>13,16</sup> Because surgery is delayed in this group of patients, time to return-to-sport is prolonged and longer sick leave times are observed compared with patients with immediate surgery.<sup>18</sup> Therefore, early identification of patients who would benefit from early ACL reconstruction, or in contrast from rehabilitation alone, is necessary to reduce resource consumption and decrease unnecessary overtreatment. It is hypothesised that treatment success depends on clinical factors (such as MRI findings) but also on quality of rehabilitation<sup>19</sup> and psychological factors such as expectations,<sup>20</sup> fear for reinjury<sup>21,22</sup> and

locus of control.<sup>23</sup> To assess this, a large RCT should be performed that (1) compares clinical effectiveness of both treatment options and (2) assesses which patient-specific factors predict successful outcomes after conservative treatment of ACL injuries.

Before running a large, adequately powered RCT, that answers these research questions, it seems necessary to perform a pilot study that assesses the feasibility to recruit patients with ACL for such RCT. This is necessary, as many patients have a preference for a particular treatment.<sup>5</sup> For example, Thorstensson *et al* reported that a subset of patients still believe that timely surgery is a prerequisite for restoring knee function, for returning to sports and for preventing cartilage degeneration.<sup>5</sup> On the other hand, other patients are not willing to undergo surgery because of poor experience or the belief that their recovery period would be longer.<sup>5</sup> These individual preferences might affect recruitment (which involves randomisation) and adherence to the protocol. Therefore, a pilot study will be performed to demonstrate whether a large RCT is feasible with regard to (1) participant recruitment, (2) adherence to the treatment arm they were allocated to and (3) protocol feasibility. The findings of this pilot study will help deciding about progressing to a future definitive RCT.

## OBJECTIVES

The main objective of this pilot trial is to demonstrate feasibility with regard to recruitment, protocol adherence and protocol feasibility. The results of this pilot trial will determine the progression towards a future full RCT that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical repair in acute ACL injuries.

### Primary objective

The primary objective of this pilot trial is to demonstrate the feasibility of recruiting patients for an RCT that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical reconstruction of acute ACL injuries. More specifically, the primary aims are:

- ▶ To assess the proportion of patients with ACL that are eligible to participate.
- ▶ To assess the proportion of eligible patients who accept to participate.
- ▶ To explore why eligible patients are not willing to participate.
- ▶ To determine whether certain inclusion or exclusion criteria were too open or too restrictive.

### Secondary objective

The secondary objective of this pilot trial is (1) to explore the adherence of patients to the treatment-arm that they were allocated to and (2) to assess protocol feasibility. This will be addressed by the following aims:

- ▶ To investigate the proportion of patients who received the allocated treatment.
- ▶ To investigate the number of patients who cross-over between groups (eg, number of patients who received the other treatment than allocated).
- ▶ To explore why patients cross over between groups.
- ▶ To determine the number of drop-outs during follow-up
- ▶ To explore why patients drop out after randomization.
- ▶ To assess for each questionnaire and functional test, the number of patients who completed these assessments.

## METHODS/DESIGN

### Study design

This is a pragmatic, multicentre, randomised controlled pilot trial with two parallel groups<sup>1</sup>: conservative treatment (consisting of rehabilitation + optional delayed surgery) and<sup>2</sup> surgical treatment (immediate reconstruction) in patients with an acute ACL injury.

The protocol conforms the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines<sup>24</sup> (the SPIRIT checklist is provided as online additional file 1) and the Consolidated Standards of Reporting Trials (CONSORT) extension to pilot and feasibility trials (the CONSORT checklist for pilot studies is provided as online additional file 2).

### Patient involvement

Six patients were involved in the design of this research. These patients completed two patient surveys on the relevance of the proposed project, the design of the research and on motivational and practical issues concerning undertaking the research. This information was used in designing the protocol (eg, length of study protocol, selection of questionnaires, design of the brochure and frequency of study visits). Once the trial is finished, participants will be informed of the results through a study newsletter suitable for a non-specialist audience.

### Participants

Patients with an acute ACL injury can be included if they meet all of the following inclusion criteria:

1. The patient sustained a rotational trauma to a previously uninjured knee for which medical advice was sought within 4 weeks after the injury
2. The medical diagnosis of ACL injury is confirmed on MRI (both partial and complete ruptures)
3. The patient is 16 years or older.

