
CLINICAL TRIAL PROTOCOL

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

IODA trial

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Sponsor

University Hospitals Leuven (UZ Leuven)

Herestraat 49, B-3000 Leuven

Coordinating Investigator

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KCE Trials Number

INV18-1158

Confidentiality Statement

The information in this document is strictly confidential and is available for review to Investigators, potential Investigators and appropriate Ethics Committees, Institutional Review Boards or Competent Authorities. No disclosure should take place without written authorization from the Sponsor.

LIST OF PARTICIPATING SITES

List Of Participating Sites

UZ Leuven

University Hospital of Liège

Clinique Saint-Luc Bouge

Jessa Ziekenhuis Hasselt

UZ Brussel

|

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SIGNATURES

Title: |Comparison of Immediate versus Optional Delayed surgical repair for treatment of acute Anterior cruciate ligament injury through a parallel, multicentric, pragmatic randomized controlled trial|

Protocol: |ODA trial|

The undersigned confirm that the above referenced protocol has been acknowledged and accepted, and agree to conduct the Trial in compliance with the approved protocol, and will adhere to: the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in Directive 2001/20/EC or the EU Clinical Trial Regulation 536/2014 (as soon as in effect) and any subsequent amendments thereto, the ICH guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th 2017 related to clinical trials on medicinal products for human use (as soon as in effect), the EU General Data Protection Regulation 2016/679 (GDPR), relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights, and any other regulatory requirements and Standard Operating Procedures (SOPs), as applicable.

The undersigned agree not to disclose the confidential information contained in this document for any purpose other than the evaluation or conduct of the Trial, without prior written consent of the Sponsor.

The undersigned also commit to making the findings of the Trial publicly available through publication and/or other dissemination tools, in accordance with this protocol and applicable regulations, without any unnecessary delay and to provide an honest, accurate and transparent account of the Trial; and to explain any discrepancies or deviations from the approved Trial protocol.

Coordinating Investigator

		
Name & Title	Signature	Date

Principal Investigator (Participating Site) *(in case of monocentric Trial, the Principal Investigator is the same as the Coordinating Investigator)*

		
Name & Title	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
ACL	Anterior Cruciate Ligament
AE	Adverse Event
APR	Annual Progress Report
ASR	Annual Safety Report
AR	Adverse Reaction
CA	Competent Authority
CI	Coordinating Investigator
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
DMP	Data Management Plan
DPA	Data Processing Annex
DTA	Data Transfer Agreement
EC	Ethics Committee
EU	European Union
EoT	End of Trial
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
GDPR	General Data Protection Regulation
ICF	Informed Consent Form
ISF	Investigator Site File
LPLV	Last Patient Last Visit
MP	Monitoring Plan
PI	Principal Investigator (Participating Site)
PROM	Patient Reported Outcome Measure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

FUNDING AND SUPPORT

Funder	Type of Financial or Non-Financial Support
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Belgian Health Care Knowledge centre (KCE)	Project funding + site costs
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Reasonable travel expenses incurred by Trial participants and directly related to participation in the Trial, will be reimbursed by the Sponsor, as follows: by means of gift vouchers with a total value of €25 per trial visit

A travel reimbursement payment log will be kept by the Investigator Site staff and made available for monitoring and verification purposes.

ROLES AND RESPONSIBILITIES

The Principle Investigator (PI) is responsible for the conduct of the Trial at his/her Participating Site, and for protecting the rights, safety and well-being of the Trial participants. As such the PI must ensure adequate supervision of the Trial conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Trial-related duties. The PI will ensure that adequate training is provided and documented for all Trial staff, prior to conducting assigned Trial-related activities.

It is the Coordinating Investigator's (CI's) responsibility to supervise the general conduct (e.g. Trial progress, communication, protocol training and support of the participating sites, annual reporting to the Ethics Committee (EC), end of Trial notification(s) and results reporting...) of the Trial. The CI fulfils both Investigator and Sponsor responsibilities, as outlined in International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) E6(R2) and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

TRIAL SYNOPSIS

Title of clinical Trial («Trial»)	Comparison of Immediate versus Optional Delayed surgical repair for treatment of acute Anterior cruciate ligament injury through a parallel, multicentric, pragmatic randomized controlled trial
Protocol Short Title Acronym	IODA trial
Trial Phase (I, II, III, IV)	Phase IV
Sponsor name	University Hospitals Leuven (UZ Leuven)
Coordinating Investigator	Prof. dr. Koen Peers
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Principal Investigators and Participating Sites	- UZ Leuven (Prof. Koen Peers) - University Hospital of Liège (Prof. Jean-Francois Kaux) - Clinique Saint-Luc Bouge (Dr. Jérémy Daxhelet) - Jessa Ziekenhuis Hasselt (Pieter-Jan Loos) - UZ Brussel (Dr. Marc Schiltz)
Medical condition or disease under investigation	Acute Anterior cruciate ligament injury
Trial rationale	Conservative treatment (with optional delayed surgery) compared to immediate surgery with post-surgery rehabilitation is equally effective at long term in terms of patient reported outcomes and even more effective at short term in terms of return to activity/sport. Additionally, this may result in considerable costs savings for society and the health system.
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. Outcome parameters of interest are functional knee outcomes reported by the patients themselves, the decrease in co-morbidities associated with the chosen therapy, as well as adverse events such as re-rupture rates. These outcome parameters will be compared between both treatment arms with an intention-to-treat analysis.
Secondary objective(s)	To identify individuals who would benefit the most from early reconstruction versus those who should rather be treated conservatively through a predictive analysis.
Trial Design	A parallel, multicentric, pragmatic, randomised controlled trial comparing immediate ACL reconstructive surgery (control group) with optional delayed surgery (intervention group).
Endpoints	I) Non-inferiority testing at 1 year follow-up for the primary outcome (difference in mean change between baseline to 1 year follow-up on the KOOS QOL between both groups)

	2) Superiority testing at 7 months follow-up for the primary outcome (difference in mean change between baseline and 7 months follow-up on the KOOS QOL between both groups)
Sample Size	280
Intervention	Rehabilitation and optional delayed ACL reconstruction
Control	Immediate ACL reconstruction and rehabilitation
Maximum duration of treatment and Follow Up of a Participant	36 months
Maximum duration of entire Trial	60 months
Date anticipated First Patient First Visit (FPFV)	15/01/2023
Date anticipated Last Patient Last Visit (LPLV)	15/01/2028
Third parties	None

TRIAL FLOWCHART

Procedures/ Assessment	Screening	Randomisation + baseline assessment	Intervention	Follow-Up Visits				
Visits / Contacts	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Timing		Baseline	²	4 months post-injury	7 months post-injury	12 months post-injury	24 months post-injury	36 months post-injury
Visit Window	< 8 weeks after injury	< 8 weeks after injury	NA	± 14 Days	± 14 Days	± 14 Days	± 14 Days	± 14 Days
Enrolment								
Informed consent	X ¹							
Inclusion / Exclusion criteria	X	X						
Demographics	X							
Medical history	X							
Randomisation		X						
Intervention								
1a. Rehabilitation			X ²					
1b. Delayed surgery			X ²					
2. Immediate surgery			X ³					
Assessments								
Physical knee examination	X	X		X	X	X	X	X
MRI	X ⁴			X ⁴				X ⁴
PROMS ⁵		X		X	X	X	X	X
Isokinetic strength test				X	X	X	X	X
Functional test: hop test					X	X	X	X
Return to work/sport		X		X	X	X	X	X
(Serious) Adverse event (S)(AE)				X	X	X	X	X

Table 1. Overview of study visits and trial assessments. The trial specific procedures are indicated in blue, the procedures that are part of the standard care are marked in green.

