

Y HOSPITALS LEUVEN



UZ
LEUVEN



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1. IODA pilot trial

1.1. Background

Rupture of the anterior cruciate ligament (ACL) is a common injury, especially in young, physically active individuals, with an indicate rate of 0.7/1000 person-years in Belgium. The ACL has an important role in both static and dynamic stabilisation of the knee joint with a primary role limiting anterior translation of the tibia relative to the femur. In more than 70% of the injuries, the rupture occurs during a non-contact mechanism, such as a sudden change of direction or landing with the knee near full extension. Frequently, not only the ACL is ruptured but typically also injuries to the menisci, cartilage, collateral ligaments and subchondral bone are present. 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. Furthermore, ACL injuries are associated with increased risk of post traumatic knee osteoarthritis (PTOA) (1) and athletes who return to sport have a high risk to sustain a re-injury (2).

In Belgium, standard care for ACL injuries is reconstructive surgery(3). **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 (4) and to avoid long term disadvantages** such as persistent knee instability, re-injury (2) and post-traumatic knee osteoarthritis (1,5). **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 (6) and up to 23% suffer a new ACL injury (ipsilateral or contralateral) within two years after return to sport (7). Furthermore, Ardern et al. (8) 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 from long-term disadvantages.

In 2016, Monk et al. (9) 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 randomized controlled trial (RCT) (KANON trial) available at that time (10). The KANON trial found no differences in patient-reported, structural or functional outcomes at 2 and 5 years follow-up (10,11). Since this publication of the systematic review of Monk et al. in 2016 (9), two more RCTs have been initiated (a Dutch trial: COMPARE trial, NTR2746 and an English trial: ACL SNNAP study, NCT02980367) (12)). The COMPARE trial (13) found, at two 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 to 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 (12). The results of this trial seem less relevant for Belgian care as the SNNAP trial investigated chronic ACL ruptures (no acute ACL ruptures).

Based on the results of the KANON trial (10) and the COMPARE trial (14), one can conclude that conservative management with optional delayed surgery does not result in inferior clinical outcomes compared to immediate ACL reconstruction, on population level. However, on patient-level, large between-subject differences were found. Both trials reported that about 50% of the ACL patients in the conservative group showed persistent knee instability requiring a delayed surgery (10,13). Because surgery is delayed in this group of patients, time to return-to-sport is prolonged and longer sick leave times are observed compared to patients with immediate surgery (15). 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 hypothesized that treatment success depends on clinical factors (such as MRI findings) but also on quality of rehabilitation (16) and psychological factors such as expectations (17), fear for re-injury (18,19), and locus of control (20). 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 ACL patients for such RCT. This is necessary, as **many patients have a preference for a particular treatment** (4). 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 (5). 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 (4). **These individual preferences might affect recruitment (which involves randomization) and adherence to the protocol.** Therefore, a pilot study has been 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.

1.2. Trial objectives

The main objective of this pilot trial was to demonstrate feasibility with regard to 1) recruitment and 2) protocol adherence. The results of this pilot trial serve to decide on the progression towards a future definitive RCT that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical ACL reconstruction.

1.2.1. Primary objective

The primary objective of this pilot trial is to demonstrate the feasibility of recruiting patients that agree to be randomized. The specific trial objectives are as follows:

- To assess how many eligible patients **accept** participating in the RCT that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical reconstruction of an acute ACL injury.
- To explore why eligible patients are not willing to participate in an RCT that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical reconstruction of an acute ACL injury.
- To assess the percentage of all ACL patients in two Belgian hospitals **eligible** to participate in an RCT that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical reconstruction of an acute ACL injury.
- To determine whether certain inclusion or exclusion criteria were too open or too restrictive.

1.2.2. Secondary objective

The secondary objective of this pilot trial is 1) to explore the adherence of patients to the treatment arm they were allocated to and 2) to assess protocol feasibility. The secondary objectives of the trial are as follows:

- To investigate the number of patients that received the allocated treatment
- To investigate the number of patients that cross over between groups (e.g., number of patients that received the other treatment then allocated)
- To explore why patients crossover 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 that completed these assessments.

1.3. Summary of the protocol

Trial design

A parallel, multicentric, pragmatic, pilot randomised controlled trial comparing immediate ACL reconstructive surgery (control group) with optional delayed surgery (intervention group).

Recruitment

We recruited ACL patients from 2 participating centres:

- UZ Leuven
- University Hospital of Liège

Interventions

- 1) Rehabilitation and optional delayed ACL reconstruction
- 2) Immediate ACL reconstruction

Both interventions are routine treatments. We did not change anything to the current practice, to keep the trial pragmatic. All patients completed rehabilitation with their own physiotherapist and the type of surgery was not predetermined by the study, this was the choice of the orthopaedic surgeon.

Follow-up

Three follow-up visits are planned at 3, 6 and 12 months after randomization. An overview of all assessments that will be performed at the different study visits can be found in Table 1.

Outcomes

- 1) Primary outcome: recruitment rate
- 2) Secondary outcome: adherence to the allocated treatment arm and protocol feasibility

Trial registration number

This trial is registered on ClinicalTrials.gov (NCT04408690) on 29 May 2020.

Publication

The full protocol was published in BMJ open – Sports and exercise medicine (Open access):

Smeets A, Ghafelzadeh Ahwaz F, Bogaerts S, 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:e055349.

<http://dx.doi.org/10.1136/bmjopen-2021-055349>

Procedures/ Assessment	Screening	Randomisation + baseline assessment	Intervention	Follow-Up Visits		
Visits	V1	V2		V3	V4	V5
Timing (months)	<12 weeks after injury	Baseline <12 weeks after injury		3 months after baseline $\pm$ 14 days	6 months after baseline $\pm$ 14 days	12 months after baseline $\pm$ 14 days
Enrolment						
Eligibility screen	X					
Informed consent	X					
Randomisation		X				
Intervention						
1. Rehabilitation + optional delayed surgery			(X) ¹	(X) ¹	(X) ¹	(X) ¹
2. Immediate surgery			X ²			
Assessments*						
Demographics		X				
Physical knee investigation		X		X	X	X
MRI	(patient record)			X		
PROMS [#]		X		X	X	X
Functional tests				X	X	X
Adverse events				X	X	X
Return to work/sport				X	X	X

Table 1. Overview of trial procedures

1.4. Results

1.4.1. Primary objective: recruitment feasibility

The primary objective of this pilot study was to assess recruitment feasibility. The flowchart below (Figure 1) summarizes the total number of ACL patients that were screened in both hospitals, the number of eligible patients and the number of patients that were recruited.

In total, 29 patients (25 in UZ Leuven - 4 in CHU Liège) accepted to participate in the IODA pilot study and signed the ICF. To calculate the recruitment rate, we obtained the total number of ACL surgeries from the medical registration office of both hospitals (Table 9 and Table 10 in appendix A). Based on this information we made a rough estimation of the percentage of recruited patients per month for both hospitals (Figure 2 and Figure 3), and this starting from the first month after the site initiation visit (UZ Leuven: SIV 25th august 2020, CHU Liège: 13th September 2021).

In UZ Leuven, we obtained an average recruitment rate of 32%. However, in CHU Liège, the recruitment period was shorter because the SIV was delayed (first because of COVID, later due to the absence of the PI during the summer of 2021). The average recruitment rate was lower compared to UZ Leuven, with an average recruitment rate of 17% (January-February-March 2022).

We want to emphasize that this recruitment percentage is a rough estimation. This number is based on all ACL *reconstructions* performed in the hospital, which is not a reflection of the number of eligible patients:

- On the one hand, some patients chose themselves for conservative treatment (and are thus not included in this number of ACL reconstructions (there is no specific registration code for conservative ACL treatment, so the medical registration office could not provide the number of conservative treatments).
- On the other hand, not all ACL patients are *eligible* for the study. For example some patients required immediate surgery because of additional joint damage that required surgery (fracture or meniscus injury that blocks the knee), some ACL injuries were no acute injuries etc.). As a result, the number of eligible patients is much smaller than the number represented in Figure 2 and Figure 3. More details about eligibility can be found in Figure 4.

Furthermore COVID had a serious impact on the study. There were 2 periods with major impact:

- November 2020 – May 2021 :
 - The government imposed hospitals to reduce non-essential surgeries (including ACL surgeries) to upscale their capacity for COVID patients.
 - Travelling was forbidden and thus there were (almost) no skiing accidents.
 - Team sports were not allowed. This reduced the number of ACL injuries (as can be seen on Figure 2) as they mainly occur during cutting- and landing sports.
- October 2021 – november 2021 :
 - The government asked again to reduce non-essential surgeries to upscale the capacity for COVID patients.
 - In UZ Leuven, the orthopedic surgeons could still perform ACL surgeries but the availability of the surgery ward was reduced. Consequently, the ACL surgeries could not be scheduled in advance (only a few days before the surgery). This made it very difficult to recruit patients for the study as we had to be sure that a timely surgery could be scheduled for every patient randomized to the immediate surgery arm.
 - In CHU Liège, there were no patients recruited during this period. The investigators told us that recruitment was very challenging because of the same uncertainty of scheduling ACL surgeries.