Patients cannot be included if they meet any of the following exclusion criteria:

1. The patient had a previous ACL injury or knee surgery to the index knee (contralateral injury is allowed).
2. There is a medical indication for acute surgery because of serious concomitant knee lesions (such as multiligament injuries, additional fractures, meniscal lesions that need repair)

3. The patient suffers from any disorder, which in the investigator's opinion might jeopardise the participant's safety or compliance with the protocol.
4. The patient is pregnant or plans to become pregnant in the first 3 months of the study. Since MRI assessment at the 3-month follow-up visit cannot be performed.

All reasons for non-eligibility or reason(s) why patients refuse to participate will be logged (eg, beliefs that surgery is necessary, time-issues, fear of surgery, etc.) in the pre-screening log (anonymously).

### Study setting

This pilot study will be performed in two Belgian hospitals: University Hospital of Leuven and University Hospital of Liège. Participants will be recruited at the department of Orthopaedics and department of Physical and Rehabilitation Medicine of the participating sites.

### Patient identification and screening

Patients referred to any of the participating sites with an acute ACL injury will be asked for potential interest in participating in the study and screened for eligibility by the principal investigator or a delegated member of the research team.

In current practice, patients who have had a knee injury that might be an ACL injury are referred to either (1) the Department of Orthopaedics or (2) the Department of Physical and Rehabilitation Medicine. In both cases, the identification and screening procedure will be performed in the same way. As per routine practice, in the first consultation, the medical doctor takes a patient history and performs a physical examination of the knee, including clinical tests to diagnose ACL injuries. If history and clinical tests raise suspicion for an ACL injury, an MRI is scheduled to confirm the ACL tear. If the patient meets the eligibility criteria, the medical doctor will already give some information about the possibility of participating in the study. The patient receives a brochure with detailed practical information and background information about the limited existing knowledge and clinical equipoise.

During the second medical consultation, the results of the MRI are discussed. If the MRI confirms the ACL tear, the medical doctor inquires about the potential interest in participating in the study. If the patient is interested, the informed consent can be signed immediately. If the patient wants more time to think about his/her participation, a member of the research team will call the patient 1 week later to ask whether the patient wants to participate. In case the patient is less than 18 years old, we will obtain informed consent of one of his/her parents.

Prescreening logs will be implemented at each participating centre to document the reasons for non-participation (eg, reasons for ineligibility, reasons for declining to participate).

### Interventions

The study compares two routine treatment options for patients with an acute ACL injury<sup>1</sup>: conservative treatment

**Table 1** Overview of the rehabilitation guidelines per treatment arm.

	Rehabilitation + optional delayed surgery	Immediate reconstruction + rehabilitation	Criteria for progression
<b>Phase 0:</b> Preoperative phase	Not applicable	<ul style="list-style-type: none"> <li>▶ Restore full knee extension</li> <li>▶ Activation hamstrings and quadriceps to avoid atrophy</li> <li>▶ Patient education</li> <li>▶ Instruction of postoperative exercises</li> </ul>	
<b>Phase 1:</b> Acute phase	<ul style="list-style-type: none"> <li>▶ Restore full knee extension, patella mobility, full flexion ROM</li> <li>▶ Eliminate effusion</li> <li>▶ Restore gait pattern</li> <li>▶ Improve muscle control and activation</li> <li>▶ Restore proprioception</li> </ul>	<ul style="list-style-type: none"> <li>▶ Restore full knee extension, patella mobility, start flexion ROM</li> <li>▶ Eliminate effusion</li> <li>▶ Restore gait pattern</li> <li>▶ Improve muscle control and activation</li> <li>▶ Restore proprioception</li> </ul>	<ul style="list-style-type: none"> <li>▶ Full passive knee extension, flexion: active flexion ROM <math>\geq 115^\circ</math></li> <li>▶ Minimal/ no joint effusion</li> <li>▶ Independent walking</li> <li>▶ Quadriceps strength 60% of contralateral side</li> </ul>
<b>Phase 2:</b> Progressive strengthening + neuromuscular control	<ul style="list-style-type: none"> <li>▶ Restore full knee ROM</li> <li>▶ Improve lower extremity muscular strength + endurance</li> <li>▶ Improve proprioception, balance and neuromuscular control</li> </ul>	<ul style="list-style-type: none"> <li>▶ Restore full knee ROM</li> <li>▶ Improve lower extremity muscular strength + endurance</li> <li>▶ Improve proprioception, balance and neuromuscular control</li> </ul>	<ul style="list-style-type: none"> <li>▶ Full ROM</li> <li>▶ Quadriceps strength 80% of contralateral side</li> <li>▶ Single leg hop test: 80% of contralateral side</li> <li>▶ No pain or effusion</li> </ul>
<b>Phase 3:</b> Return to activity/ sports	<ul style="list-style-type: none"> <li>▶ Normalise lower extremity strength</li> <li>▶ Improve muscle power + endurance</li> <li>▶ Perform sport-specific drills</li> <li>▶ Gradually return to full sport</li> </ul>	<ul style="list-style-type: none"> <li>▶ Normalise lower extremity strength</li> <li>▶ Improve muscle power + endurance</li> <li>▶ Perform sport-specific drills</li> <li>▶ Gradually return to full sport</li> </ul>	<ul style="list-style-type: none"> <li>▶ Strength quadriceps + hamstrings &gt; 90% contralateral side</li> <li>▶ Single leg hop test: &gt;90% contralateral side</li> </ul>