1 : Informed Consent be obtained prior to performing any other Trial-related procedures; 2: patients randomized to the intervention arm, start with rehabilitation. A delayed surgery can occur after randomization; 3: patients randomized to the control arm, receive an ACL surgery within 12 weeks after injury; 4: the MRI will be scored by a central reader, according to the ACLOAS scale; 5: the following PROMS will be assessed at V2-V7: KOOS, IKDC, Modified Tegner score + sport participation, EQ-5D-5L, IPQ-R, TSK, iMCQ, iPCQ

I Background, Rationale and Risk Assessment

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 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 performed (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. The results of the ACL SNNAP trial are less relevant for Belgian care as the SNNAP trial investigated chronic ACL ruptures (no acute ACL ruptures) (14).

Based on the results of the KANON trial (10) and the COMPARE trial (15), 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 (16). 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 (17)) but also on quality of rehabilitation (18) and psychological factors such as expectations (19), fear for re-injury (20,21), and locus of control (22). 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.

Risk assessment and recruitment feasibility:

The trial is categorised as a low risk intervention clinical trial (see justification in Appendix 3: [Risk assessment of the trial intervention](#)).

We recently performed a pilot study to assess recruitment feasibility (S62004, Open Access publication: (23), [clinicaltrials.gov: NCT04408690](https://clinicaltrials.gov/ct2/show/study/NCT04408690)). This feasibility study was performed as many patients have a preference for a particular treatment, potentially affecting recruitment (which involves randomization) and adherence to the protocol (4).

In our pilot study we proved that recruitment is feasible if patients receive adequate information, and if there is a good collaboration between different departments of the hospital (eg. Orthopaedics, Physical Medicine & Rehabilitation, emergency department).

The protocol of this full trial is mostly the same as the pilot trial (S62004), although the sample size is much larger, there are more participating centres and follow-up is longer.

2 Trial Objectives and Design

The figure below provides an overview of the different objectives and endpoints of the trial.

	Primary endpoints	Secondary endpoints	
Primary objectives	Non-inferiority at long-term (1y FU) - ITT¹: control vs intervention group - Δ KOOS QOL	Non-inferiority at long-term (2y + 3y FU) - ITT¹: control vs intervention group - Δ KOOS QOL	Non-inferiority at long-term (1-2-3y FU) - ITT¹: control vs intervention group - Secondary outcome parameters²
	Superiority at short time (7m FU) - ITT¹: control vs intervention group - Δ KOOS QOL	Superiority at short time (4m FU) - ITT¹: control vs intervention group - Δ KOOS QOL	Superiority at short time (4+7m FU) - ITT¹: control vs intervention group - Secondary outcome parameters²
Secondary objectives	Prediction analysis - Intervention group - Prediction of delayed surgery (binary outcome) - 5 predictors (baseline assessments)		
Explorative objectives	Prediction analysis - All patients: control + intervention - Prediction of longterm outcomes: • KOOS QOL at 2-3y FU • time to return to work • time to return to pre-injury activities • subsequent knee injuries and cartilage health (assessed with MRI at 3y FU)		

Figure 1. Overview of the different objectives and endpoints.

¹ for all primary objectives, the main analysis is an intention-to-treat analysis comparing the 2 treatment groups. Additionally, an as-treated analysis will be performed (3 groups: rehabilitation alone, rehabilitation + delayed surgery, immediate surgery). ² secondary outcome parameters are Δ KOOS subscales, Δ IKDC, functional tests, time to return-to-work, time to return to pre-injury activities, subsequent knee injuries and cartilage health (assessed on MRI) and adverse events.

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this research proposal is to compare the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical reconstruction of an acute ACL injury. Outcome parameters of interest are functional knee outcomes reported by the patients themselves, the decrease in co-morbidities associated with the chosen therapy, as well as adverse events such as re-rupture rates. Additionally, socio-economic benefits will be investigated.

This primary objective is translated in following hypotheses:

1. the optional delayed surgery approach for acute ACL injury will result in non-inferior patient reported outcome measures at long term, i.e. 1 year post-injury, compared to immediate surgery
2. the optional delayed surgery approach for acute ACL injury will result in better patient reported outcome measures at short term, i.e. 7 months post-injury, compared to immediate surgery
3. the optional delayed surgery approach will lead to less socio-economic costs both at short and long term, compared to immediate surgery

2.1.2 Secondary objective

The secondary objective is to identify individuals who would benefit the most from reconstruction versus those who should rather be treated conservatively. To investigate this, a prediction model will be built in the intervention group (rehabilitation with optional delayed ACL reconstruction). Five predictor variables will be considered to predict whether delayed reconstruction is necessary or not.

The secondary objective is translated into the following hypothesis:

1. Patients who score high on the KOOS QOL do less likely need a delayed ACL reconstruction.
2. Patients who have pathologic MRI features (fiber continuity disturbed, high/heterogenous signal intensity, more horizontal slope of the ACL, unclear boundaries) do more likely need a delayed ACL reconstruction (17).
3. Patients who have less hemarthrosis determined by MRI do less likely need a delayed ACL reconstruction
4. Patients who have low expectations regarding the effectiveness of physical therapy (eg. low scores on the MODEMS expectations scale), will more likely need surgery (24).
5. Patients who are less active pre-injury (lower Tegner score), are less likely to have a delayed ACL reconstruction (25).

2.2 Primary Endpoints

A hierarchical approach of statistical testing will be used. First, **non-inferiority will be assessed at 1 year** follow-up as our first hypothesis is that patients in both groups will have reached similar clinical outcomes at long term (i.e. 1 year post-injury), based on the KANON trial (10). Subsequently, if non-inferiority will be confirmed, **superiority testing will be performed on the 7 months** post-injury data to assess whether rehabilitation with optional delayed ACL reconstruction is better than immediate ACL reconstruction at short term. The patients who start with rehabilitation (with optional delayed ACL reconstruction) do not have iatrogenic knee joint damage due to surgery, which may result in better outcomes at short-term which may allow them to return to work and sport earlier. Proving the superiority on short term is necessary to change current clinical practice.

Furthermore, the patient representatives reported that the superiority on short term (eg. earlier return to sport) is a very important advantage of conservative treatment.

The **primary outcome parameter** that will be assessed to compare non-inferiority at long term and superiority at short term is the knee-related quality of life measured with KOOS QOL. The KOOS questionnaire consists of 5 subscales: pain, symptoms, ADL, sport and recreational function and knee-

related QOL and is commonly used to assess knee function and symptoms in ACL patients to monitor changes over time (26). Since most ACL patients report no/small problems with pain, symptoms and ADL function, there is less room for improvement on those subscales and therefore the subscales Sport/Rec and QOL are recommended to follow-up ACL patients (27,28). We chose for the subscale QOL as primary outcome since not all participants will be involved in sports and therefore the Sport/Rec is less useful in our trial.

2.2.1 Non-inferiority analyses for the primary outcome at long term (1 year follow-up)

The primary outcome is the difference in mean change between baseline to 1 year follow-up on the KOOS QOL between both groups. A non-inferiority margin of 7 points is chosen as Collins et al. report this as the minimal detectable change in KOOS QOL (29). Non-inferiority will be concluded when the lower limit of the confidence interval will be above the non-inferiority margin of -7.