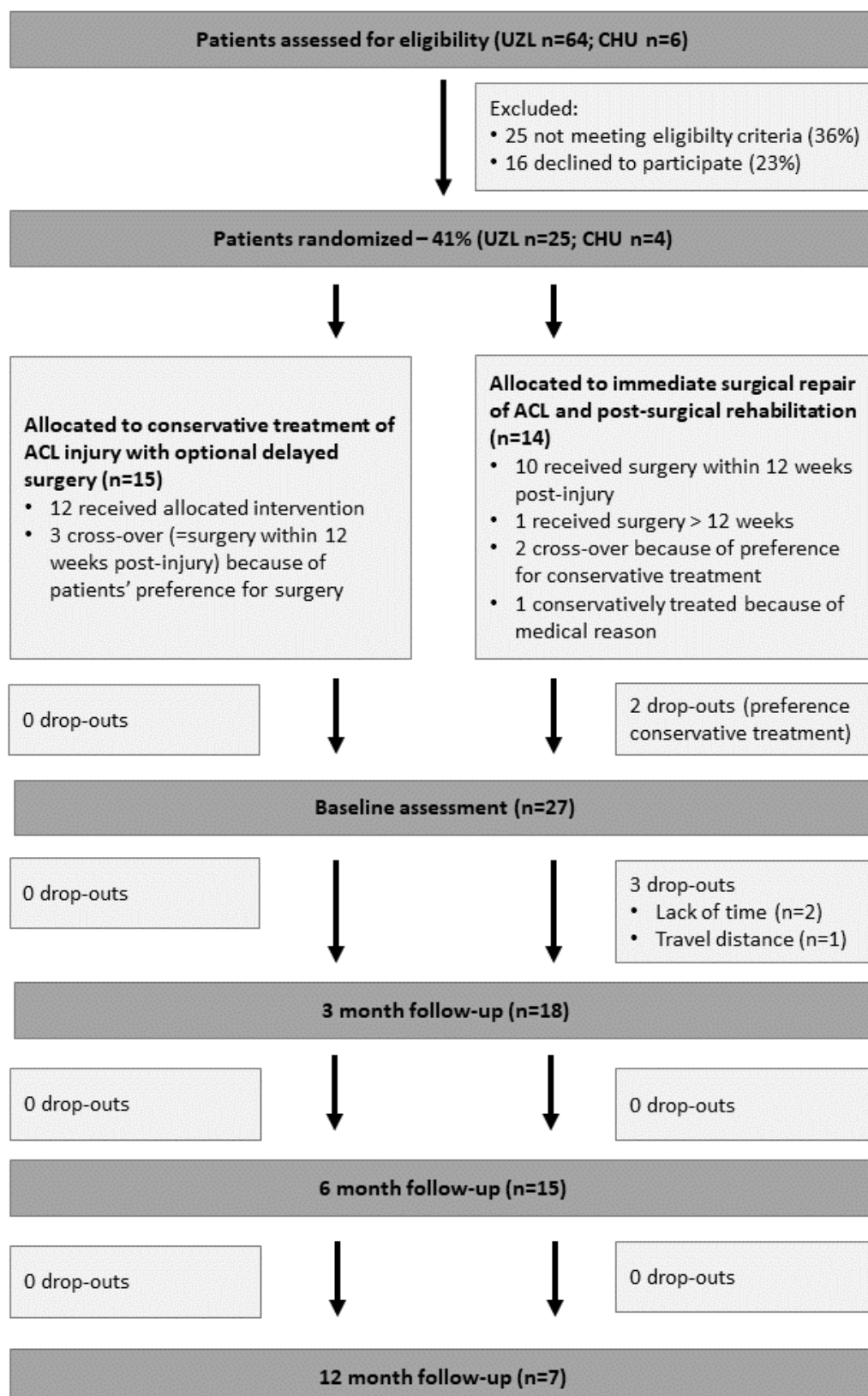


Figure 1. Trial flowchart

Recruitment - UZ Leuven

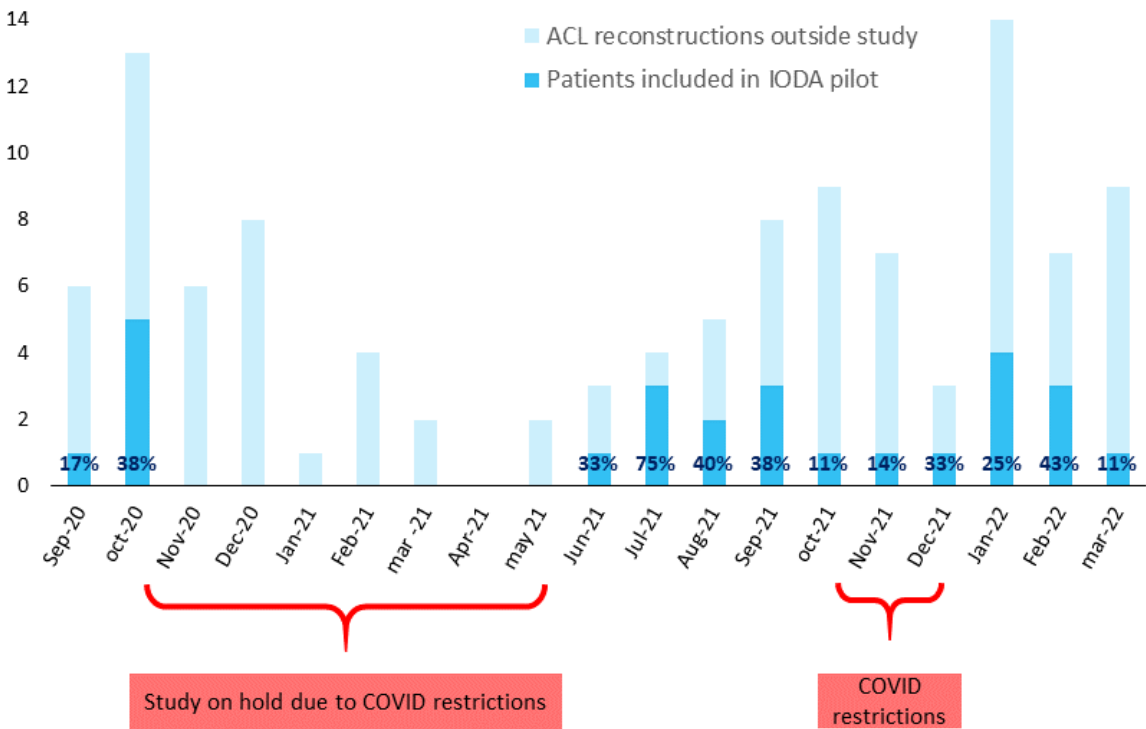


Figure 2. Recruitment in UZ Leuven

Recruitment – CHU Liège

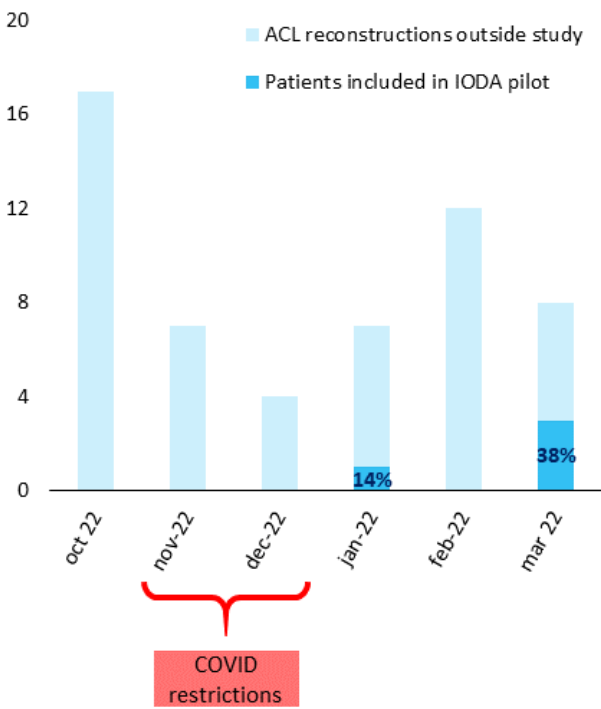


Figure 3. Recruitment in CHU Liège

B) Eligibility

A prescreening log was kept with the reasons why screened patients were 1) not eligible and 2) why eligible patients were not willing to participate.

This prescreening log is an anonymous list that was filled in based on the information provided by the physicians who performed the screening. Although we tried to fill in this document as good as possible, we noticed that some information got lost since the total number of ACL patients of UZ Leuven (n=74 for sept-oct 2020 + June-March 2022, see Figure 2) was higher than the number of patients documented on the prescreening log (n=64). In addition, in some cases, the physicians forgot to inform when a patient was not included in the trial.

CHU Liège only recorded 6 patients on the prescreening log, of which 2 were not included in the study. One patient was not eligible (MRI did not confirm ACL rupture) and 1 patient was not willing to participate because of the long travel distance to the hospital. The low number of patients on the prescreening log of CHU is due to the fact that the surgeon withdrew his participation. He treated many ACL patients but outside the study.

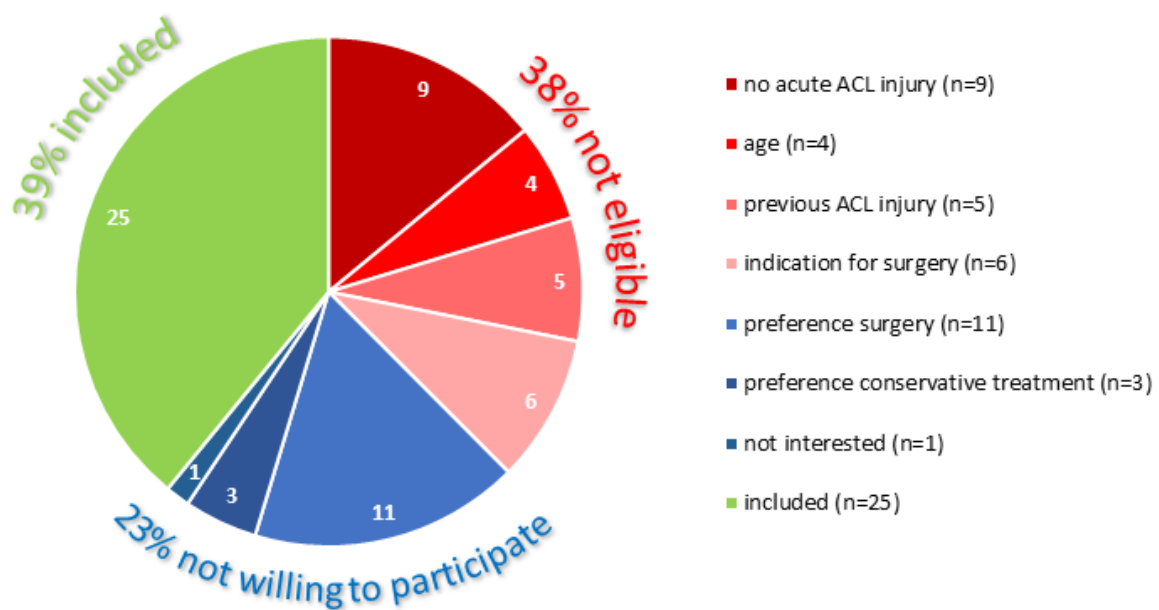


Figure 4. Overview of prescreening data UZ Leuven

Based on the prescreening log 24 patients out of 64 screened patients (39%) were not eligible to participate in our trial. The main reasons were:

- Age (n=4)
- A non-acute ACL injury (n=9) (> 4 weeks post-injury)
- Previous ACL injury or knee surgery to index knee (n=5)
- Indication for acute surgery because of related knee injuries (n=6)

Age

During the first month of the trial, we noticed that two patients could not be included because they were younger than 18 years (this was the minimum age in the first version of the inclusion criteria). After a meeting with the study team, this criterion was changed to 'a minimum age of 16 years old'. Literature states namely that 16-year-old children are already skeletally mature. There is thus no rationale for a difference in treatment approach at this age. An amendment was submitted for this change. So far, no child (<18 years) has participated after changing this inclusion criterion.

Time post-injury

This trial focuses on acute ACL injuries. This was defined as an ACL injury for which medical advice was sought within 4 weeks after the injury. Furthermore the injury should not be older than 10 weeks at the time of first contact with one of the investigators. This ensures that if the patient was randomized to immediate surgery, a timely surgery could be scheduled (within 12 weeks post-injury).

The prescreening log revealed that 9 patients could not be included because there was too much time between injury and first contact.

Major trauma to the knee

In 6 cases there was a clear indication for surgery, mainly because of associated fractures and meniscal damage that required surgery.

Previous ACL injury or knee surgery

A few patients (5 in UZ Leuven) could not participate because they already had an ACL injury in the past or were already operated on the index knee previously.

C) Willingness to participate

Based on the information of the pre-screening log, we could conclude that 15 patients out of 39 eligible patients were not willing to participate because of the following reasons:

- Preference for surgery (n=11)
- Preference for conservative treatment (n=3)
- Not interested (n=1)

D) Description of recruited sample

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

	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
Time to randomization	24,28 ± 10,59 days post-injury

Table 2. Patient demographics of total sample

A non-parametric between-group comparison was performed to assess whether the two randomization groups differed from each other in terms of baseline characteristics (Table 3). For continuous variables, a Mann Whitney-U test was performed, for categorical variables, a Chi-square test. The between-group comparisons showed that the conservative treatment group had more male patients and a significantly higher weight compared to the immediate surgery group. Furthermore, there was more time between injury and randomization in the conservative group compared to the immediate surgery group.

We can thus conclude that both groups have important demographic differences at baseline. However, we expect that if we continue recruitment, these differences will disappear.

	Statistical outcome			
	Immediate surgery (median, Q1, Q3)	Conservative treatment (median, Q1, Q3)	Mann-withney U	Chi square
Number	14	15		
Gender	5 female /9 male	1 female/14 male		0,07
Age (years)	23 (18,5 - 30)	31 (22 - 34)	0,17	
Height (cm)	177 (168 - 179,5)	178 (176 - 183)	0,17	
Weight (kg)	69 (61 - 74)	82 (72 - 87)	<0.01	
Education				
- secondary school	5	4		
- bachelor degree	6	8		
- master degree	3	3		0,62
Time to randomization (days)	17 (14 - 30,5)	26 (18 -32)	0,07	
Time to surgery (days)	58 (44,5 - 66,5)	NA		

Table 3. Comparison of baseline characteristics between both treatment groups

1.4.2. Secondary objective : adherence and protocol feasibility

The secondary objective of this pilot trial was 1) to explore the adherence of patients to the treatment-arm that they were allocated to and 2) to assess protocol feasibility.

A) Adherence to allocated treatment arm

The trial flowchart (Figure 1) and Table 4 provide an overview of the patients who crossed-over between treatment arms.

Immediate surgery

In total 10 out of 14 patients randomized to immediate surgery received an ACL reconstruction within the prescribed 12 weeks. Four patients did not undergo immediate surgery. Two patients decided themselves to opt for conservative treatment and also decided to stop their participation in the study. One patient wanted to postpone his surgery because he had a very busy period and preferred to undergo surgery at a later time. For one patient the surgeon decided not to operate because of a medical reason that did not allow immediate surgery. This patient agreed to continue study participation and is thus still followed.

Conservative treatment

In total 12 out of 15 patients randomized to conservative treatment effectively received conservative treatment (= no ACL reconstruction within 12 weeks post-injury). Three patients underwent an ACL reconstruction within 12 weeks post-injury. These 3 patients had a strong preference for surgery and decided to undergo immediate surgery despite being randomized to conservative treatment. These 3 patients agreed to continue participation and are thus still followed by the study.

Delayed surgery

Until May 2022, no patient underwent a delayed ACL reconstruction. However, follow-up is not yet finished thus, this number can still change.

In UZ Leuven, one patient randomized to conservative treatment got the medical advice to undergo delayed surgery as he had several incidences of instability that resulted in significant swelling and pain in the knee and a setback in the rehabilitation period. However, the patient was not willing to undergo surgery yet.

Patient	Randomiz- ation arm	Received immediate surgery?	Remained conservative?	Drop out (+timing)	Reason cross-over	Reason drop-out
Leuven1	Surgery	Yes				
Leuven2	Conservative		Yes			
Leuven3	Conservative		Yes			
Leuven4	Conservative		Yes			
Leuven5	Surgery	Yes				
Leuven6	Surgery	Yes				
Leuven7	Conservative		Yes			
Leuven8	Surgery	No		after baseline	postponed surgery due to job	lack of time
Leuven9	Surgery	Yes				
Leuven10	Conservative		Yes			
Leuven11	Surgery	Yes				
Leuven12	Conservative		No		preference surgery	
Leuven13	Surgery	No		after randomiz.	preference conservative	preference conservative
Leuven14	Conservative		Yes			
Leuven15	Surgery	Yes		after baseline		lack of time
Leuven16	Conservative		Yes			
Leuven17	Conservative		Yes			
Leuven18	Surgery	Yes		after baseline		travel distance
Leuven19	Surgery	Yes				
Leuven20	Surgery	No		after randomiz.	preference conservative	preference conservative
Leuven21	Conservative		Yes			
Leuven22	Conservative		Yes			
Leuven23	Surgery	Yes				
Leuven24	Conservative		Yes			
Leuven25	Conservative		No		preference surgery	
Liège1	Surgery	Yes				
Liège2	Conservative		Yes			
Liège3	Conservative		No		preference surgery	
Liège4	Surgery	No			medical reason	
	Cross-over	4 patients	3 patients			
	Drop-out	5 patients	0 patients			

Table 4. Detailed overview of cross-overs and drop-outs

B) Drop-out

In total 5 of 29 patients dropped out the study:

- 2 patients dropped out after randomization because they had a preference for conservative treatment but were randomized to the immediate surgery group
- 2 patients dropped out after the baseline visit because of a lack of time
- 1 patient dropped out after the baseline visit because the travel distance to the hospital was too long.