The rehabilitation protocol consists of three phases. Each phase focus on specific aims and progression criteria are provided to decide on progression to the next phase.

consisting of rehabilitation and optional delayed ACL reconstruction and<sup>2</sup> surgical treatment consisting of immediate ACL reconstruction and rehabilitation. To keep the trial pragmatic, we will infer as little as possible with current practice. Therefore, patients will complete rehabilitation with a physiotherapist of their own choice and the study does not predetermine the type of ACL surgery. However, to ensure a minimal level of quality of the rehabilitation, which is necessary for the integrity of the comparison, evidence-based guidelines and progression criteria for ACL rehabilitation are provided to the physiotherapists (table 1).

#### Conservative treatment consisting of rehabilitation and optional delayed ACL reconstruction

##### Rehabilitation

Patients allocated to this treatment arm will complete rehabilitation with their own physiotherapist. As mentioned above, the physiotherapist will receive evidence-based guidelines and criteria for ACL rehabilitation leaving sufficient flexibility how to implement those guidelines in clinical practice. The guidelines are based on the consensus in the literature.<sup>25–27</sup> The rehabilitation protocol consists of three phases (see below) and progression is based on goal-based criteria, not on strict time criteria. Patients can progress to the next phase if the specific goals of the previous phase are achieved.

To estimate the quality of the rehabilitation, the participant will complete a modified version of the Exercise Adherence Rating Scale (EARS)<sup>28</sup> (see Outcomes

section) at every follow-up visit (visit 3–7, see table 2). This questionnaire contains questions about the type of exercises performed, the frequency and intensity of the rehabilitation programme and barriers and facilitators for adherence to the prescribed exercises.

##### Indications for delayed surgery

If a patient complains about persistent symptomatic knee instability or other symptoms that result in the inability to progress in rehabilitation, delayed surgery can be considered. ACL insufficiency induced instability in combination with a positive pivot shift and an additional MRI are needed to confirm the cause of instability (Criteria based on the KANON trial<sup>13</sup>). The delayed surgery will not be performed within the first 12 weeks postinjury, according to current practice.

##### Immediate ACL reconstruction and rehabilitation ACL reconstructive surgery

Patients allocated to this treatment arm will undergo an ACL reconstruction within 12 weeks after the ACL injury. This strict time criterion is imposed to avoid that patients of the immediate ACL reconstruction already had a considerable amount of preoperative physiotherapy sessions, keeping a clear distinction between both treatment arms.

No guidelines on surgical technique or graft type will be imposed to keep the trial pragmatic. The orthopaedic surgeons of the participating sites make this clinical



**Table 2** Overview trial procedures

Procedures/assessment	Screening	Randomisation + baseline assessment	Intervention	Follow-up visits		
Visits	V1	V2		V3	V4	V5
Timing (months)	<12 weeks after injury	<12 weeks after injury		3 months after baseline ± 14 days	6 months after baseline ± 14 days	12 months after baseline ± 14 days
<b>Enrolment</b>						
Eligibility screen	X					
Informed consent	X					
Randomisation		X				
<b>Intervention</b>						
1. Rehabilitation + optional delayed surgery			(X)*	(X)*	(X)*	(X)*
2. Immediate surgery			X†			
<b>Assessments‡</b>						
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

\*Optional delayed surgery can occur after randomisation.