2.2.2 Superiority analyses for the primary outcome at short term (7 months follow-up)

The primary outcome is the difference in mean change between baseline and 7 months follow-up on the KOOS QOL between both groups. A superiority margin of 13.5 points is chosen based on the study of Roos et al. (28) who found that 13.5 was the minimal change in KOOS QOL that patients consider important. Superiority will be concluded when the lower limit of the confidence interval will be above the superiority margin of 13.5.

2.3 Secondary Endpoints

2.3.1 Non-inferiority and superiority analyses for the primary outcome at other time points

The primary outcome measure (mean change in KOOS QOL from baseline) will be administered at other time points:

- short term superiority at 4 months post-injury
- long term non-inferiority at 2 and 3 years follow-up

Proving superiority at 4 months post-injury will be an additional reason to change current practice and motivate patients to choose for rehabilitation with optional delayed reconstruction. For example earlier return to work and pre-injury activities because additional iatrogenic knee joint damage because of surgery is avoided. Furthermore this is an important time point to decide whether delayed surgery is necessary or not.

Proving non-inferiority at 2 and 3 years follow-up is necessary to demonstrate that both treatment groups are doing equally well after stopping or reducing the intensity of the rehabilitation.

2.3.2 Non-inferiority and superiority analyses of secondary outcome parameters

At long term (i.e. 1, 2 and 3 years follow-up) and at short term (i.e. 4 and 7 months post-injury) following secondary outcome parameters will be administered for superiority and non-inferiority analyses, respectively:

- Mean change on the other KOOS subscales from baseline
- Mean change on the IKDC subjective from baseline
- The mean score on functional knee tests (Single leg hop for distance, isokinetic strength of the hamstrings and quadriceps)
- Time to return to pre-injury activity level (scored with Modified Tegner Scale)
- Time to return to work
- Structural knee joint damage and cartilage health (based on MRI assessment at 3 years follow-up)
- The amount of adverse events in both intervention groups

All outcome parameters are described in detail in 4.4 Visit schedule and assessments.

2.3.3 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 binary outcome and where an initial set of the five predictor variables will be considered:

1. Knee-related quality of life at baseline, measured with the KOOS QOL
2. MRI findings at baseline scored with the modified ACLOAS
3. Degree of hemarthrosis determined by MRI at baseline
4. Expectations regarding the effectiveness of physical therapy at baseline, measured with the MODEMS scoring system
5. Pre-injury activity level, measured with the Tegner Activity Score

The event of 'delayed surgery' was considered as binary outcome and not as time-to-event since the main question is to investigate whether it is possible to predict who will need a delayed surgery. The timing of the delayed surgery is less relevant as the timing is often influenced by several personal factors such as work, school, holiday and also by the availability of the surgeon etc.

This prediction analysis can improve clinical practice in the future. Identifying variables that can predict if surgery is necessary can improve clinical decision making in the future. Based on these variables patients who would benefit from surgery could already be identified at baseline.

2.4 Exploratory endpoints

2.4.1 Exploratory predictive analyses

To assess which outcomes predict long term outcomes after ACL injury in general, we will build a prediction model in the entire study population (e.g. all patients, thus combination of intervention and control group). We are interested in factors that predict 1) KOOS QOL at 2 and 3 year follow-up, 2) the time to return to work and 3) the time to return to pre-injury activity level. This prediction analysis is explorative as it will not directly improve current practice. However, information of this explorative analyses can result in valuable information for future research that aims to improve ACL treatment.

The initial set of predictor variables that will be considered is:

- KOOS QOL at baseline and follow-up measurements
- MRI findings at baseline and 4 months follow-up: fiber continuity, signal intensity, slope of ACL, clear boundaries
- Associated meniscal or cartilage damage in the index knee (detected on the baseline MRI, scored with the ACLOAS score)
- Type of intervention + timing of intervention: immediate reconstructive surgery or rehabilitation with optional delayed ACL reconstruction
- Perceived self-efficacy of knee function at baseline measured with the K-SES (Thomé et al. 2008).
- Limb symmetry index of the isokinetic strength tests of quadriceps and hamstrings at 4 and 7 months follow-up.
- Limb symmetry index on the Single leg hop for distance test at 7 months post-injury
- Age and gender
- Preference for a certain treatment

The study of Filbay et al. (30) found that lifestyle factors influence long term outcomes. Therefore comorbidities, smoking and education level will be included as covariates in the prediction analyses.

2.4.2 Responder criteria

Previous studies (27,28,31) showed that the use of responder criteria improves the clinical interpretation of the results of clinical randomized trials as this method allows one to specifically assess the number of patients that feel well, the number of patients that feel better/worse and/or determine the number of patients that experience treatment failure. These proportions might be clinically more meaningful compared to absolute average KOOS scores or average change scores only.

Therefore responder criteria will be established using anchor-based methods according to previous studies (27,28,31). Subjects will respond to a set of anchor items for minimal important change (MIC), patient acceptable symptom state (PASS) and treatment failure (TF) at 2 years follow-up. Subsequently PASS and TF values will be calculated as mean summery scores of the subjects who responded 'yes' to the PASS and TF questions. MIC values will be calculated with the predictive modelling method and represent the smallest change in KOOS score that patients consider as important change (27). Subsequently the proportions of patients that report a KOOS score higher than the MIC, PASS and TF values will be compared between both groups.

2.5 Trial Design

A parallel, multicentric, pragmatic randomised controlled trial comparing immediate ACL reconstructive surgery (control group) with optional delayed surgery (intervention group) will be performed (see Figure 2 – Trial flow chart).

A *hierarchical approach* of statistical testing will be used. First, non-inferiority will be assessed at 1 year follow-up for the patient reported outcomes. Second, if non-inferiority is confirmed, superiority testing will be performed on the 7 months post-injury data. The superiority is necessary to change current clinical practice.

The study will run simultaneously in 5 Belgian centers of wich 2 are universital hospitals and 3 regional hospitals. Participants will be recruited at the department of Orthopaedics and department of Physical Medicine and Rehabilitation of the participating sites.