C) Protocol feasibility

The protocol includes mainly questionnaires but also a strength test (isokinetic strength) and a knee function test. The percentage of completeness of these assessments was very high, indicating that the protocol is feasible. The questionnaires (administered electronically via RedCap) had a completion rate of 100%. Sometimes one or more reminders were sent to the patients, but by doing this timely we achieved this high rate.

The strength test was performed in all subjects, except for 1 patient (first follow-up visit). The reason for this was a mistake in the administration.

1.4.3. Patient experience

A) Patient experience of study participation

We performed an intermediate assessment when the first 6 patients completed the 6 month follow-up visit. This assessment investigated how patients experienced their study participation. We used the SPFQ questionnaire (Study Participant Feedback Questionnaire) of transcelerate (<https://www.transceleratebiopharmainc.com/assets/patientexperience/study-participant-feedback-questionnaire/>). We used Microsoft Forms to administer this questionnaire digitally and anonymously. The results of this intermediary assessment can be found in the figures below.

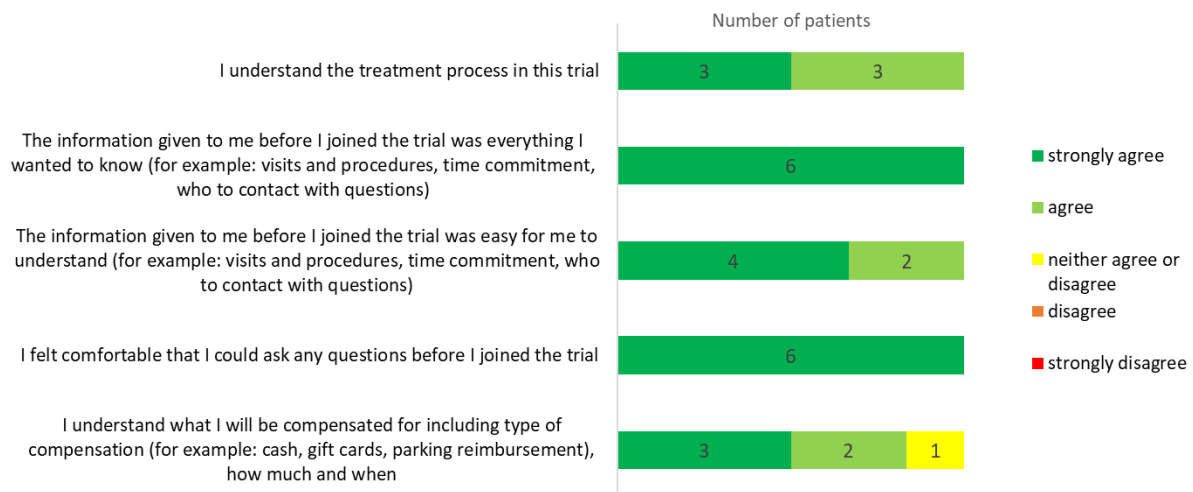
Based on these results we conclude:

- Patients have a very good experience with study enrollment. They reported that the information was clear and, they felt comfortable asking questions. However, not all patients were aware of the compensation that they receive after completing the study.
- Patients have a good experience with study participation. They feel comfortable and have the experience that they are treated with respect. In general, patients are happy with the organization of the trial visits. However some report that the timing was not convenient for them. (Comment: all study visits took place on Tuesdays because there is a multidisciplinary consultation at that time. Both the surgeon and physical medicine and rehabilitation specialist

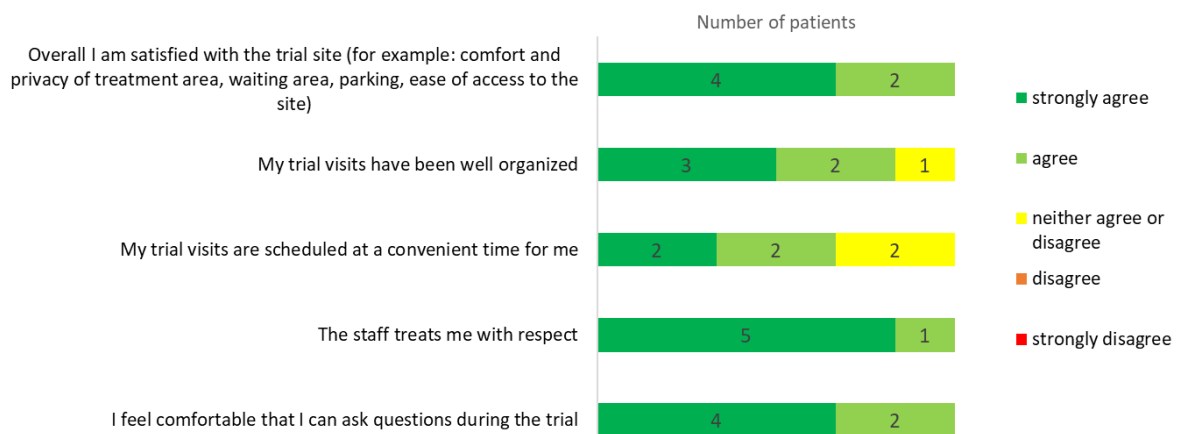
are present). To address this we tried to be as flexible as possible. Patients that could not come on Tuesdays received other options within our availabilities. This to prevent drop-out as much as possible.

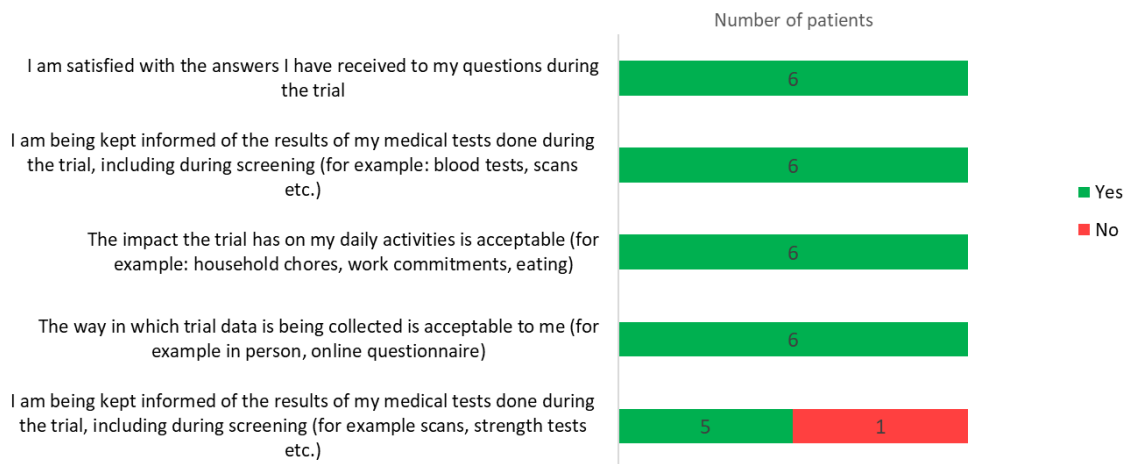
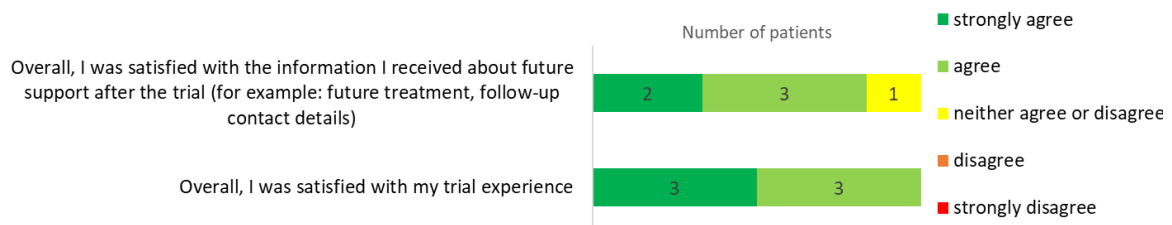
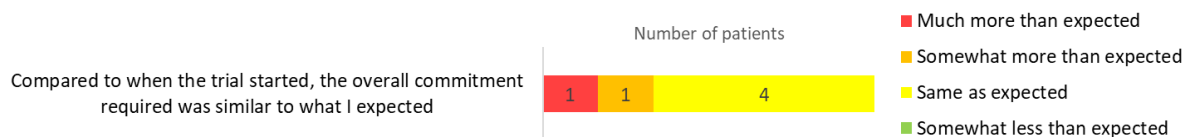
- Patients report that they are satisfied with the communication (answers to questions, communication of results of medical tests, etc.)
- Overall, patients report that they were satisfied with study participation. Most patients report that study commitment was similar to what they expected. However, two patients reported that it took more commitment than expected.

Study enrollment



Participation (part 1)



Participation (part 2)**End of trial (part 1)****End of trial (part 2)****B) Experience of investigators****Recruitment @UZ Leuven**

In Leuven, we were able to recruit patients through three pathways:

- Patients who presented at the Emergency department
- patients who were scheduled for a consultation with the orthopaedic surgeon (Dr. Berger)
- patients who presented themselves at the department of Physical Medicine and Rehabilitation (Prof. Dr. Peers or Prof Dr. Bogaerts)

Not to miss a single patient, we contacted the Emergency department every Friday for the first eight weeks. All patients that were eligible for the study were scheduled at the multi-disciplinary consultation. This is a bi-weekly consultation with Dr. Berger (orthopedic surgeon), Prof. Dr. Peers, and/or Prof. Dr. Bogaerts (both physical & rehabilitation medicine specialists) and Feryal Ghafelzadeh (PhD-Student - physiotherapist) all present on that day. This made the recruitment flow relatively easy.

Since patients presented themselves through three different departments, we initially experienced a lack of consistent explanation of the study to all eligible patients. We tackled this obstacle during our

IODA-team meetings. We agreed on two ways of explaining the study. First, the short explanation: mentioning the ongoing IODA trial without full study protocol information and scheduling the patient at the bi-weekly multi-disciplinary consultation (these were mainly the patients who came from the emergency department). Second, the detailed explanation mostly happened at the multi-disciplinary consultation by Prof. Dr. Peers or Prof. Dr. Bogaerts and Mrs. Ghafelzadeh. In this manner, a detailed explanation was only given to the patients who were interested and eligible for the study. We introduced the study by explaining to potential patients that there are 'three treatment options' for their ACL injury: 1) undergoing immediate surgery, 2) conservative management or 3) taking part in the trial which means that randomisation decides which treatment the patient will receive. We spent much time explaining clinical equipoise on ACL treatment, based on the results of the KANON en COMPARE trial. We explained that, at the moment, it is not possible to predict which treatment will be best for them based on existing literature and that we are therefore performing this trial. The advantage of participating is that they have a very close follow-up and that being randomized to the conservative treatment arm does not mean that they can not undergo ACL surgery at all: we clearly explained that a delayed surgery can be discussed in case of persistent instability.

Another obstacle we experienced is that UZ Leuven is a University hospital which means that there is a lot of rotation between medical trainees. Therefore, not all trainees were aware of the IODA trial initially. Therefore, we decided to keep the trainees up to date by sending out an email every three to six months to all new trainees starting their traineeship at the hospital - Department of Orthopaedics. In this email, Dr. Berger mentioned the most important study information and the video we made about the IODA trial. Furthermore, we made pocket-size reminder notes with a short explanation of the study and contact details.

Follow-up @UZ Leuven

To keep the trial pragmatic, we interfered as little as possible with current practice. Therefore, patients completed rehabilitation with a physiotherapist of their own choice and the study did not predetermine the type of ACL surgery. However, to ensure a minimum quality of the rehabilitation that the ACL patients received, we provided evidence-based guidelines and progression criteria for ACL rehabilitation to the physiotherapists. Furthermore, we followed all patients very close by asking the physiotherapists for a two-weekly update. We did this both by mail and by phone. We noticed that this approach resulted in high commitment of both patient and physiotherapist.

During the follow-up study visits, we experienced some difficulties scheduling the MRI test, which is required in our protocol at three months. The first two patients were scheduled via the 'regular MRI' open spots, which was not always easy to combine with the isokinetic biodex test and consultation. By contacting the Radiology department and asking for permission to use the study-specific MRI, we

created fixed MRI slots for the study patients on Tuesdays combined with the isokinetic biodex test, which we also perform at three, 6 and 12 months follow-up. As a result, we could schedule all the necessary tests at one fixed moment (Tuesday mornings). This made it more convenient for the patient.