†Immediate surgery has to be performed within 12 weeks after injury.

‡A detailed description of all assessments can be found in online additional file 3.

§The following PROMs will be assessed at V2–V4: KOOS, return-to-sport, return-to-work, IPQ-R, TSK, EARS and quality of rehabilitation.

EARS, Exercise Adherence Rating Scale; IPQ-R, revised Illness Perceptions Questionnaire; KOOS, Knee injury and Osteoarthritis Outcome Score; PROMs, patient-reported outcome measures; TSK, Tampa Scale for Kinesiophobia.

decision. The surgery technique, graft type and repair of concomitant lesions will be recorded.

### Rehabilitation

All patients will complete a rehabilitation programme with their own physiotherapist, similar to the patients in the conservative treatment arm (see table 1). Rehabilitation starts the first days after surgery. Furthermore, also pre-operative rehabilitation sessions will be prescribed by the surgeon.

### Outcomes

#### Primary feasibility outcomes

The primary objective is to determine the recruitment rate 4 months after both study sites are initiated. More specifically we will count the number of eligible patients who agree to participate in the trial and compare this to:

1. The expected recruitment rate:

Based on the KANON trial, we expect that 50% of the patients with an acute ACL injury will agree to participate in the trial. Thus the expected recruitment rate is calculated by taking 50% of the average number of patients with ACL who visited one of both participating centres in the respective month during the last 3 years.

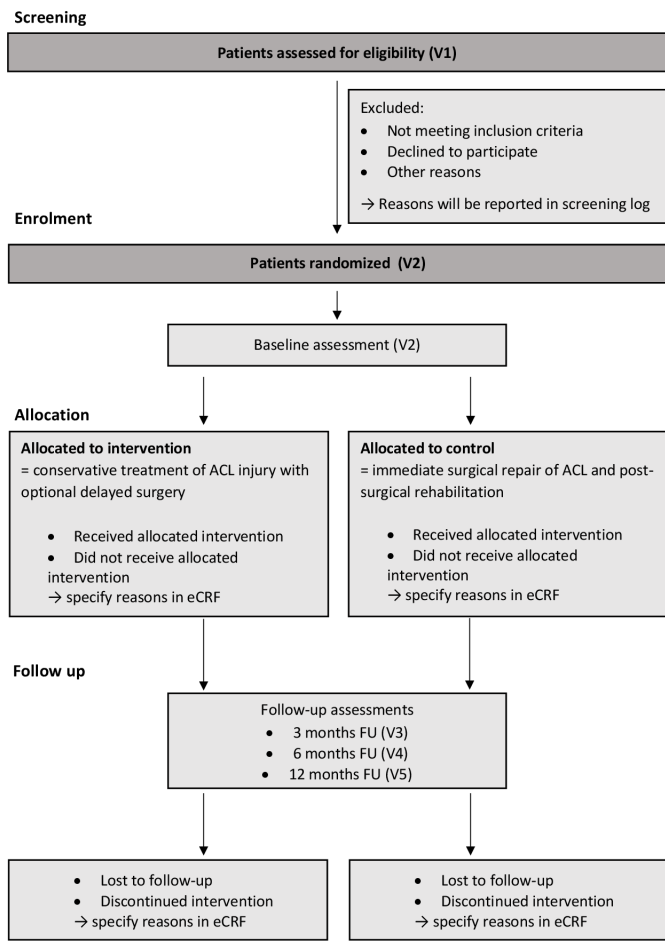
2. The total number of patients with an acute ACL injury who visits one of both participating centres during the recruitment phase of this pilot trial.

Furthermore, the main reasons (1) for being not eligible and (2) for refusing to participate will be listed (see figure 1).

#### Progression criteria

The results of the primary analyses will be used to decide on progression to a future definitive RCT:

- ▶ Green: indicates that the recruitment rate is >75% of what we expected. In this case, the future definitive RCT will be performed without any changes from the pilot trial (except changes in the primary and secondary endpoints, additional follow-up sessions at 24 and 36 months, that include the same questionnaires and functional tests as the follow-up session at 6 and 12 months of the pilot trial).
- ▶ Amber: indicates that the recruitment rate is 50%–75% of what we expected. In this case, changes to the protocol will be made to improve recruitment (eg, optimise screening, broaden inclusion criteria, optimise information for the patient). These changes will be based on the qualitative data (eg, reasons why patients refused to participate, were not eligible).
- ▶ Red: indicates that the recruitment is lower than 50% of what we expected. In this case, the future full RCT will not be performed.