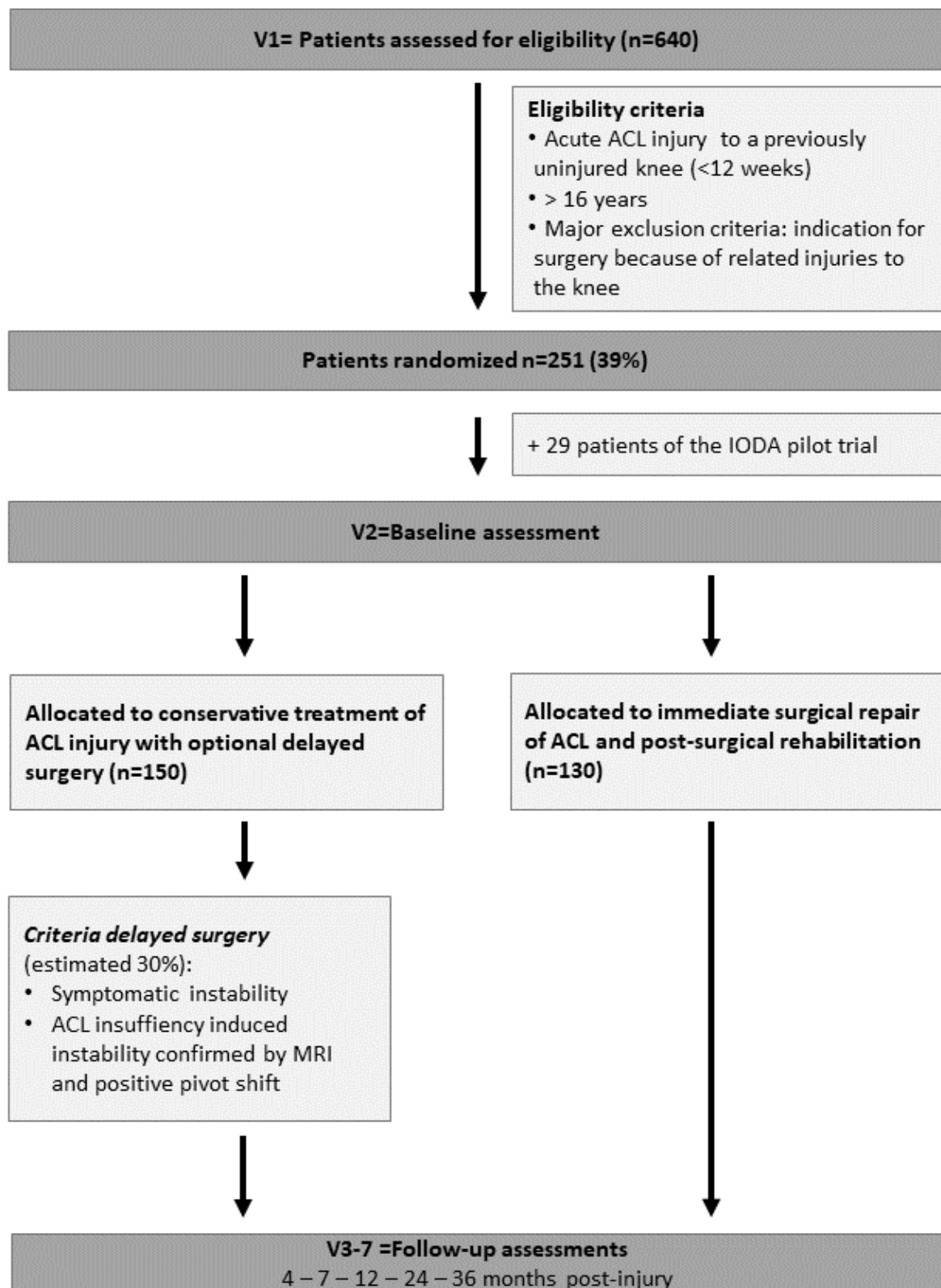


Figure 2. Trial flow chart

2.6 Expected Duration of the Trial

Time point	Event
Month 0	KCE Trials Board recommendation for funding • Additional feasibility checks • Budget check • Contract negotiations
Month 3	Contract signature • EC approval • preparing data management aspects and logistics (eCRF, DM plan, risk management plan, monitoring plan etc)
Month 6	First patient first visit • 280 patients to include in 2 years • 7 study visits, 3 years follow-up
Month 30	Last patient first visit
Month 66	Last patient last visit • Collection of all data • Cleaning database
Month 68	Database lock for primary analysis
Month 80	Final report and manuscripts submitted (primary and secondary outcomes)

3 Trial Population / Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this Trial must meet **all** of the following criteria:

1. Rotational trauma to a knee that had no previous serious injury and for which medical advice was sought within 4 weeks after the injury. (With serious injury we mean: previous ACL injury or knee surgery)
2. Medical diagnosis of ACL insufficiency including MRI (both partial and complete ruptures)
3. Minimum of 16 years

All participants that are considered for Trial participation, per the above criteria will be documented on the precreening Log, including Screen Failures.

3.2 Exclusion criteria

Participants eligible for this Trial must **not** meet any of the following criteria:

1. Participant has a history of a previous ACL injury or knee surgery to the index knee
2. Indication for acute surgery because of related injuries to the knee
3. Female who is pregnant or plans to become pregnant in the first 4 months of the trial. Since MRI assessment cannot be performed.

Since the pragmatic aspect of the trial, we do not want to impose strict criteria for excluding certain patients because of other related knee injuries. Therefore, we decided to not further specify exclusion criteria 2. 'Indication for acute surgery because of related injuries to the knee'. In this way, the decision to

exclude patients because of severe other knee-injuries remains a clinical decision of the medical doctor him/herself, and remains thus more pragmatic. Furthermore, for most associated injuries, it will be self-evident if immediate surgery is necessary such as multiligamentar injuries, additional fractures, meniscal lesions that need repair.

Furthermore, we will not exclude patients who had a previous contralateral ACL injury or previous contralateral knee surgery as in clinical practice, this does not influence the outcome of knee function and the doctor's decision to undergo surgery or not. Based on this, and the pragmatic aspect of the trial, there is no reason to exclude them. However, we do expect that some patients who had a previous ACL injury will be biased because of good or bad experience with a previous surgery or conservative treatment.

Finally, elite athletes will not be excluded from the trial. However we expect that most professional athletes will refuse to participate as often their team manager and/or team doctor decide on the treatment of the athlete.

The reason(s) for refusal to participate of all ACL patients that came for a consultation will be registered anonymously on a screening log. This can be for medical reasons but also because patients are not willing to participate (e.g. beliefs that surgery is necessary, time-issues, fear of surgery...).

Participants who meet one or more of exclusion criteria must not proceed to be enrolled/randomized in the Trial and will be identified on the Screening Log as Screen Failure.

4 Trial Procedures

4.1 Participant consent and withdrawal of consent

The Trial will be conducted only on the basis of prior informed consent by the Trial participants and/or their legally authorized representative(s). As such, no Trial-related procedures will be conducted prior to obtaining written informed consent from potential Trial participants.

The process for obtaining and documenting initial and continued informed consent from potential Trial participants will be conducted in accordance with ICH-GCP E6(R2), applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the Investigator Site File (ISF) at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the protocol section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the Trial for any reason at any time. The participant's request to withdraw from the Trial must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant's medical record.

Trial data and samples collected before withdrawal can be used in the trial. No new trial data or samples will be collected after withdrawal of the participant.

4.2 Selection of Participants / Recruitment

4.2.1 Patient identification

Patients referred to any of the participating sites with an acute ACL injury will be assessed for eligibility. In current practice, patients who have had a knee injury that might be an ACL injury, are referred to either 1) the orthopaedic department or 2) the department of physical medicine and rehabilitation. In both cases, the identification and screening procedure will be performed in the same way.

As per routine practice, in the first consultation (V0), the medical doctor will take a patient history and perform a physical examination of the knee, including clinical tests to diagnose ACL injuries. Based

on these findings the suspicion of an ACL injury can be supported or rejected. If the clinical tests were positive, an MRI is scheduled to confirm the ACL tear. Furthermore, if the patient meets the inclusion criteria, the medical doctor will already give some information about the possibility to participate in the study.

During the second consultation (VI) with the medical doctor, the results of the MRI are discussed. If the ACL tear is confirmed by the MRI, the medical doctor asks potential interest in participating in the study and will discuss this with the patient. If the patient is interested, he/she is referred to a study nurse for further eligibility check and further information about the study. After eligibility is confirmed by the investigator, patients who are willing to participate, sign the informed consent.