Experience of investigators @CHU Liège

A survey was sent to the investigators of CHU Liège to evaluate their experience of participating in the trial. The complete report is attached as Appendix B.

In summary:

- The collaboration with the orthopaedic department and emergency department was difficult to establish. The surgeon withdraw participation before recruitment start.
- Very few patients present themselves at the department of Physical Medicine & Rehabilitation
- Most patients directly go to the department of Orthopedics and were thus not screened for study participation
- The team had difficulties with scheduling timely MRIs for the patients because of limited availability of the MRI scanner.

1.4.4. Lessons learned

A) Strong collaboration between orthopedics and physical medicine & rehabilitation is necessary

In UZ Leuven, there was an existing collaboration between the department of physical medicine & rehabilitation and the department of orthopedics before the study (every two weeks, we have a multidisciplinary consultation for knee and other sports injuries). There is surveillance of a knee surgeon and a physician specialized in physical medicine & rehabilitation during these consultations. We experienced that conducting this study together only improved this existing collaboration and resulted in a very strong team. The communication was open and the involved physicians of both disciplines were easy to approach. But, of course, we had to invest in this collaboration. For example, for the first few months, our Ph.D. student called the 'orthopedic on call' every Friday to ensure that patients seen during the weekend received an appointment for the multidisciplinary consultation.

After a while, the study was very well known in the hospital, which made recruitment much easier. In addition, during the study, we tried to emphasize and value the involvement of the orthopedic department as much as possible and gave regular update meetings.

In CHU Liège, there was no existing collaboration between the department of physical medicine & rehabilitation and the department of orthopedic surgery before the study. Also, during the study, they did not succeed in building collaboration to recruit patients. At the start of the study, the surgeon of CHU Liège agreed to participate in this trial: he was present at the first investigator meeting, signed

the protocol, and did not mention any doubts. However, a few months later, he withdrew his intention to collaborate. His motivation for withdrawal was that his patients are referred by other physicians (such as general practitioners) to undergo surgery specifically. Furthermore, he sees most ACL patients at an average time of 8 weeks post-injury. Therefore, it is very difficult to schedule a timely surgery (within 12 weeks) if a patient is randomized to immediate surgery.

The withdrawal of the surgeon had a major influence on the recruitment rate in CHU, as almost all ACL patients are seen by the surgeon and not by the department of physical medicine and rehabilitation. This was confirmed by the pre-screening log of CHU Liège that only contains 6 screened patients.

Together with the study team in Liège, we sought solutions for the withdrawal of the surgeon. Plan B was to collaborate with the emergency department. The emergency department agreed that the study coordinator of Liège could call the emergency ward two times a week to get the information on patients who injured their knee and had a potential ACL injury. Subsequently, the study coordinator could contact the patient and make an appointment at the physical medicine & rehabilitation department. This collaboration started in December 2021 and has led to 3 inclusions.

We believe that this plan B could be further optimized if potential patients were directly referred by the emergency department for a consultation at the physical medicine & rehabilitation department, as we did in UZ Leuven. We experienced that it was easier to convince patients in real-life than by phone. Furthermore, patients might go to another hospital/physician if you do not immediately give them a follow-up appointment. We explained our thoughts to the study team in Liège, but they did not manage to get this done from the emergency department.

Lessons learned: the orthopedic department needs to be involved in the trial. Only a good collaboration between the department of physical medicine & rehabilitation and the department of orthopedic surgery makes recruitment feasible.

When we approached the new hospitals for participating in the full trial, we did ensure that both disciplines agreed to participate. Furthermore, we asked if they have an existing collaboration and/or are willing to collaborate.

Besides a good interdisciplinary collaboration, we noticed that team work was necessary to ensure continuity of the trial when someone of the team was absent. We made very clear standard-operating-procedures and assigned substitutes for all investigator roles. For example in UZ Leuven: prof. K. Peers and prof. S. Bogaerts could replace each other and A. Smeets could replace F. Ghafelzadeh when she was absent.

In CHU Liège this was not well arranged. The weeks that prof. J-F. Kaux was absent, there was less attention for the study.

Lessons learned: when initiation a new site, we need to ask the centres to provide a plan who clearly describes who is substitute when someone of the team is absent.

B) Organising a fluent recruitment takes time

We noticed a slow recruitment start in both hospitals. After the SIV, it took 24 days in UZ Leuven to include the first patient and 42 days to include the second patient. In CHU Liège this was even more: 113 days for the first patient and 179 days for the second patient. The slow start in CHU Liège, may be partially attributed to COVID restrictions in November and December 2021.

Based on our own experience, we believe that the major reasons for the slow start were:

- *Practical aspects*

At the start of the study, we experienced that it was difficult to schedule a timely MRI (= required for diagnosing ACL rupture and one of the inclusion criteria). However, we could solve this in UZ Leuven by asking the radiology department to reserve some MRI slots for our study.

In CHU Liège, the study team could not arrange such MRI reservations for the study. Consequently many patients were not diagnosed within the imposed time (e.g. an immediate surgery had to be scheduled within 12 weeks post-injury).

Lessons learned: during the screening of potential centres for the full trial, we already asked the investigators how long the waiting period for MRIs are in their hospital. Furthermore, we asked if they could reserve MRI slots for the study.

- *Recognition of the study*

At the start, the trial was not yet known by colleagues, physicians, surgeons, patients, sports coaches etc. This implied that 1) there were no referrals of patients and 2) that patients got the study information when they were already been biased by information of other physicians, physiotherapists, internet or their surroundings.

To address this:

- We gave several presentations for the physicians and interns of the departments of orthopedic surgery, physical medicine & rehabilitation and the emergency ward. We stressed that the information that they provide to patients is very crucial. It is important to explain the clinical equipoise and explain that there are different treatment options after an ACL rupture as many patients still believe that surgery is the only treatment.
- We made a short movie of the study that was shared on social media (<https://twitter.com/SMACLeuven/status/1409910044997689361>) and spread by the investigators to their personal network of sports clubs, sports physicians and general practitioners.

Lessons learned: it is very important that patients are not biased towards any treatment by (wrong) information of colleagues. We will stress this when training the new centres for the full trial.

C) Still many patients undergo surgery

Figure 2 and Figure 3 show that many patients still undergo an ACL reconstruction. The existing evidence (KANON trial and COMPARE trial) has thus not convinced Belgian physicians, caregivers, and patients to change their treatment approach. The numbers in Table 9 and Table 10 show that every year about 200 surgeries are performed in the two participating hospitals together. Based on the results of the KANON and COMPARE trial, up to 50% of these patients might undergo unnecessary surgery with potential extra iatrogenic damage.

Our patient perspectives show that many patients want to go for the *perceived* immediate certainty of a surgery. Patients, but also many surgeons do not want to risk a potential prolonged rehabilitation time associated with a delayed surgery if they opt for conservative treatment.

In addition, the COMPARE trial showed that patients who had a delayed surgery are doing worse concerning patient-reported symptoms and quality of life compared to those who undergo immediate surgery (and those who remain conservative).

These two negative consequences of a delayed surgery further strengthen the need for a predictive study that assesses if we can identify, at an early stage, which patients benefit from immediate surgery. We strongly believe that such criteria are needed to convince physicians and patients to change their treatment approach.

D) Providing patients clear information and education is key for recruitment

We noticed that investing time in providing good patient education, was fruitful for recruitment. Often patients were not aware that conservative treatment is an option for their ACL tear. Therefore we took plenty of time (+/- 30 min) to clearly explain the different treatment options after ACL rupture as noted explained in 1.4.4. The physician clearly explained clinical equipoise and the rationale for the IODA study. Subsequently the patient received enough time to consider all options. We also provided a patient brochure with (scientific) background, key misconceptions and more information on the study. This to ensure that patients make a well-considered decision on their participation.

We noticed that despite our effort, it occurred that patients crossed over between treatment arms. In most cases, these patients had strong beliefs that the other treatment was better. This belief was in 2 cases influenced by a second opinion (patients went to another hospital where the surgeon said that surgery was necessary).

Lessons learned: investing time in patient education is very important. A clear explanation of all options and their (dis)advantages is the key for successful recruitment.

1.5. Quality control and data management

Data monitoring

Regular monitoring visits were scheduled : a site initiation visit at the start of the study, three monitoring visits in UZ Leuven, and two monitoring visits in CHU Liège.

A monitor of UZ Leuven Clinical Trial Center (CTC) performed these visits. In general, we received positive evaluations: « the center is well organized and committed to conducting the study. PI and study team work well together ».

After the first monitoring visit one of the inclusion criteria was further specified as it was not well defined (one of the patients had a wound on his knee, such skin 'injury' was for us no good reason to exclude so we changed it to 'serious knee injury').

Data management

We worked together with UZ Leuven CTC for data management :

- CTC developed our electronic CRF in REDCap
- CTC wrote the data management plan
- CTC performed data cleaning on the eCRF at the end of recruitment (April 2022). They sent out queries to us, and we had a meeting to discuss this. Based on this discussion, we identified some instruments and fields that can be improved if we go to a full trial.

2. Why is a full trial necessary ?

This second chapter motivates why performing a full trial seems still necessary. In summary:

- Current evidence on ACL treatment is limited (only 2 RCTs), and has limitations
- The existing evidence did not influence current practice in Belgium
 - The number of ACL surgeries is not reduced
 - Immediate ACL surgery is still the standard treatment option in Belgium and often provided as the only treatment option after an ACL injury

To elaborate on our motivation, we will first provide a summary of the existing evidence.

2.1. Current evidence is limited and has limitations

Until now high quality RCTs comparing immediate surgery versus conservative management are scarce. In total 2 RCTs compared both treatment strategies in acute ACL ruptures (KANON trial and COMPARE trial). Furthermore there is another RCT that investigate the clinical effectiveness of both treatment strategies in non-acute ACL injuries (SNNAP trial, UK). Therefore the KANON trial and COMPARE trial better reflect the Belgian Care model in ACL injuries and are further discussed below (Table 5).

	KANON trial	COMPARE trial
Location	Sweden	Netherlands
Participants	Acute ACL rupture Age : 18-35y At least recreationally active in sports	Acute ACL rupture Age : 18-65y No eligibility criteria on activity level
Follow-up	3-6-9-12-24 months + 5y follow-up	3-6-9-12-24 months
Randomization	62 patients : early surgery (<10 weeks post-injury) 59 patients : rehabilitation + optional delayed surgery	85 patients : early surgery (<6 weeks post-randomization) 82 patients : rehabilitation + optional delayed surgery (>3m)
Main outcome	KOOS4	IKDC score
Main result	No sign difference in KOOS4 change scores over the 2y follow-up	Early surgery group had sign. better IKDC compared to conservative group at 9-12-24months, this difference was not clinically relevant
Secondary findings	• 39% of the patients in conservative group had delayed surgery • No sign differences in secondary outcomes at 2y-follow up	• 50% of the patients in conservative group had delayed surgery • 7 reinjuries in early surgery group vs. 3 in conservative group
Main publication	10.1056/NEJMoa0907797	https://doi.org/10.1136/bmj.n375

Table 5. Summary of the KANON trial and COMPARE trial.

2.1.1. Clinical effectiveness on short term outcomes

(=first 2 years after injury)

Both the KANON trial and the COMPARE trial concluded that the two treatment strategies were equally effective in terms of patient reported symptoms, knee function and activity level at 1 and 2-year follow-up (10,13).

In the COMPARE trial a slightly larger improvement in perception of symptoms, knee function and ability to participate in sports after two years in the immediate surgery group compared to the conservative group. At 12 months post-injury, the immediate surgery group had an IKDC score of 5.3 points larger than the conservative group. The authors concluded that this difference was not clinically relevant as this is smaller than the minimum clinical important difference (11.5-20). Furthermore, the authors admit that their study might be underpowered. At the time they performed their sample size calculation, the psychometric properties of the IKDC were not yet available. Therefore, they used a difference score of 7 points (effect size of 0.5) for their sample size calculation. But later, minimal clinical important difference seemed to be much higher, namely 11.5 (22).

On a group-level, immediate surgery and conservative treatment result in the same clinical outcomes, 2 year after ACL rupture.

2.1.2. Clinical effectiveness on long term outcomes

Several ancillary analyses have been performed on the data of the KANON trial to compare long term knee health between immediate ACL reconstruction and conservative management with optional delayed reconstruction. Most of these analyses are performed on the 5 year follow-up data. Such long-term analyses are not yet available on the more recent COMPARE trial.

These ancillary analyses are of major interest for the entire society as it is known that patient who had an ACL injury in the past are more prone for early cartilage degeneration and the development of knee osteoarthritis at an early age. The meta-analysis of Cinque et al. (6) showed for example that 20% of the patients who had an ACL reconstruction has developed post-traumatic knee OA (PTOA) 10 years after their ACL injury, and that 50% of the patients has PTOA 20 years post ACL injury. This implies that about half of the ACL patients suffer from the debilitation disease of knee OA already at an age between 40-50 years old, where they are thus still relatively young and active. Literature often states this problem as 'young patients with old knees'. It is thus of major importance to also know the effect of both ACL treatments on long-term knee health.