**Figure 1** Trial flow chart. ACL, anterior cruciate ligament; eCRF, electronic case report form; FU, follow-up; V1, visit 1.

### Secondary feasibility outcomes

The secondary objective of this pilot study is to evaluate<sup>1</sup> adherence to the allocated treatment arm and<sup>2</sup> adherence to the protocol. This will be evaluated 8 months after both study sites are initiated by calculating:

1. The proportion of patients who discontinued the intervention or crossed over to the other treatment. Furthermore, the main reasons for cross-over will be listed.
2. The proportion of patients who did not fulfil an assessment. For every functional test and questionnaire, we will calculate the percentage of patients who completed this assessment. Furthermore, we will explore why certain assessments are not fulfilled if necessary.

These findings will be used to explore whether additional strategies need to be taken to optimise adherence.

### Outcomes for the full RCT

If recruitment turns out to be feasible, the patients participating in this pilot trial will be asked to continue with the full trial that will have a longer follow-up period (up to 36 months after baseline). To allow for use of the data, the variables that are considered necessary to evaluate the research questions of a future full RCT will be collected during this pilot study. However, as these variables are

outside the scope of the pilot study, these variables are only described in brief below. A detailed explanation of all assessments and questionnaires is provided in additional file 3.

Additionally, [table 2](#) gives an overview of which variables are assessed at the different study visits.

Variables collected for the full RCT:

- ▶ *Patients' reported symptoms and knee function*: assessed with the Knee injury and Osteoarthritis Outcome Score.
- ▶ *Return-to-work and return-to-sport*: administered with customised questionnaires.
- ▶ *Adverse events (AEs)*: registration of surgical complications, arthrofibrosis, infection any additional acute injury to the ipsilateral or contralateral knee (such as reinjury, graft rupture or contralateral ACL injury, lesions of menisci, cartilage or other ligament).
- ▶ *Strength of the thigh muscles*: isokinetic strength of the quadriceps and hamstrings muscles will be measured bilateral.
- ▶ *Functional knee performance*: measured with the Single Leg Hop for Distance task.<sup>29</sup>
- ▶ *Structural knee joint damage on MRI*: assessed with the Anterior Cruciate Ligament OsteoArthritis Score<sup>30</sup> at baseline and 3 months postrandomisation.
- ▶ *Psychological factors*: patients' expectations and perceptions will be administered with the revised Illness Perceptions Questionnaire<sup>31–33</sup> and fear of reinjury<sup>21 22</sup> will be assessed with Tampa Scale for Kinesiophobia (TSK-11).<sup>34</sup>
- ▶ *Quality and adherence of rehabilitation*: evaluated with the EARS and a customised questionnaire that contains questions about the exercises that the participants performed, the intensity, duration and frequency of their rehabilitation.

### Timeline

An overview of all assessments that will be performed at the different study visits can be found in [table 2](#). Three follow-up visits are planned at 3, 6 and 12 months after randomization (see [figure 1](#)).

### Sample size

As this is a pilot study to assess the feasibility to recruit patients, no formal power calculation is needed.

### Randomization

Once a patient signed the informed consent, he/she will be randomised into one of both treatment arms by one of the investigators. For this, the investigator will use the randomisation tool of REDCap (data management software package). On beforehand, a randomisation list will be prepared and incorporated in REDCap by the Sponsor's designated staff, not involved in the trial. This ensures that the randomisation sequence is concealed for all investigators, once the patient is entered in REDCap. Random sequence generation (computer-generated, using variable block randomisation) will be

used. Stratification by centre will be applied. When all the patients have finished the trial and the database is locked, the randomisation code will be broken to analyse response data. At each participating site, the responsible study member will have access to the randomization tool in REDCap.

A 1:1 allocation ratio will be used: 50% of the patients will be allocated to the immediate surgery treatment arm and 50% to the conservative treatment arm.

The maximum time period between injury and immediate surgery is 12 weeks. Therefore, screening and randomisation have to be performed within the first 12 weeks post-injury.