To optimise recruitment and to not miss potential candidates the study nurse of the participating centre will weekly check the planning of both the orthopaedic and physical medicine department and remind the medical doctors of all potential candidates. Furthermore, regular contact with the emergency department is necessary to ensure that all patients who present themselves at the emergency department are correctly referred to either a consultation at the department of Physical Medicine and Rehabilitation or the department of Orthopedics.

Screening logs will be implemented at each of the recruiting sites in order to document the reasons for non-inclusion in the study (e.g. reason of decline or exclusion).

Transfer of patients that participated in the pilot study of this project (S62004)

To assess the feasibility of this trial, a pilot study (with similar procedures) was performed. The 29 patients that participate in this pilot study will be asked to participate in this full trial. If they consent, their data will be transferred to this study.

4.2.2 Screening

The screening requirements are:

- Clinical diagnosis of ACL tear by history taking and clinical test for diagnosing ACL tears (Lachman + pivot shift). This is routine care and is performed in the first consultation with the medical doctor.
- MRI to confirm the diagnosis of ACL tear. This is standard care in Belgium. This is performed after the first consultation with the medical doctor.

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

The consultations with the medical doctors at baseline, 4, 7 and 12 months post-injury and also the MRI for diagnosis are standard care and will thus be paid by the patient.

4.3 Randomization Procedure / Blinding

4.3.1 Randomization

To ensure the integrity of the Trial, the following randomization procedures have been established: A randomization list will be prepared by the Sponsor's designated staff, not involved in the trial. The randomization list will be incorporated in the data management tool 'REDCap'. After all patients have finished the Trial and the database is locked, the randomization code will be broken for analysis of response data.

Random sequence generation (computer generated, using block randomisation) will be performed and allocation will be concealed. An allocation ratio of 1:1.15 will be applied (130 patients allocated to immediate surgery and 150 patients allocated to conservative treatment). With this we comply with the sample size calculation (see 7.1 Sample Size determination). We will have 1) minimum 130 patients per arm for the primary analysis and 2) 150 patients in the conservative arm for the secondary analysis.

At each participating site, the responsible study nurse/principal investigator will have access to the randomisation tool in REDCap.

4.3.2 Blinding

Given the nature of the trial, blinding of participants and care providers is not feasible.

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

After all participants have completed the Trial, the database will be locked and the collected Trial data will be unblinded to allow analysis of the Trial data.

4.4 Visit schedule and assessments

Below all assessments are described in detail. An overview of the timing and duration of every assessment and further information about who performs the test and whether it is standard care or not, can be found in Table 2.

4.4.1 Baseline data

Demographics (V2)

- BMI (Height & weight), age, leg dominance
- Lifestyle factors that might predict worse ACL reconstruction/recovery outcomes: smoking, education (32), employment type, type of job. These factors will be included as potential confounders in the predictive analyses.
- Comorbidities
- Medication use

Physical investigation of the knee (V2)

- Knee joint effusion
Effusion will be assessed with the grading scale of Sturgill (33). The examiner performs a stroke test and observes the wave of fluid. Subsequently the amount of effusion is quantified by using a 5 point scale (0 is no effusion, 3+ is so much fluid that it is not possible to move). The intra-rater reliability of this grading scale was proved moderate with a kappa value of 0.75 (33).
- Range of motion (ROM)
Passive knee flexion and extension ROM will be assessed with a goniometer. Literature has shown that a baseline knee extension deficit >10 degrees might negatively influence long term outcomes (30).
- Giving away, knee instability
Both the pivot shift test and the Lachman test will be performed to assess passive knee joint stability (34).
During the Lachman test the examiner applies an anteriorly directed force on the tibia to displace the tibia anteriorly relative to the femur. Subsequently, anterior tibial translation is quantified following the IKDC 2000 guidelines: normal (-1 to 2mm), nearly normal (3-5mm), abnormal (6-10mm) or severely abnormal (>10mm), based on the amount of greater tibial translation on the injured side compared to the contralateral knee.
During the pivot shift test the examiner internally rotates the knee and flexes the knee from full extension, while applying valgus stress. A sudden reduction of the anteriorly subluxed lateral tibial plateau indicates a positive pivot shift test. The examiner gives a score following the IKDC 2000 criteria: + (equal, glide), ++ (clunk) or +++ (gross).

MRI (V2)

- The Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS)
This scoring system will be used for assessment of **baseline structural knee joint damage** and monitor the **development of post-traumatic** structural changes (35). This following joint features are assessed with this scoring system: acute osteo-chondral injuries, traumatic and degenerative bone marrow lesions, meniscus morphology and extrusion, osteophytes, collateral and cruciate ligaments including ACL graft, Hoffa-synovitis and effusion-synovitis. In addition to the MRI features assessed with the ACLOAS, the following MRI features will be assessed to detect recovery of the ACL: slope of ACL with respect to the Blumensaat line, distance between the Blumensaat line and the ACL, boundaries and tension of the ACL (17).
- Central MRI reading
All MRI images will be scored by a central reader of UZ Leuven. This central reader will be a physician with expertise in musculoskeletal imaging. The central reader scores the images according to ACLOAS. The score will be shared with the local investigator.
Pseudonymized MRI images of visits 1, 3 and 7 (baseline – 4 months – 36 months post-injury) will be transferred by the participating site to the central reader via LiquidFiles during the study (at the latest 1 month after the study visit).

PROMs (V2)

- Knee injury and Osteoarthritis Outcome Score (KOOS)
This questionnaire assesses the patient's opinion about their **knee symptoms and associated problems**. It can be used over short and long term intervals, to assess changes from week to week induced by a treatment or changes over several years due to a primary injury (26). The KOOS has been validated and is used for patients undergoing ACL reconstruction (36,37).

The KOOS collects data on five knee-specific patient-centered outcomes:

1. KOOS Pain: knee pain
2. KOOS Symptoms: other symptoms such as swelling, restricted range of motion, mechanical symptoms
3. KOOS ADL: disability on the level of daily activities
4. KOOS Sport/Rec: disability on the level of sport and recreation
5. KOOS QOL: knee related Quality of life, mental and social aspects

When answering the questions, patients are asked to consider the previous week. Standardized answer options are given on a Likert scale and each question is assigned a score from 0 to 4. A normalized score is calculated for each subscale (100 indicating no symptoms and 0 indicating extreme symptoms). The KOOS QOL will be seen as primary outcome in our study, the other subscales are secondary outcomes. Since most ACL patients report no/small problems with pain, symptoms and ADL function, there is less room for improvement on those subscales and therefore the subscales Sport/Rec and QOL are recommended to follow-up ACL patients (27,28). We chose for the subscale QOL as primary outcome since not all participants will be involved in sports and therefore the Sport/Rec is less useful in our trial.

Test-retest reliability of the KOOS is high with ICC values between 0.83-0.95 voor KOOS QOL and between 0.61-0.95 for the other subscales (38). The minimal detectable change is 7-7.2 for the KOOS QOL and between 5-12 for the other subscales (38).

- International Knee Documentation Committee Subjective Knee Form (IKDC subjective)

This questionnaire also administers patient's perception of **knee symptoms during daily living and sports activities**. This questionnaire consists of 18 items and a total score is calculated (range 0-100, with higher scores representing lower levels of symptoms, higher levels of function and participation). A study of van Meer et al. (39) compared the KOOS and IKDC subjective to investigate which was the best questionnaire to monitor knee symptoms and associated problems in ACL patients during the first year after injury. They found that the IKDC subjective was more useful to detect short-term changes (higher responsiveness + higher construct validity). The KOOS seems more appropriate for long term follow up (37). We decided to include both questionnaires as we are interested in both short-term changes (3, 6 and 12 months follow-up) and long-term changes (2 and 3 year follow-up).