First of all, Frobell et al. (11) found no evidence that early surgical treatment was superior to optional delayed surgery with respect to meniscus surgeries or incident radiographic OA over 5-years follow-up. In addition, no differences were observed in the KANON trial regarding frequencies of incident

cartilage damage, bone marrow lesions and osteophyte formation scored from MRI between those treated with early or delayed ACLR or those treated with rehab alone (21).

Two recent studies investigated the effect of ACL treatment on cartilage thickness in the KANON trial. Culvenor et al. (22) concluded that participants randomised to early ACLR had significantly greater loss of patellar cartilage thickness compared with participants randomised to rehabilitation with optional delayed ACLR over the first 2 years as well as over 5 years. The second study (23) investigated cartilage thickness on tibiofemoral contact surfaces in the same population and found no differences between both treatment options. However, they reported greater cartilage thinning (represents disease activity) in all patients that underwent ACLR (early or delayed) compared to those treated with rehabilitation only. This finding supports the hypothesis that surgical ACLR represents a second trauma to the already injured knee resulting in additional inflammation and perturbation of the cartilage matrix (24).

Besides long-term knee health, also long-term knee-related self-efficacy was assessed in the KANON population. At 6 year follow-up no difference in knee-related self-efficacy were found between patients treated with early ACLR, delayed ACLR or exercise therapy alone (25).

Based on the ancillary analyses on the data of the KANON trial, it seems unlikely that immediate surgery is beneficial for cartilage health or integrity. These results raise concerns whether performing an early ACLR in all patients is an optimal strategy in the context of long-term joint health and the prevention of knee osteoarthritis.

2.1.3. Cost effectiveness

Avoiding ACL surgery and returning faster to work could save medical costs. However, on the other hand undergoing delayed ACLR might be more expensive because of the prolonged rehabilitation and absence from work. Economic analyses were performed to assess this.

Mather et al. performed a first cost-effectiveness analysis comparing both treatment options of the KANON trial. For their analyses they did not solely use the KANON data, but also added data from the MOON registry (prospective cohort of > 800 primary ACLRs from the Multicenter Orthopaedic Outcomes Network in Sweden). The authors concluded that early ACLR was less costly than rehabilitation plus optional delayed ACLR. This study received criticism because the analyses relied heavily on expert opinions on the future risk of developing osteoarthritis rather than the actual 5-year radiographic osteoarthritis outcome (26). They assumed an advantage of ACL reconstruction over non-surgical management with regard to the risk of osteoarthritis development. However, this has never been confirmed and the opposite might be even true (see previous paragraphs).

Therefore, Kiadaliri (26) performed another health-economic analysis, this time solely on the actual data of the KANON trial. They found no statistically significant difference in economic value between early ACL reconstruction compared with a strategy of rehabilitation with the option of delayed ACL reconstruction. In addition, their as-treated analysis showed that subjects treated with rehabilitation alone consumed fewer resources (13 650 euros) than the early ACL reconstruction group. This highlights the need to identify those who benefit from rehabilitation alone at an early stage. Such early identification would spare patients from surgery that may provide no or marginal additional benefit and consequently prevent overtreatment.

Recently, Eggerding et al. (27) performed a first economic analysis on the 2-year follow-up data of the COMPARE trial. They calculated the cost-effectiveness as incremental costs per quality-adjusted life year (QALY) gained. Patients treated with an early ACL reconstruction experienced a slightly higher QoL (1.73 vs 1.69) over the 2-year follow-up period. On the other hand, early ACL reconstruction was associated with higher costs (both medical and non- medical). From the healthcare perspective it takes 48 460 € and from a societal perspective 78 179 €, to gain a QALY when performing early surgery compared with rehabilitation plus an optional reconstruction. The authors concluded that early surgery is therefore unlikely to be cost-effective (Given the low burden of disease, the maximum willingness to pay would be up to 20 000 €/QALY in the Netherlands, according to the advice of the Dutch Healthcare Institute). Furthermore the authors found that patients treated with a delayed ACL reconstruction have the lowest QALY and highest healthcare and societal costs. This further highlights that early identification of patients that perform well with rehabilitation from those who do not, is necessary to decrease costs as this reduces the number of patients who have two rehabilitation programmes; one before the reconstruction and one after.

Results from this and previous reports of the KANON-trial imply that early identification of individuals who would benefit from either early ACL reconstruction or rehabilitation alone might reduce resource consumption and decrease risk of unnecessary overtreatment.

2.1.4. Prediction

Early identification of patients that fail with conservative treatment seems necessary. This will have the following positive effects:

- Improvement of clinical outcomes: gain of quality of life and knee function due to avoidance of 2 rehabilitation periods in the delayed ACLR group, faster return and no additional iatrogenic trauma due to surgery part of the patients who stay non-operatively treated.
- Generation of evidence necessary to convince physicians to change current practice. Nowadays, many surgeons want to 'play safe', and therefore perform surgery in all patients to avoid that patients need a delayed surgery and have a setback.
- Reduction of costs: providing patients their optimal treatment as soon as possible is the most cost-effective approach

Early patient identification is a hot topic in musculoskeletal medicine research. A very recent editorial of Moathse et al. in BJSM (28) highlights the urgent need for patient identification guidelines in ACL treatment. They stress again that patients who fail non-operative treatment and undergo consequential ACLR have the lowest quality of life and highest costs.

To develop such patient identification guidelines, one should use prognostic risk modelling (29). Such models can aid clinicians in making treatment decisions based on their clinical profile. So, far such evidence does not yet exist. In the IODA trial we will try to predict delayed ACL reconstruction. We will use multivariable logistic regression models for this. Our ultimate aim is to provide outcome probabilities for different combinations of predictors. This will enable care providers to estimate the risk that a patient will fail non-operative treatment. Based on this information a well concerned, evidence-based decision can be made, together with the patient. This in contrast with current practice where clinicians still use their gut-feel, clinical experience and patient beliefs.

The research group of the COMPARE trial performed a first explorative analysis to investigate why, when and which patients randomized to conservative treatment in the COMPARE trial required reconstructive surgery(30). They used between-group comparisons to determine differences between the non-operative and delayed ACL reconstruction group. They found that patients who required reconstructive surgery had a younger age and higher preinjury activity level compared with patients who did not undergo reconstruction. Their statistical approach (between-group comparisons) is limited to describing both groups, but does not allow to identify predictors for who will fail conservative treatment. For this, prognostic modelling is needed on a larger data set and more clinical variables.

Besides this explorative study that describes a few characteristics of those who fail conservative treatment, a new Dutch study was initiated: the ROTATE trial. The protocol of this trial was published

very recently (31). The main aim of the ROTATE study is to evaluate the effectiveness and cost-effectiveness of a treatment algorithm for patients with a complete primary ACL rupture compared to current practice in the Netherlands. The treatment algorithm was developed based on existing evidence and verified by an expert group consisting of orthopaedic surgeons and researchers specialized in traumatic knee injuries. The algorithm generates an advice if a single patient has a high probability that they a) will not respond to an exercise program under supervision of a physical therapist, and are therefore indicated for early surgical reconstruction or b) will respond to an exercise program. Although we strongly believe that developing such treatment algorithm is the way to change current practice on treatment decisions in acute ACL ruptures, we believe that developing a well-funded treatment algorithm is definitely not yet possible because of the lack of prognostic studies. A treatment algorithm that is based on group-comparisons (no prognostic studies) and expert opinions seems not appropriate. In our opinion prognostic modeling need to precede the development and validation of a treatment algorithm.

2.2. Limitations of the KANON trial and COMPARE trial

The KANON trial and the COMPARE trial both come with some limitations that we will address in the IODA study.

- **Relatively small samples**

The KANON trial included 121 patients, the COMPARE trial included 167 patients. The sample size of the IODA trial (280 with an assumed drop-out rate of 10%) will be much larger than the existing RCTs. As stated earlier in 2.1.1 the authors of the COMPARE trial admit that their study might be underpowered. At the time they performed their sample size calculation, the psychometric properties of the IKDC were not yet available. Therefore, they used a difference score of 7 points (effect size of 0.5) for their sample size calculation. But later, minimal clinical important difference seemed to be much higher, namely 11.5 (32).

Our sample size was powered on the existing psychometric properties of the KOOS QOL: minimal detectable change of 7 points (33), a smallest important difference of 13.5 change-points (34) and a standard deviation of 18 (35). This resulted in a much larger sample size.

- **Lack of inclusion of young and active patients**

As you will read in 2.4, in Belgium, it is believed that young and active patients need surgery to safely return to their sport. Therefore, we strongly believe that only an RCT that also includes such young and active patients will change current practice.

In the COMPARE trial the average age of the participants was 31.3 ± 10.5 years, in the IODA trial we had a much younger population (27.3 ± 8.3 years). The patients in the KANON trial had similar age (26.9 ± 5.2 years) as our sample.

In addition, the patients in the IODA trial were very active and mainly performed ‘high-risk’ sports such as soccer and other team sports that involve cutting, pivoting or landing activities (Table 6).

In the COMPARE trial the patients were less involved in these high activity levels. The investigators of the COMPARE trial used the Tegner activity score, a standardized method to grade work and sporting activities (range from 0-10) (36). They did not provide a detailed list of which sports were performed pre-injury. The COMPARE trial reports that 37% of the participants had a Tegner score of 9 or higher, in the IODA pilot 66% of the patients had a score of 9 or higher. In the KANON trial 67% of the patients had a pre-injury Tegner score of 8 or higher.

Competitive level	Recreational level	No regular sport participation
17 soccer	3 soccer	1
2 ultimate frisbee	1 cycling	
2 volleyball		
1 handball		
2 basketball		

Table 6. Overview of sports involved in IODA pilot trial

- **ACL rehabilitation has improved since recruitment of existing RCTs**

Recruitment for the KANON trial took place between 2002-2006, and for the COMPARE trial, recruitment was performed from 2011 to 2016. The data of these 2 RCTs and mainly the data of the KANON trial is thus ‘rather old’, especially if you consider the rapid evolution that takes place in the field of ACL rehabilitation. The field moved, for example, from a time-based rehabilitation approach toward a criteria-based approach. With very important clinical publications in 2016 (37) and 2017 (38). The rehabilitation provided in the other trials will thus probably differ from what is offered to our participants (definitely in the KANON trial).

One might expect that with the optimization of ACL rehabilitation programs, the success of conservative treatment might improve.

Furthermore, in the IODA pilot, we performed quality control of the rehabilitation that patients received (in both treatment arms). We provided criteria-based rehabilitation guidelines to every

physiotherapist and regularly contacted them via mail or phone. Furthermore, we provided a short report after every follow-up visit.

Maybe, our high care for qualitative rehabilitation, partially explains why no delayed surgeries are yet recorded in the IODA pilot trial (one patient was advised to have surgery but refused it), while in the KANON trial, about 1/3 of patients received a delayed ACL reconstruction within 2 years, and in the COMPARE trial, about 50% of the patients. Of course, the patients of the IODA trial are not yet followed for 2 years, so the number of delayed surgeries will increase. Then again, based on the COMPARE trial, one would expect most delayed ACL surgeries within 10 months post-randomization (almost half of our patients already passed this time point).

2.3. Patients' voice

We sent a survey to 3 patients who participated in the IODA pilot trial, and to 3 patients who refused to participate to know why patients believe such RCT is relevant (or not).

Several times, we read that patients were not aware that conservative treatment is a potential treatment option. They appreciate that we clearly explained both treatment options, including all known advantages and disadvantages. Most patients report that the study is relevant as it can give important insights to their physician. One of the patients indicated that he fully trusts the expertise of his physician in determining which treatment is necessary.

Patients indicate that earlier return-to-sport motivates them to opt for conservative treatment. But on the other hand, some patients refused to participate because they did not want to risk needing to undergo a delayed surgery, which would elongate the rehabilitation period.

Patients who took part in the study, reported that the close follow-up was one of the most important reasons to participate in the trial. On the other hand, the patients who refused to participate in the trial, said they did not want to be randomized.

2.4. Current practice in Belgium is eminence-based

Today, the standard treatment of ACL injuries still consists of early surgery. We can conclude this based on several findings:

1) The high numbers of ACL reconstructions per year

Table 9 and Table 10 provide the number of ACL reconstructions performed in UZ Leuven and CHU Liège. On average, about 200 surgeries are performed a year in these two hospitals together. This number was almost consistent across the years.

In the last 2 years, there was a small decrease in this number, but we are convinced that this is due to COVID. As explained earlier, restrictions of non-essential surgeries and team sports participation had

a major influence on the number of ACL injuries and reconstructions. The number of ACL reconstructions seemed unchanged in the months when there were few COVID restrictions.

2) Our search for potential centres willing to participate in the full trial confirmed that many physicians (mainly surgeons) are hesitant towards conservative treatment. They put forward several arguments, none of them based on scientific evidence:

- Many surgeons believe that conservative treatment is only possible in a selected amount of patients (older patients and/or patients that are less active).
- They claim that patients are coming to them specifically for surgery. Often they are referred by a (sports) physician, general practitioner, physiotherapist, sports coach that told them a surgery is necessary.
- Furthermore surgeons are concerned that if they propose conservative treatment to a patient, that they 'lose' the patient. They are for example convinced that patients go for a second opinion to another surgeon, who might suggest surgery.