### Blinding

Given the nature of interventions, blinding of participants and care providers is not feasible. However, measures will be taken to ensure that the same uniform information (eg, the existence of clinical equipoise) is given in all centres.

Data collectors and data analysts will be blinded to the extent possible. Outcomes will be collected in the same way in both groups, for example, by electronic questionnaires for which assessors and collectors can be blinded. However, because of the subjective and self-reported nature of the assessed outcomes, detection bias may be a potential risk of bias.

### Statistical analyses

The feasibility and adherence outcomes will be reported descriptively and narratively.

All other outcomes (such as the patient-reported outcome measures, functional tests and MRI) will not yet be analysed in this pilot trial as it is underpowered to perform analyses on these outcomes. However, as we progress to the full study (that will have enough power), the data of the participants of the pilot trial will be transferred if the participant agrees.

### Data monitoring

The trial will be monitored by trial monitors (independent from trial staff) to ensure that the trial is being conducted in compliance with Good Clinical Practice and current legislation, verify that written informed consent has been obtained correctly, verify that the trial procedures have been followed as shown in this protocol and that the data have been recorded for which the source data will be compared with the data recorded in the electronic case report form. More details about the monitoring strategy for this trial are described in the trial-specific monitoring plan.

### Access to data

The investigator will permit trial-related monitoring, audits, ethics committee review and regulatory inspection, providing direct access to all related source data/documents.

At the end of the trial, the funder (KCE) will have access to the study data. This will only be the pseudonymised study data.

### Safety recording and reporting

The risk of AEs occurring as a consequence of the intervention in this trial is unlikely. Therefore, safety reporting will be limited to the safety reporting necessary for routine care. The participant will be asked to report any AE related to the study-specific intervention to the study team. The following AEs will be registered at every follow-up visit: surgical complications, arthrofibrosis, infection, any additional acute injury to the ipsilateral or contralateral knee (such as reinjury, graft-rupture or contralateral ACL injury, lesions of menisci, cartilage or ligament and so on).

These reported events will be documented by the investigator in the source documents. The following minimum information should be recorded for each adverse reaction by the reporting investigator (AE description, start and stop date of the AE, severity, seriousness, causality assessment to the study interventions, outcome). The sponsor will keep detailed records of all AEs reported to him by the investigators and will perform an evaluation with respect to seriousness, causality and expectedness.

### Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the trial steering committee, added to the trial registration on clinical trials.gov and approved by the Ethics Committees prior to implementation.

## DISCUSSION

More large-scale RCTs are needed to compare the clinical effectiveness between immediate ACL reconstruction and conservative treatment (consisting of rehabilitation and optional delayed surgery) for acute ACL injuries. Additionally, these RCTs should assess whether patient-specific factors could predict which patients benefit from conservative treatment and which patients benefit from immediate ACL reconstruction.

However, conducting an adequately powered RCT is expensive and time-invasive. Therefore, substantial work should be done prior to the trial to know that it is feasible. This is especially important in trials comparing surgical and non-surgical interventions as in such trials randomisation can be challenging.<sup>5</sup> Treatment preferences and the common belief that timely surgery is a prerequisite for restoring knee function, for returning to sports and for preventing cartilage degeneration<sup>5</sup> which might affect recruitment and adherence to the protocol. Therefore,

we will perform a pilot study to investigate the feasibility of recruiting participants and to investigate participants' adherence to the treatment arm they were allocated to. Strict criteria were imposed to decide on progression to a full adequately powered trial. If the recruitment rate is at least 75% of what we expect (eg, half of the patients with ACL will agree to participate in this RCT), we will proceed to a definitive RCT without any changes. In contrast, in case the recruitment rate is lower than 50% of what we expected, it seems not appropriate to proceed to a definitive RCT. Finally, if the recruitment rate is between 50% and 75% of what we expect, changes to the protocol will be made to improve the recruitment (eg, optimise screening, broaden inclusion criteria, optimise information for patient). These changes will be based on the qualitative data that will be collected (eg, reasons why patients refused to participate, were not eligible).

In conclusion, the results of this pilot study will in the first place provide the necessary information to decide whether it is feasible to recruit patients for an RCT comparing surgical and conservative treatment for acute ACL injuries. Furthermore, this pilot study might provide insights on how to optimise recruitment and protocol adherence for such RCT.

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