- **Modified Tegner Score**
This scale will be used to grade the **activity level** of the patients (40). A score is given from 1 (sick leave or disability pension because of knee problems) to 10 (competitive sports) based on the highest level of activities the patient performs regularly. Beside the current activity level, we will also ask the pre-injury activity level to determine when the patient returned to normal activities
- **Illness perception questionnaire (IPQ-R)**
The illness perceptions questionnaire measures patients' beliefs and feelings about their illness (such as whether they think the illness can be cured or controlled by their treatment) (41). Evidence exists that patients' expectations are an important indicator for success of non-operative treatment (32). This questionnaire will be used in a predictive analysis to investigate if they could (partially) predict successful outcomes in the intervention treatment arm (eg. conservative treatment with optional delayed surgery).
- **Tampa Scale for Kinesiophobia**
This questionnaire measures the fear of movement. It is a 11 item scale that uses a 4-point likert scale. Psychological factors such as fear of movement might be an important predictor of outcome after ACL injury, regardless of surgical treatment or not. Hartigan et al. (2013) showed for example that kinesiophobia is related to knee function after surgery (42).
- **The EQ-5D-5L questionnaire**
This questionnaire measures generic health status in 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The sum of the score on the 5 dimensions describes the patient's health state. We will administer this questionnaire for the economic evaluation to compute quality-adjusted life years (QALYs).

Assessment	Time	Duration	Investigator	Retrieved from patient record	Standard care	Protocol specific
Demographics		total: 10 min				
Age	V2		SN	X	X	
Height & weight	V2		SN			X
Smoking status	V2		SN			X
Comorbidities & medication use	V2		SN	X		X
Employment type, education level	V2		SN			X
Physical knee investigation		total: 5 min				
Knee joint effusion	V2		SN		X	
Range of motion	V2		SN		X	
Knee instability tests	V1		PI	X	X	
MRI		total: 30 min		X		
MRI for diagnosis	V1	30 min	Radiologist	X	X	
MRI for follow-up	V3&V7	30 min	Radiologist	X		X
PROMS		total: 40 min				
KOOS	V2-V7	10 min	SN			X
IKDC	V2-V7	10 min	SN			X
Modified Tegner score	V2-V7	1 min	SN			X
IPQ-R	V2	5 min	SN			X
TSK	V2	5 min	SN			X
Health-economic data	V2-V7	10 min	SN			X
Functional tests		total: 30 min				
Single leg hop for distance	V3-V7	10 min	SN			X
Quadriceps and hamstrings strength	V3-V7	20 min	SN	X		X
Adverse events	V3-V7		PI + SN	X		X
Return-to-work & return to pre-injury activity level	V3-V7	total: 10 min	SN			X
Rehabilitation	V3-V7	total 5 min	SN			X

Table 2. Overview of the assessments

4.4.2 Follow-up Visits

All baseline assessments will be repeated during the follow-up visits, except for the MRI which is only performed at 4 and 36 months follow-up. Furthermore functional test will be performed to assess muscle strength of the quadriceps and hamstrings and to assess functional knee stability (single leg hop for distance test).

Physical examination of the knee

- ROM
- Effusion
- Passive joint stability

MRI (only at 4 and 36 months follow-up visit)

- ACLOAS

PROMs

- KOOS

Besides the standard KOOS questionnaire, we will also administer seven anchor questions (27,28,31) that can be used to determine the following responder criteria:

- MIC = minimal important change
- PASS = patient acceptable state
- TF = treatment failure

For example for PASS, the following question is asked: "Considering your knee function, do you feel that your current state is satisfactory?". Patients should answer this question with yes or no. PASS and TF values will be calculated as mean KOOS scores for subjects who responded 'yes' to the PASS and TF question, respectively (31). For MIC, predictive modelling will be used to estimate the smallest change in KOOS score that seems important by the patient (27).

- IKDC subjective
- Modified Tegner Score
- IPQ-R
- TSK
- EQ-5D-5L

Functional tests

- The single leg hop for distance

This functional test assesses knee functional performance. The patient is asked to jump as far as possible on 1 leg and to maintain his/her balance after landing. The task is performed on the injured and uninjured leg. Subsequently the limb symmetry index (LSI) is calculated by dividing the distance jumped on the injured leg by the distance jumped on the contralateral, uninjured leg (43). This test is often used to decide on return-to-sport, with an LSI > 90% as criterium for readiness for return-to-sport (44). Furthermore, performance on this test is correlated with re-injury risk after ACL reconstruction (45).

- Isokinetic strength of the quadriceps and hamstrings

Isokinetic strength of the quadriceps and hamstrings will be measured on an isokinetic dynamometer (Biodex or Cybex), *in the centra that have such device available*. This to assess recovery of strength. For both the quadriceps and hamstrings maximal concentric strength will be

measured at 60°/sec and 240°/sec. Similar to the single leg hop for distance, the symmetry between the strength of the injured leg and uninjured leg will be calculated. Again an LSI of > 90% is often used as criterium for readiness for return-to-sport as a score <90% is correlated with increased risk for re-injury risk after ACL reconstruction (44,45).

Adverse events

The following adverse events will be registered by the study nurse at every follow-up visit:

- 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 ligament, ...)

Furthermore clinical records will be retrospectively reviewed for medical appointments that took place outside the study (e.g. consultation with other medical doctor).

Return to work/ return to pre-injury activity level

A customized questionnaire will be developed to administer the following data:

- Days of sick-leave
- Previous and current occupational level
- Type of job, job-related activities
- Pre-injury sport level
- Time to return to pre-injury activity level

Rehabilitation

A customized questionnaire will be developed to collect information about the rehabilitation:

- Number of physiotherapy sessions + frequency (amount of sessions per week).
- Whether the rehabilitation involved active exercise therapy and the type of exercises. A list of end stage exercises will be provided and the patient has to check which of them were performed during the rehabilitation.
- Whether the patient performed exercises at home or performed strength training (in a fitness center) or not.

4.5 Premature discontinuation of Trial intervention

Participants may voluntarily discontinue from Trial treatment and/or prematurely end their participation in the Trial for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g. via telephone, e-mail, letter) in order to understand the primary reason for this decision and record this information (if given by patient) in the patient's chart and on the appropriate (e)CRF pages.

Patients that do not undergo the treatment that they were allocated to during the randomization, can stay in the Trial. These patients are considered as 'cross-over'.

Patients who will drop out during the study, will not experience any disadvantage because of drop out. They will continue standard care. The follow-up study visits will be cancelled.

We will try to limit the number of drop-outs by the following measures:

- If patients do not show up on a follow-up visit, the study nurse will call them and ask if the patient can fill in the questionnaires digitally. The KOOS is the primary outcome and only takes 5 min to fill this questionnaire, thus patients that have time restrictions, are asked to fill in at least this questionnaire.
- A compensation will be paid to the patients that completed all visits.

The Investigator may also decide at any time during the course of the Trial, to temporarily interrupt or permanently discontinue the Trial if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

Similarly, the Sponsor, Ethics Committee or authorized regulatory authority can decide to halt or prematurely terminate the Trial when new information becomes available whereby the rights, safety and well-being of Trial participants can no longer be assured, when the integrity of the Trial has been compromised, or when the scientific value of the Trial becomes obsolete and/or unjustifiable.