3) The majority of ACL patients only receive information about operative treatment when they contact a Flemish physician for their ACL injury.

In the context of a master thesis, we performed a retrospective survey investigating patient education and information after ACL rupture in Flanders (this thesis is not yet published). The survey was completed by 411 ACL patients and revealed that only 37.7% of the ACL patients who consulted a Flemish physician received information of both treatment options. Further analyses showed that those who received the full explanation were mainly the patients who performed sports at a lower level. When the content of the information was analysed, only 17 % received adequately correct information (for example information about return-to-sport, risk of re-injury and development of osteoarthritis). This suggests that in current practice, likely the vast majority (83%) of patients will not receive correct information on treatment options after ACL injury.

4) Patient information in brochures and on website of hospitals is inadequate and mostly eminence-based

Patient information on the websites of hospitals is often shameful. We read:

- that ACL surgery is listed as the only treatment
- that conservative treatment is only for older and/or inactive patients
- that ACL surgery prevents cartilage degeneration and meniscus lesions
- That ACL surgery is necessary to return to certain types of sports

We noticed several examples of inadequate educational material during the performance of our study. Even more, a quick search in the context of this feasibility report, confirmed that this was not

limited to a few cases. Appendix C provides print screens of what you can read on the websites of Belgian hospitals.

We can thus conclude that eminence-based practices still take place in Belgium. The strong opinions of Belgian physicians towards the necessity for surgery are based on non-scientific arguments, and critical appraisal of scientific evidence is scarcely provided to patients and also seldomly available in patients documents.

2.5 Potential impact of the IODA full trial

We believe that performing a Belgian RCT is necessary to change current eminence-based practice:

- The patient population of the IODA trial will be more representative of the ‘Belgian ACL patient.’ Physicians and patients cannot argue that the study is performed in another country with another health care system and context. Furthermore, we aim to recruit patients of all sports levels and ages to demonstrate whether or not the current beliefs are true (young and active patients need surgery – older inactive patients do not). In the IODA pilot trial we showed that we could recruit young and active patients.
- We believe that the active participation of Belgian surgeons in this multicentre trial, could also support changing current practice. First of all, the surgeons who participate in the trial will experience themselves if conservative treatment is a potential option (and in which patients). This exposure is expected to have a much higher impact on their practices compared with literature guidelines. Second, we believe that if we can already start by involving 5-10 surgeons, they can act as a role model and further share their findings with other surgeons. We noticed, for example, that during our conversations with new potential centres, the surgeons attached great importance to how dr. Berger (surgeon in UZ Leuven) experienced his participation.
- It could be that all our efforts are not enough to immediately change the strong beliefs of patients and physicians. In that case, we are convinced that the IODA trial could provide enough scientific evidence to government agencies. For example, if the IODA trial shows equal effectiveness of both treatment options, adaptations to remuneration could be implemented to avoid overtreatment of ACL patients.

3. Full trial

3.1. Summary of the protocol

Title

Comparison of Immediate versus Optional Delayed surgical repair for treatment of acute Anterior cruciate ligament injury through a parallel, multicentric, pragmatic randomised controlled trial - IODA trial

Trial design

A parallel, multicentric, pragmatic, pilot randomised controlled trial comparing immediate ACL reconstructive surgery (control group) with optional delayed surgery (intervention group). Figure 5 contains a flow chart of the study.

Interventions

Both interventions are routine treatments. We do not change anything to the current practice, to keep the trial pragmatic. All patients complete rehabilitation with their own physiotherapist and the type of surgery is not predetermined by the study, this is the choice of the orthopaedic surgeon.

1) Rehabilitation and optional delayed ACL reconstruction

The patient completes rehabilitation with his/her own physiotherapist. The rehabilitation consists of three phases and progression is based on goal-based criteria.

If a patient complains about persistent symptomatic instability of the knee or 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.

2) Immediate ACL reconstruction + rehabilitation

An ACL reconstruction is performed within 12 weeks after the ACL injury. The decision of graft type and surgery technique is a clinical decision made by the orthopaedic surgeons of the participating centres. All details of the surgery will be noted down in the patient register and can be retrieved if necessary.

The same goal-based rehabilitation protocol will be applied as in the intervention group.

Objectives

1) Primary objective

To compare the effectiveness of conservative treatment with optional delayed surgical reconstruction (intervention group) versus immediate surgical repair (control group) of an acute ACL injury (non-inferiority at 12 months, superiority at 6 months). Outcome parameters of interest are functional knee outcomes reported by the patients, the decrease in co-morbidities associated with the chosen therapy, and adverse events such as re-rupture rates. Additionally, socio-economic benefits will be investigated.

2) Secondary objectives

To identify individuals who would benefit the most from early reconstruction versus those who should rather be treated conservatively through predictive analyses.

Sample size calculation

We kept the sample size calculation of the earlier submitted dossier for the full trial as our pilot data was insufficient to run a new sample size calculation. The main reason is that only a few patients (6) completed the 12 months follow-up visits, thus, the data is limited.

1) Primary objective – clinical effectiveness

The outcome of the non-inferiority analysis is the change in the KOOS QOL between baseline and 1-year follow-up. The sample size was calculated using SAS 9.4 to show with 80% of power that conservative treatment is not inferior to standard treatment, where a non-inferiority margin of 7 (change-points) was adopted based on the study of Collins et al. who report a minimal detectable change in KOOS QOL of 7 points (Collins et al. 2011). Assuming a drop-out of 10%, a total number of 260 patients is required for randomization.

The outcome of the superiority analysis is the change in the KOOS QOL between baseline and 6 months follow-up. Considering equal group sizes, a two-sided 5% significance level, 80% power, the smallest important difference as 13.5 change-points (Roos et al. 2019), and a standard deviation of 18 for the change in KOOS QOL versus baseline (Roos et al. 1998), and a 10% drop-out rate, the calculation indicates a total sample size of 66 patients.

2) Secondary objective – prediction analysis

A prediction model will be built in the intervention group (rehabilitation and optional delayed ACL reconstruction) with the event of delayed surgery as a binary outcome and where an initial set of the five predictor variables described above will be considered. Following the rule of thumb of including

at least 10 events per parameter in the model, this analysis requires at least 50 events (i.e. delayed surgeries in the experimental group). Assuming that 1/3 of patients in the experimental group will need delayed surgery (KANON Trial), a minimum of 150 patients will be needed in the intervention group in order to develop such a prediction model.

Conclusion:

In total the study requires:

- 130 patients per treatment arm for the non-inferiority analysis
- 66 patients for the superiority analysis
- 150 patients in the conservative treatment arm for the prediction analysis

To fulfil these requirements we will recruit 280 patients in total, of which 130 patients will be randomized to immediate surgery and 150 patients randomized to conservative treatment.

Recruitment

This trial will run in multiple Belgian hospitals (university + regional hospitals). A detailed overview of hospitals that are interested to participate can be found in '3.2 selection of centres'.

Inclusion criteria:

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

Exclusion criteria:

- The patient had a previous ACL injury or knee surgery to the index knee (contralateral injury is allowed).
- There is a medical indication for acute surgery because of serious concomitant knee lesions (such as multi-ligament injuries, additional fractures, meniscal lesions that need repair)
- The patient suffers from any disorder, which in the investigator's opinion might jeopardize the participant's safety or compliance with the protocol.
- The patient is pregnant or plans to become pregnant in the first three months of the study. Since MRI assessment at the 3-month follow-up visit cannot be performed.

These eligibility criteria were slightly modified based on our experience of the pilot trial. We changed the age from 18 years to 16 years old, and better defined the first inclusion criterium.

Follow-up

Five follow-up visits are planned at 3, 6, 12, 24 and 36 months after randomization. An overview of all assessments that will be performed at the different study visits can be found in Table 7.

The following outcomes will be assessed during follow-up:

- *A physical investigation of the knee* is performed to assess knee joint effusion, range of motion and passive knee instability.
- *Patients' reported symptoms and knee function*: assessed with the Knee injury and Osteoarthritis Outcome Score (KOOS).
- *Return-to-work and return-to-sport*: administered with customized questionnaires.
- *Adverse events*: registration of surgical complications, arthrofibrosis, infection, any additional acute injury to the ipsilateral or contralateral knee (such as re-injury, 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 (SLHD) (39).
- *Structural knee joint damage on MRI*: assessed with the Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS) (40) at baseline and 3 months post-randomization.
- *Psychological factors*: patients' expectations and perceptions will be administered with the revised Illness Perceptions Questionnaire (IPQ-R) (41–43) and fear of re-injury (18,19) will be assessed with Tampa Scale for Kinesiophobia (TSK-11) (44).
- *Quality and adherence of rehabilitation*: evaluated with the Exercise Adherence Scoring System (EARS) and a customized questionnaire that contains questions about the exercises that the participants performed, the intensity, duration and frequency of their rehabilitation.
- *Quality-adjusted life years* : the EQ-5D-5L questionnaire will be administered to compute quality-adjusted life years for a potential economic analysis.

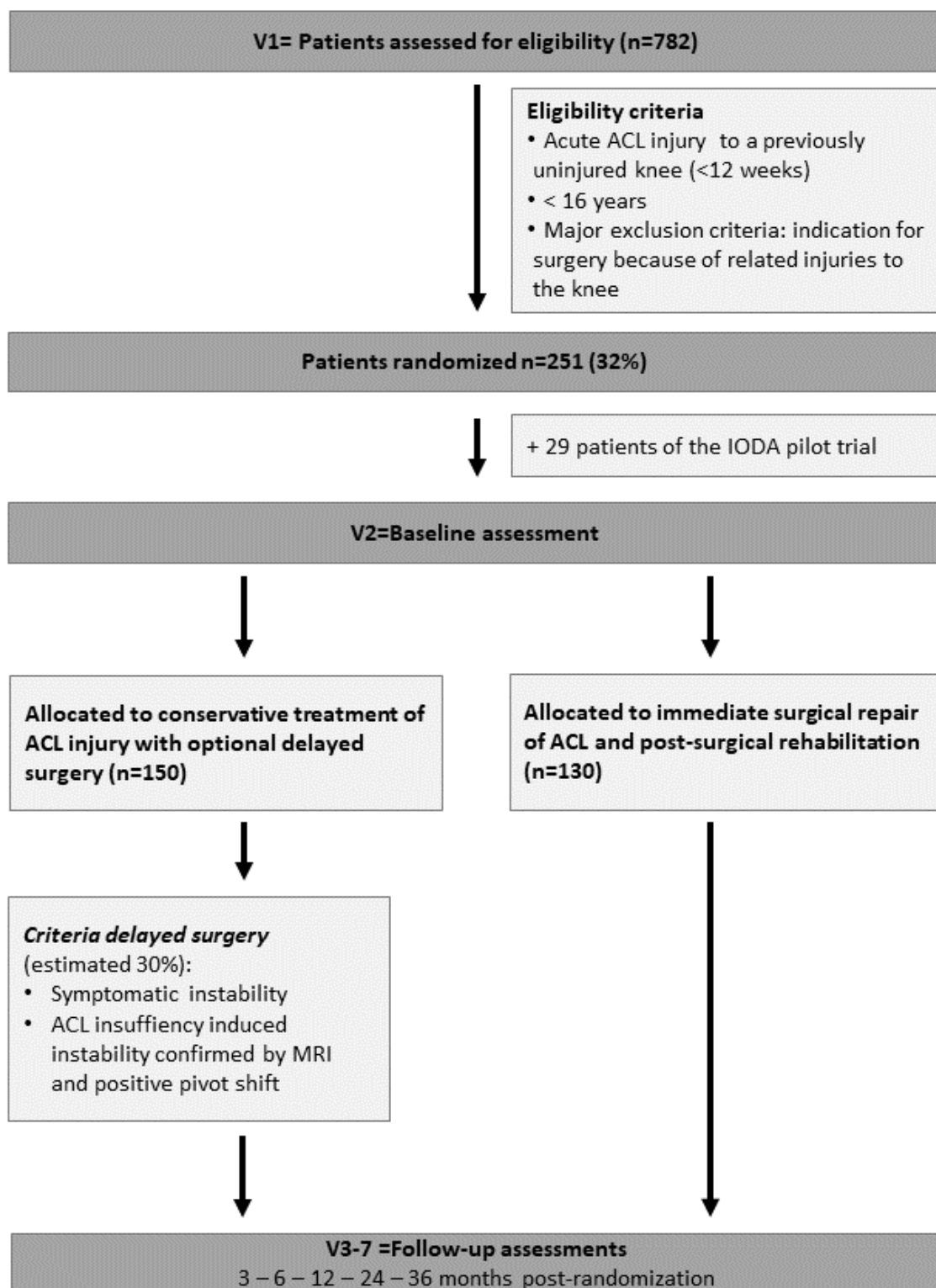


Figure 5. Flow chart of full trial

Procedures/ Assessment	Screening	Randomisation + baseline assessment	Intervention	Follow-Up Visits				
Visits	V1	V2		V3	V4	V5	V6	V7
Timing (months)	<12 weeks after injury	Baseline <12 weeks after injury		3 months ±14 days	6 months ±14 days	12 months ±14 days	24 months ±14 days	36 months ±14 days
Enrolment								
Eligibility screen	X							
Informed consent	X							
Randomisation		X						
Intervention								
1. Rehabilitation + optional delayed surgery			(X) ¹	(X) ¹	(X) ¹	(X) ¹	(X) ¹	(X) ¹
2. Immediate surgery			X ²					
Assessments*								
Demographics		X						
Physical knee investigation		X		X	X	X	X	X
MRI	X			X				
PROMS		X		X	X	X	X	X
Functional tests				X	X	X	X	X
Adverse events				X	X	X	X	X
Return to work/sport				X	X	X	X	X

Table 7 Trial procedures for a single patient

¹Optional delayed surgery can occur between randomization and V7; ²Immediate surgery has to be performed withing 12 weeks after injury

3.2. Selection of centres

We approached different hospitals to participate in the full trial. The hospitals in Table 8 expressed their sincere interest and motivation to participate. We listed all hospitals that showed potential interest. In Table 8 it is clearly indicated which hospitals already signed a formal letter of intent, and which hospitals showed interest but are still in consideration because of uncertainties of the full trial (e.g. practicalities, timing of the study , financial aspects etc), or because they still need more time to discuss participation with other departments, direction etc. We strongly believe that convincing these hospitals will be easier if the full trial is confirmed. In that case, we can provide the hospitals a formal contract with more concrete information on the time line, support, fees etc.

Untill now, prof. Koen Peers and prof. Jean-François Kaux contacted their professional network to find interested hospitals. We intend to contact more hospitals (also outside the network of prof. Peers and Kaux) once the full trial is confirmed and/or if additional hospitals are required to reach the targeted sample size. For example, we would like to contact UZ Brussel and UCL (Saint-Luc hospital).

Hospital	Principal Investigator	Expected recruitment rate
Signed letter of intent		
UZ Leuven	Prof. Koen Peers (Dept. of Physical Medicine and Rehabilitation) and Dr. Pieter Berger (Dept. of Orthopaedics)	+/- 80 ACL reconstructions a year Expected recruitment 32% (based on pilot) = 26 patients a year
University Hospital of Liège	Prof. Jean-Francois Kaux (Dept. of Physical Medicine and Rehabilitation)	+/- 120 ACL reconstructions a year Expected recruitment 17% (based on pilot) = 20 patients a year
Clinique Saint-Luc Bouge	Dr. Jérémy Daxhelet (Dept. of Orthopaedics) and Dr. Francis Marchant (Sports Medicine)	+/- 50 ACL reconstructions a year Expected recruitment 32% = 16 patients a year
Heilig Hart Lier	Dr. Michaël Schreurs (Dept. of Physical Medicine and Rehabilitation) and Dr. Frank Verheyden (Dept. of Orthopaedics)	+/- 100 ACL reconstructions a year Expected recruitment 32% = 30 patients a year
Jessa Ziekenhuis Hasselt	Dr. Pieter-Jan Loos (Dept. of Physical Medicine and Rehabilitation) and Dr. Cedric Vanderstappen (Dept. of Orthopaedics)	+/- 70 ACL reconstructions a year Expected recruitment 32% = 22 patients a year
Total		+/- 420 ACL reconstructions a year Expected recruitment 32% = 134 patients a year
Showed sincere interest, but no formal confirmation yet (by signature)		
Centre Hospitalier Régional de la Citadelle	Dr. Vincent Beckers (Dept. of Physical Medicine and Rehabilitation) and Dr. Jean Rondia (Dept. of Orthopaedics)	+/- 45 ACL reconstructions a year Expected recruitment 32% = 15 patients a year

<i>The orthopaedic department of Jessa Ziekenhuis will soon collaborate with 3 other regional hospitals in Limburg. This significantly enlarge our potential sample.</i>		
Sint-Trudo ziekenhuis Sint-Truiden		+/- 80 ACL reconstructions a year Expected recruitment 32% = 26 patients a year
AZ Vesalius Tongeren		+/- 40 ACL reconstructions a year Expected recruitment 32% = 13 patients a year

Table 8. Potential hospitals for the full trial

Our sample size calculation showed that we need to recruit 280 patients in total. Since we already randomized 29 patients in the pilot study, 251 patients still need to be recruited. This seems feasible within a recruitment period of 2 years.

Based on this list of potential hospitals, we strongly believe that we can recruit more than 130 patients a year:

- Based on the numbers of the hospitals that signed the letter of intent, we will be able to recruit +/- 134 patients a year.
- If also the regional hospitals of Sint-Truiden, Tongeren and Centre Hospitalier Régional de la Citadelle confirm participation, we will be able to recruit +/- 187 patients a year.
- Furthermore UZ Brussel and Cliniques Universitaires Saint-Luc (UCL) will be contacted if this seems necessary.

3.3. Feasibility assessment of potential centres

During our conversations with potential hospitals we explored feasibility based on 3 lessons learned from the pilot trial.

1) Collaboration between department of orthopedics and department of physical medicine & rehabilitation

We noticed that a good collaboration is necessary to recruit patients for this study. The surgeon should be open to explaining that two treatment options exist and also to patients who believe that surgery is necessary. Therefore, we asked a physician from both departments be present during all our conversations. In addition, we asked if both departments already collaborate and how this goes. We only selected hospitals who either already have a good collaboration or clearly expressed their motivation to collaborate.

2) Organisation – patient flow

We noticed that some organisational issues could preclude timely randomisation during our pilot. First of all, a patient that presents himself at the emergency department should 1) get a timely MRI (for diagnosis), 2) should be seen by a physician of the study team as soon as possible and 3) not get biased by other physicians for a specific treatment (for example at the emergency department). This ensures that a surgery could be scheduled within 12 weeks post-injury if a patient is randomized to immediate surgery.

We discussed these issues with the potential centres, and they all agreed to anticipate this as far as possible by, for example, updating the emergency department and providing them instructions on what to do if they see a potential patient, and if possible, also reserve some MRI slots for the study.

3) Number of ACL patients per year

The total number of ACL reconstructions a year was registered in every center. This provides a rough estimate of the total number of ACL patients, as the number of conservatively treated patients is not taken into account. Unfortunately, it was impossible to get the total number of ACL patients since conservative treatment of an ACL injury has no specific registration code in all included hospitals.

We estimated the expected recruitment a year for all new centres, based on the recruitment rate that we obtained in UZ Leuven during the pilot trial and the provided number of ACL reconstructions a year. Taking the recruitment rate of UZ Leuven might be an overestimation because this is the sponsor, but this might be compensated by an underestimation of the total number of ACL patients a year (as only surgeries were counted). Furthermore, we strongly believe that sharing our experience of the pilot trial and the careful selection of new centres will make it possible to recruit one patient out of three.

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Appendix A – Amount of ACL reconstructions per month in UZ Leuven and CHU Liège

UZ Leuven	2017	2018	2019	2020	2021	2022
January	7	11	5	6	1	12
February	7	6	6	3	4	5
March	7	10	7	3	2	8
April	2	3	7	2		2
May	8	4	5	1	2	
June	4	6	5	6	2	
July	6	7	4	4	2	
August	5	10	3	6	4	
September	10	6	7	6	6	
October	5	5	7	10	8	
November	10	8	2	6	6	
December	9	2	8	8	3	
Total	80	78	66	61	42	22

Table 9. Amount of ACL reconstructions per month in UZ Leuven

CHU Liège	2017	2018	2019	2020	2021	2022
January	13	11	10	12	11	7
February	6	9	7	11	13	12
March	9	7	5	5	10	5
April	11	10	16	0	6	10
May	10	2	5	2	9	3
June	16	9	6	8	12	
July	18	13	16	19	5	
August	13	8	2	10	4	
September	11	6	20	16	7	
October	13	5	16	4	17	
November	17	12	6	0	7	
December	4	18	15	10	4	
Total	141	110	124	97	105	37

Table 10. Amount of ACL reconstructions per month in CHU Liège.

Appendix B – Experience of investigators of CHU Liège

Barriers and facilitators for recruitment for IODA pilot study

Site: CHU Liège

PI: Jean-François Kaux

CTA: Rita Deroisy

A) Recruitment strategy: please give a short summary of how patients were approached (by who, when, at which department?)

Patients were approached at the consultation of PI or of his assistants or colleagues at the PMR Department.

At the annual meeting of the MPR department, the study was presented to the doctors and physiotherapists. A summary of the protocol were also published in our hospital newsletters.

Meeting with the Emergency Room and then collaboration with them has been has been set up, and they have to contact us when a patient with ACL injury came to the Emergency room

At the beginning, the surgeon specialized in LCA injuries was also involved in the study

PI has also posted our request for recruitment on social networks

B) Which barriers for recruitment did you experienced?

The first contacts were made in May 2020 and the initiation visit was scheduled for 14/10/2020.

Unfortunately from the end of October 2020, due to the evolution of the COVID, the hospital has to postpone the non-urgent interventions, the sports activities are also reduced.

During the winter of 2020-2021, there were great restrictions on winter sports.

Therefore the actual start of the study for the Liège site has been postponed with a new initiation visit on 13/09/2021.

Unfortunately, at that time, the surgeon specializing in knee ligament injuries withdrew from the study. Collaboration with the Emergency and Orthopedic Surgery Departments was difficult to establish. Finally when the surgeon gave us a list of patients :

1) it was one week too late, the randomisation was ended

2) most of patients which came directly to surgeon's consultation have old LCA trauma when the protocol is devoted to acute injuries

Most importantly, he has no patients presenting to the Emergency Room, or to our physical medicine department. There have never been so few patients with an ACL injury in our department.

Recruiting via social networks has not been more productive either.

C) Were there changes/optimizations that you applied to overcome any of these barriers?

Multiplie the phone calls to the Emergency Room to be sure not to miss a patient

Try to convince the surgeon to change his mind. One week after the end of the randomisation, he gave us a list of 11 patients, but in fact, as written in part B, it would not have much difference.

Give flyers for waiting rooms

D) What could be changed to improve recruitment in the full trial?

Create a multidisciplinary consultation for better discussion between departments of Emergency Room, Orthopaedic Surgery and Physical Medicine Rehabilitation.

Create a very, very short video in French for patients, posted on screens in the patients waiting rooms

Barriers and facilitators for recruitment of PI

Name: Jean-François Kaux

Role: PI

Listed below are factors that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment and rate them from -3 to +3 as below:

-3 strong barrier

-2 intermediate barrier

-1 weak barrier

0 not applicable

+1 weak facilitator

+2 intermediate facilitator

+3 strong facilitator

A) Trial specific

	-3	-2	-1	0	+1	+2	+3
Patient inclusion criteria	☐	☐	x	☐	☐	☐	☐
Study protocol compared to clinical practice	☐	☐	☐	x	☐	☐	☐
Clinical equipoise	☐	☐	☐	☐	☐	☐	☐
Seasonal variation in injuries	☐	☐	x	☐	☐	☐	☐

B) Site specific

Time to complete administrative work related to the trial	☐	☐	☐	x	☐	☐	☐
Number of trained staff	☐	☐	☐	x	☐	☐	☐
Local clinical arrangements	☐	☐	☐	x	☐	☐	☐
Competing local research projects	☐	☐	☐	x	☐	☐	☐
Local research culture	☐	☐	☐	x	☐	☐	☐

C) Patient specific

Patient attitude towards conservative treatment vs surgery	☐	☐	x	☐	☐	☐	☐
Patient's preference for a particular treatment	☐	☐	x	☐	☐	☐	☐
Duration of trial and follow up	☐	☐	☐	x	☐	☐	☐
Treatment choice by random allocation	☐	☐	☐	x	☐	☐	☐
Additional trial investigations	☐	☐	☐	x	☐	☐	☐
Additional travel and extra costs	☐	☐	x	☐	☐	☐	☐

D) Clinical team

Research experience of clinical team	☐	☐	☐	x	☐	☐	☐
Motivation of clinical team	x	☐	☐	☐	☐	☐	☐
Clinical workload	☐	☐	☐	x	☐	☐	☐
Perceived importance of research generally in clinical practice	☐	x	☐	☐	☐	☐	☐
Perceived importance of the particular research question	☐	x	☐	☐	☐	☐	☐
Clinician preference for particular treatment	x	☐	☐	☐	☐	☐	☐

Clinician attitude to involving patients in research	☐	x	☐	☐	☐	☐	☐
Difficulty in approaching patients for consent	☐	☐	☐	x	☐	☐	☐

E) Information and consent

Amount and complexity of trial information provided	☐	☐	☐	x	☐	☐	☐
Clarity in presentation of trial information	☐	☐	☐	x	☐	☐	☐

F) Study team factors

Motivation of study team at site	☐	☐	☐	x	☐	☐	☐
Communication and coordination between study team members at site	☐	☐	☐	x	☐	☐	☐
Communication and coordination between study team at site and sponsor	☐	☐	☐	x	☐	☐	☐
Research experience of PI and study team members at site	☐	☐	☐	x	☐	☐	☐

G) Do you have additional comments on any of your answers?