In any such case of early Trial termination and/or treatment interruption/discontinuation, the Investigator will continue to closely monitor the participant's condition and ensure adequate medical care and follow-up.

For participants whose status is unclear because they fail to appear for Trial visits without stating an intention to discontinue or withdraw, the Investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the participant to clarify their willingness and ability to continue their participation in the Trial (e.g. dates of telephone calls, registered letters, etc.).

A participant should not be considered lost to follow-up until due diligence has been completed.

5 Interventions

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

5.1 Intervention group: rehabilitation and optional delayed ACL reconstruction

5.1.1 Rehabilitation program

As mentioned above, all patients will complete rehabilitation with their own physiotherapist. We will give some guidelines and criteria, but it is the physiotherapist's choice how to implement these guidelines in clinical practice. The guidelines are based on the consensus in literature (46–48). The rehabilitation consists of three phases and progression is based on goal-based criteria, not on strict time points (see Table 3). Patients can start with the next phase only if specific goals of the previous phase are achieved. In the first phase the aim is to eliminate effusion and range of motion (ROM) deficits and minimise muscle atrophy. The aim of the second phase is to regain neuromuscular control and to regain $\geq 80\%$ muscle strength and hop performance. The last phase, the return-to-sport phase, aims at regaining $\geq 90\%$ muscle strength and hop performance, while transitioning to sport through sport-specific drills and gradual participation.

Each participating center will assign a physiotherapist of their hospital to the study, who will contact the external physiotherapists. At the start of the study they introduce the study and explain the rehabilitation guidelines. Furthermore they call once between 2 study visits to repeat the rehabilitation guidelines and answer questions. Throughout the rest of the study, the external physiotherapists can contact the assigned physiotherapist as needed for further support and guidance. The contact moments will be registered. Providing this support to external physiotherapists seems recommended as many of them are not familiar with conservative treatment, leaving them with questions and uncertainties.

	Rehabilitation + optional delayed surgery	Immediate reconstruction + rehabilitation	Criteria for progression
Preoperative phase	Not applicable	- Restore full knee extension - Activation hamstrings and quadriceps to avoid atrophy - Patient education - Instruction of post-operative exercises	
Phase 1: acute phase	- Restore full knee extension, patella mobility, full flexion ROM - Eliminate effusion - Restore gait pattern - Improve muscle control and activation - Restore proprioception	- Restore full knee extension, patella mobility, start flexion ROM - Eliminate effusion - Restore gait pattern - Improve muscle control and activation - Restore proprioception	- Full passive knee extension, flexion: Active flexion ROM $0 \geq 115^\circ$ - Minimal/ no joint effusion - Independent walking - Quadriceps strength 60% of contralateral side
Phase 2: progressive strengthening + neuromuscular control	- Restore full knee ROM - Improve lower extremity muscular strength + endurance - Improve proprioception, balance and neuromuscular control	- Restore full knee ROM - Improve lower extremity muscular strength + endurance - Improve proprioception, balance and neuromuscular control	- Full ROM - quadriceps strength 80% of contralateral side - single leg hop test: 80% of contralateral side - no pain or effusion
Phase 3: return to activity/sports	- Normalize lower extremity strength - Improve muscle power + endurance - Perform sport-specific drills - Gradually return to full return to sport	- Normalize lower extremity strength - Improve muscle power + endurance - Perform sport-specific drills - Gradually return to full return to sport	- Strength quadriceps + hamstrings > 90% contralateral side - Single leg hop test: >90% contralateral side

Table 3. Rehabilitation guidelines

5.1.2 Delayed surgery

If a patient of the rehabilitation + optional delayed surgery group 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 (Criteria based on the KANON trial (10)). Optional delayed surgery can occur between randomization and visit 7. The delayed surgery will not be performed within the first 12 weeks post-injury, according to current practice. If a patient of this treatment arm undergoes surgery earlier because of reasons not related with knee instability, he/she will be still be included in the trial. This can for example be a poor judgement of the surgeon in case of serious additional knee lesions (e.g. multiligamentar injuries, additional fractures or meniscal

lesions) or patients of the conservative group who decide themselves to have surgery despite that they do not experience knee-instability.

5.2 Control group: immediate ACL reconstruction and rehabilitation

5.2.1 ACL reconstructive surgery

We will not impose any guidelines on type of ACL reconstruction to keep the trial pragmatic. 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.

Although the type of surgery is not predetermined by the study, we will impose strict criteria for the timing of the surgery. The immediate surgery needs to be performed within 12 weeks after the ACL injury. This to avoid that patients of the immediate ACL reconstruction already had a considerable amount of pre-operative physiotherapy sessions, and thus keeping a clear distinction between both groups.

5.2.2 Rehabilitation program

The same goal-based rehabilitation protocol will be applied as in the intervention group (see Table 3). However, depending on type of surgery, some time-restrictions in allowed ROM and weight-bearing can be imposed by the surgeon. In that case, the physiotherapist has to slightly adapt the rehabilitation protocol.

Rehabilitation starts the first days after surgery. Furthermore, also preoperative rehabilitation sessions can be performed. During these sessions the physiotherapist will work on the knee extension ROM and instruct the patient to do thigh muscle activation exercises to avoid atrophy. Furthermore information about early postoperative exercises and the rehabilitation process may be given to improve self-efficacy of the patient.

Each participating center will assign a physiotherapist of their hospital to the study, who will contact the external physiotherapists. At the start of the study they introduce the study and explain the rehabilitation guidelines. Furthermore they call once between 2 study visits to repeat the rehabilitation guidelines and answer questions. Throughout the rest of the study, the external physiotherapists can contact the assigned physiotherapist as needed for further support and guidance. The contact moments will be registered.

6 Safety – Adverse Event Reporting

6.1 Definitions

6.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or subject during an experiment, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

6.1.2 Adverse Reaction (AR)

An AR is any untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered.

6.1.3 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that results in any of the following:

- Death
- A life-threatening^a experience
- In-patient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes

^a The term “life threatening” in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

6.1.4 Adverse Events of Special Interest (AESI)

The following events should be reported within the same timelines as SAEs:

- 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 ligament, ...)

6.2 Adverse Events that do not require reporting

In general, the following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

Although these events should not be reported to the Sponsor, these should be recorded in the patient's medical notes according to routine practice.

The following events not to be considered as SAEs are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for protocol therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

6.3 Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and in the (e)CRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE page, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs.

The following minimum information should be recorded for each AE:

- AE description
- start and stop date of the AE
- severity
- seriousness
- causality assessment to the study interventions
- outcome

6.3.1 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.
- **Severity:**
 - Severity must be evaluated by an Investigator according to the following definitions:
 - *Mild* – no or transient symptoms, no interference with the subject's daily activities
 - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
 - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality:**
 - *None* – An AE which is not related to the study-related interventions
 - *Unlikely* – An AE for which an alternative explanation is more likely (e.g. concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely
 - *Possible* – An AE which might be due to the study-related interventions. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be ruled out.
 - *Probable* – An AE which might be due to the study-related intervention. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely.
 - *Definitely* – An AE which is known as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

6.3.2 Timelines for reporting

After informed consent has been obtained and after initiation of study-related interventions:

- All AEs, SAEs and AESIs causally related to a study-related intervention will be reported until 30 days after the last study-related intervention or until last follow-up visit (whichever occurs first).

All SAEs and AESI as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by Trial identification.

SAE details will be reported by the Investigator to the Sponsor by completing the SAE form in the (e)CRF.