Study team is PI + CTAx

Barriers and facilitators for recruitment of PI

Name: Rita Deroisy

Role: CTA

Listed below are factors that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment and rate them from -3 to +3 as below:

-3 strong barrier

-2 intermediate barrier

-1 weak barrier

0 not applicable

+1 weak facilitator

+2 intermediate facilitator

+3 strong facilitator

A) Trial specific

	-3	-2	-1	0	+1	+2	+3
Patient inclusion criteria	☐	☐	x	☐	☐	☐	☐
Study protocol compared to clinical practice	☐	☐	☐	x	☐	☐	☐
Clinical equipoise	☐	☐	☐	☐	☐	☐	☐
Seasonal variation in injuries	☐	☐	x	☐	☐	☐	☐

B) Site specific

Time to complete administrative work related to the trial	☐	☐	☐	x	☐	☐	☐
Number of trained staff	☐	☐	☐	x	☐	☐	☐
Local clinical arrangements	☐	☐	☐	x	☐	☐	☐
Competing local research projects	☐	☐	☐	x	☐	☐	☐
Local research culture	☐	☐	☐	x	☐	☐	☐

C) Patient specific

Patient attitude towards conservative treatment vs surgery	☐	x	☐	☐	☐	☐	☐
Patient's preference for a particular treatment	☐	x		☐	☐	☐	☐
Duration of trial and follow up	☐	☐	☐	x	☐	☐	☐
Treatment choice by random allocation	☐	☐	☐	x	☐	☐	☐
Additional trial investigations	☐	☐	x	☐	☐	☐	☐
Additional travel and extra costs	☐	☐	x	☐	☐	☐	☐

D) Clinical team

Research experience of clinical team	☐	☐	☐	x	☐	☐	☐
Motivation of clinical team	x	☐	☐	☐	☐	☐	☐
Clinical workload	☐	x	☐	☐	☐	☐	☐
Perceived importance of research generally in clinical practice	☐	x	☐	☐	☐	☐	☐
Perceived importance of the particular research question	☐	x	☐	☐	☐	☐	☐
Clinician preference for particular treatment	x	☐	☐	☐	☐	☐	☐

Clinician attitude to involving patients in research	☐	x	☐	☐	☐	☐	☐
Difficulty in approaching patients for consent	☐	☐	x	☐	☐	☐	☐

E) Information and consent

Amount and complexity of trial information provided	☐	☐	☐	x	☐	☐	☐
Clarity in presentation of trial information	☐	☐	☐	x	☐	☐	☐

F) Study team factors

Motivation of study team at site	☐	☐	☐	x	☐	☐	☐
Communication and coordination between study team members at site	☐	☐	☐	x	☐	☐	☐
Communication and coordination between study team at site and sponsor	☐	☐	☐	x	☐	☐	☐
Research experience of PI and study team members at site	☐	☐	☐	x	☐	☐	☐

G) Do you have additional comments on any of your answers?

Difficulty in approaching patients for consent: more difficult to convince patients by phone when you did not meet them in face to face discussion.

Nevertheless, we had only one refusal to participate in the study (long travel, and fear of missing physical tests needed for his job). All the other patients we offered the study agreed to participate in the protocol. It was really the lack of eligible patients that we missed

Study team is only PI and myself.

Appendix C - Patient communication about ACL treatment in Belgium

We noticed several examples of inadequate educational material during the performance of our study. We performed a quick search in the context of this feasibility report to investigate whether or not this was limited to a few cases. This appendix provides print screens of what you can read on the websites of several Belgian hospitals, confirming very poor patient education in Belgium.

Behandeling:

Een letsel van de voorste kruisband geneest niet spontaan. Afhankelijk van de leeftijd, het activiteitsniveau en het instabiliteitsgevoel zal men al dan niet overgaan tot een operatief herstel.

- **niet operatief:**
Voor "oudere" patiënten, waar eventueel zelfs al wat algemene gewrichtsslijtage aanwezig is, of die geen doorzakingsgevoel hebben, kan men een **afwachterende houding aannemen**. In de acute fase (als het pas gebeurt is), kan men rust, hoogstand, ijs doorvoeren en pijnstillers nemen. Later kan men eventueel een kniestabiliserende brace dragen.
- **operatief:**
Bij jonge actieve mensen, die nog aan sport doen, zal men een operatie voorstellen. Tijdens de operatie zal men de gescheurde kruisband vervangen door pezen (Hamstrings of patellapees of quadricepspees) van de patiënt zelf. Indien de patiënt vroeger reeds een kruisband herstel heeft gehad, kan men donorpezen gebruiken of een kunstligament.

Figure 6. Website Orthopedie Lier- <https://www.orthopedielier.be/2-patint/91-kruisband-scheur-letsel/>

Wanneer behandelen?

Het plaatsen van een vervangkruisband is een onderdeel van een strategie om vervroegde slijtage van de knie te voorkomen. Bij jonge patiënten (jonger dan 40 jaar) zullen we bijna altijd voorstellen de kruisband te vervangen. Over deze leeftijdsgrens ontstaan soms pittige discussies. Deze grens mag niet absoluut gehanteerd worden. Andere factoren zijn mee bepalend (realistische sportieve ambities, effectieve instabiliteit (zelfs in dagelijks gebruik), onveiligheid,...).

Behandelingsmogelijkheden

Uitzonderlijk kan een kruisbandletsel conservatief (niet-operatief) behandeld worden. Dit betekent wel dat de spieren maximaal opgetraind en onderhouden moeten worden. Een brace kan deze spieren absoluut niet vervangen!

Figure 7. Turnhout <https://orthopedie-turnhout.be/knie/casus/voorste-kruisbandscheur/>

Niet operatief. Bij oudere patiënten waarbij er geen instabiliteitsklachten op de voorgrond staan, kan chirurgie worden vermeden. Kinesitherapie zal dan voorgeschreven worden om de stabiliserende spieren rondom de knie sterker maken. In de meeste gevallen zal ook **sport met draaibewegingen moeten vermeden worden**.

Operatief. Bij de meeste patiënten zal op basis van instabiliteitsklachten, leeftijd, activiteitsniveau en bijkomende meniscus- of kraakbeenletsels worden beslist om de kruisband via chirurgie te reconstrueren. Naar timing van reconstructie wordt voornamelijk rekening gehouden met de stijfheid van de knie (dient vermeden te worden). Meestal kan de ingreep daarom binnen de 6 weken na het trauma worden uitgevoerd. Idealiter dient de ingreep te gebeuren voor 9 maand, aangezien nadien vaak **bijkomend uitrekken van andere ligamenten voorkomt en de risico's op bijkomende meniscusscheuren significant stijgt**.

Figure 8. Website Orthopedie Roeselare <https://www.orthopedieroeselare.be/nl/specialisaties/knie/kruisband>

Hoe wordt een gescheurde kruisband best behandeld?

Eens de diagnose gesteld is, kan bij sportieve en actieve patiënten een reconstructie van de voorste kruisband worden verricht. **Zonder herstel riskeert men doorzakkingen waarbij men nieuwe letsels in de knie kan oplopen** bijvoorbeeld meniscale scheuren en kraakbeenbeschadiging. In principe is er geen leeftijdsgrens en komen zowel jongere als oudere patiënten in aanmerking. De behandeling varieert dus vooral van de behoeften en het activiteitsniveau van iedere individuele patient. Zo kan een minder actieve of oudere patient perfect zonder operatie zijn dagdagelijkse activiteiten verderzetten mits het volgen van een goed revalidatieprogramma.

> De niet-operatieve aanpak

Een gescheurde voorste kruisband zal niet genezen zonder chirurgie. Maar een niet-operatieve behandeling kan volstaan om voldoende stabiliteit te geven **bij oudere patienten, mede omdat er op die leeftijd vaak wat meer verstijving optreedt.** Deze niet-operatieve behandeling bestaat uit een **intensief oefenschema met kinesithérapie gericht op het versterken van de spieren rond de knie.** Vaak zal er ook een brace worden voorgeschreven

die tijdelijk moet gedragen worden en bijkomende stabiliteit verschaft. Een goede spierkracht van de quadriceps (bovenbeenspier) en hamstrings kan de knie voldoende stabiliseren. **Het aanpassen van de levensstijl of het niveau van sportactiviteiten, kan een operatieve ingreep eveneens overbodig maken.**

> De operatieve behandeling

Eens de diagnose gesteld is, kan **bij sportieve en actieve patiënten** een reconstructie van de voorste kruisband worden verricht. Een reconstructie is eveneens noodzakelijk indien men, na het goed uitvoeren van van het revalidatieprogramma, toch een instabiliteitsgevoel met herhaald doorzakken blijft behouden. Zonder herstel riskeert men immers doorzakkingen waarbij men nieuwe letsels in de knie kan oplopen zoals bijvoorbeeld meniscale scheuren en kraakbeenbeschadiging. Zoals eerder aangegeven, zal de aanpak verschillen voor elke individuele patient.

Figure 9. Ziekenhuis Netwerk Antwerpen patienten brochure

https://www.zna.be/sites/default/files/33668_mi_voorste_kruisband.pdf

Behandeling gescheurde kruisband

Conservatief: met kinesitherapie (spierversterkende oefeningen) bij oudere patiënten

Operatief: momenteel zijn er drie technieken om de originele kruisband zoveel als mogelijk te bewaren en te herstellen. (zie boven)

De meeste mensen met een gescheurde voorste kruisband, die nog willen sporten, komen in aanmerking voor een kruisband operatie. Zeker als ze jong zijn, wordt een nieuwe VKB aangeraden, aangezien na verloop van jaren de instabiliteit ook in het dagelijkse leven kan toenemen. Bij een instabiliteit (doorzakken van de knie) kan er een ernstige beschadiging van menisci of kraakbeen optreden.

Figure 10. Website Orthopedisch Centrum Sint-Niklaas <https://caretomove.be/specialiteiten/knie/vkb/>

Operatie is niet strikt nodig

- Als er geen bijkomende letsels aanwezig zijn: bv. gebroken bot, beschadigde meniscus enz.
- Als de sportactiviteiten van de patiënt het toelaten: bv. wandelen, fietsen, joggen en crawl zwemmen.
- Als de patiënt geen blijvende hinder ondervindt, zoals frequent door de knie zakken.

Operatie is aangewezen

- Als de patiënt een actief leven leidt (aard van werk, sport, ...) is een ingreep nodig om opnieuw doorzakken te voorkomen. Frequent doorzakken kan nieuwe letsels veroorzaken in de knie, zoals meniscusscheuren of kraakbeenletsels.
- Voor sporten waarbij de knie veel draait, zoals voetbal, basketbal, volleybal, handbal en skiën, is de kruisband noodzakelijk voor een goede kniestabiliteit en wordt een operatie voorgesteld.

Figure 11. Website RZ Tienen <https://www.rztienen.be/nl/paginas/print-sub-page/608/>

Nos critères (indications chirurgicales)

Chez un patient souhaitant poursuivre son sport, le traitement est le plus souvent chirurgical. Il permet de stabiliser le genou, éviter les lésions méniscales et donc ralentir l'apparition de l'arthrose.

Ce traitement est donc proposé fréquemment chez l'adolescent, l'adulte jeune et l'adulte sportif et actif.

Les alternatives thérapeutiques

Un traitement fonctionnel peut être instauré. Des soins de rééducation spécifique peuvent permettre de récupérer un genou indolore et permettant la reprise de certaines activités dite « dans l'axe » (vélo, jogging sur terrain plat).

Figure 12. Website CHBA hospital https://www.chba.be/rupture_du_ligament_croise_anterieur__lca_-1590.html

Qui doit être opéré ?

Tout patient jeune et sportif doivent reconstruire leur LCA afin de pouvoir pratiquer à nouveau leur sport sans risque d'entorse, et d'autres lésions (ménisque, cartilage). Les quadragénaires peuvent opter pour un traitement conservateur de renforcement musculaire et de stabilisation. En cas d'exigences sportives importantes ou d'instabilité, il faudra néanmoins envisager l'intervention.

Figure 13. Website Brussels Knee Center <https://www.bkc.be/Informations-pour-le-patient/lca>

Si vous estimez que oui ; il s'agit d'un argument important à considérer et dans ce seul contexte, il est conseillé de reconstruire le LCA chirurgicalement.

- **L'âge du patient** : plus le patient est jeune plus il faut penser à reconstruire le LCA d'autant plus que de nouvelles techniques chirurgicales existent pour conserver le cartilage de croissance.
- **Le Type et le niveau d'activité sportive** : le LCA est le ligament particulièrement sollicité dans les sports à pivot où le genou travaille en rotation (danse, gymnastique aux agrès ...) ainsi que dans bon nombre de sports de contact (football, volley-ball, rugby) mais également bon nombre de sports où il existe des actions rapides tel que le badminton. Les sports ou les couples de force développés peuvent être importants ne sont pas laissés pour compte (ski, kitesurf). Souhaiter continuer de pratiquer ces types d'activités sans reconstruction du LCA puis rééducation spécialisée intensive n'est pas pertinent.

Figure 14. Website CHR Haute-Senne <https://www.chrhautesenne.be/fr/services/59/ligament-croise-anterieur-du-genou#.YqMpTHZBxPY>