If an authorised Investigator from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

6.3.3 Follow-up

The Investigator must record follow-up information by updating the medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the trial.

SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All SAEs must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of trial (whichever occurs first).
- *Non-serious AEs* must be followed up until the patient's last study visit, and until all related queries have been resolved.

SAEs after the end of the trial: If the Investigator becomes aware of an SAE with suspected causal relationship to the study-related interventions after the subject has ended the trial, the Investigator should report this SAE within the same timelines as for SAEs during the trial.

6.3.4 Pregnancy

Female subjects must be instructed to notify the Investigator immediately if they become pregnant during the trial. The Investigator must report any pregnancy in subjects during the trial to the Sponsor.

6.3.5 Death

All deaths will be reported without delay to the Sponsor (irrespective of whether the death is related to disease progression, study procedure or is an unrelated event). The sponsor will notify all deaths, as soon as possible after becoming aware, to the Central EC and the EC of the concerned site and provide additional information if requested.

6.4 Reporting requirements to Ethics Committee's (EC's)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs and AESIs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators and based on applicable legislation.

6.4.1 Annual reporting

The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC's containing an overview of all SARs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

6.4.2 Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	AE	AE form	sponsor	as defined in protocol
	SAE	SAE form	sponsor	Immediately (within 24 hours of becoming aware of the event) <u>Exceptions:</u> as defined in protocol
	death	SAE form	sponsor	asap
Sponsor	death	SAE form + narrative	Ethics Committees	asap
	Annual Progress Report	APR template	Ethics Committees	annually

7 Statistics and Data Analysis

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the Trial-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical trial report.

Figure 1 provides an overview of all analyses.

Below the different analyses are further explained. A hierarchical approach of statistical testing will be used. First, non-inferiority will be assessed at 1 year follow-up. Subsequently, if non-inferiority will be confirmed, superiority testing will be performed on the 7 months post-injury data to assess whether rehabilitation with optional delayed ACL reconstruction is better than immediate ACL reconstruction at short term.

The primary analyses will be performed on the intention-to-treat (ITT) population

7.1 Sample Size Determination

The outcome(s) on which the sample size calculation is based upon is the **KOOS QOL** (see above), a self-administrated questionnaire.

Following target difference is important for the key stakeholder groups consulted:

- 1. Patients:** a recent study assessing responder criteria in patients of the KANON trial (28) found that patients report a minimal clinically important change of 13.5 points on the KOOS QOL.
- 2. Clinician:** if patients do equally well (non-inferiority on KOOS QOL, change of less than 7 points) at long term and better at short term (superiority on KOOS QOL, change of more than 13.5 points) in the intervention group compared to the control group.

The calculation of the sample size below used the POWER procedure in SAS 9.4.

7.1.1 Non-inferiority analysis

The outcome for the non-inferiority analysis is the change on the KOOS QOL between the baseline measurement and 1 year after randomization. The sample size was calculated using the power

procedure in 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 (29).

The analysis consists in estimating the difference in mean change-scores between both arms with a one-sided 95% confidence interval. [Corresponding to a 5% significance level] Non-inferiority will be concluded when the lower limit of the confidence interval will be above the non-inferiority margin of -7. An equal treatment effect in both arms and a standard deviation for the change-score of 19 were assumed for the sample size calculation (10).

Assuming a drop-out of 10%, a total number of **260 patients** is required for randomization.

7.1.2 Superiority analysis

The sample size was calculated for demonstrating with a two-sample t-test a difference between the two treatment groups with respect to the change in KOOS QOL score at 7 months follow-up compared to post-injury. Considering equal group sizes, a two-sided 5% significance level, 90% power, the smallest important difference as 13.5 change-points (28), a standard deviation of 18 for the change in KOOS QOL versus baseline (26), and a 10% drop-out rate, the calculation indicates a total sample size of **88 patients**.

Note: The 5% significance level was adopted since a hierarchy of statistical testing will be used. Only if the non-inferiority test is significant at 12 months, the test of superiority at 7 months will be performed since superiority is judged necessary to change practice.

7.1.3 Predictive analysis

A prediction model will be built in the intervention group (rehabilitation and optional delayed ACL reconstruction) with the event of delayed surgery as 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.

7.2 Estimated recruitment rate

Our sample size calculation (see 7.1 Sample Size Determination) 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 the results of our feasibility study and the patient numbers of the participating centra, we estimate to recruit +/- 128 ACL patients per year.

Hospital	Number of ACL reconstructions per year	Expected recruitment per year (based on pilot: 40%)
UZ Leuven	+/- 80	+/- 26
University Hospital of Liège	+/- 120	+/- 38
Clinique Saint-Luc Bouge	+/- 50	+/- 16
Jessa Ziekenhuis Hasselt	+/- 70	+/- 22
UZ Brussel	+/- 70	+/- 25
Total	+/- 345	+/- 138
Sint-Trudo ziekenhuis Sint-Truiden	+/- 80	+/- 26
AZ Vesalius Tongeren	+/- 40	+/- 13

Table 4. Estimated recruitment rate

7.3 Statistical Analysis

Figure 1 provides an overview of all analyses. Below the different analyses are further explained.

The primary analyses will be performed on the intention-to-treat (ITT) population (subjects are included in the groups to which they were randomly assigned, even if they did not complete their treatment). For example: subjects in the conservative group that underwent ACL reconstruction or subjects in the early reconstruction group that did not undergo reconstruction.

This choice was based on the main aim of this trial: informing medical doctors which strategy (immediate surgery or conservative with optional delayed surgery) is most appropriate after acute ACL injury and therefore help them in decision-making to undergo immediate surgery or not. This ITT analysis will closely reflect everyday practice as in real life patients will not always stick to the advice of either therapy.

The as-treated population includes subjects in groups as how they were actually treated. This post-hoc as treated analysis will result in 3 groups: rehabilitation alone, rehabilitation plus early ACL reconstruction, rehabilitation plus delayed ACL reconstruction. However, this analysis will only be explorative as this will be a non-randomized comparison that will probably be biased.

7.3.1 Primary outcome analysis

The primary analysis will compare the intervention group with the control group on their mean change in KOOS QOL at 2 primary endpoints:

- 1) Non-inferiority testing at 1 year post-injury
- 2) Superiority testing at 7 months post-injury

A one-sided 95% confidence interval for the mean difference between groups excluding 7 units in the disadvantage of the conservative treatment will be considered as a demonstration of non-inferiority at 1 year. A two-sided 95% confidence interval for the mean difference between groups excluding 13.5 units in the advantage of the conservative treatment will be considered as a demonstration of superiority at 7 months.

Estimation and testing of these mean differences will be based on a single analysis model. A linear model for repeated measurements will be used, applied to outcome measures at all time points, modelling an unstructured residual variance-covariance matrix to deal with correlations due to the longitudinal data structure. Compared to separate cross-sectional analyses, this approach improves the power and minimizes the effects of possible bias due to drop-out. All patients with at least one outcome measurement are included in the analysis, even if they had no outcome measured at 7 or 12 months. The model includes group, time-point and group by time-point interaction as effects. The mean differences between the groups at 7 and 12 months and their confidence intervals will be estimated as post-hoc tests based on this model. Given the hierarchical approach of statistical testing (superiority testing only if non-inferiority is demonstrated), no correction for multiple testing will be performed.

The primary analysis will be applied to the ITT population. Patients without outcome measures apart from baseline will be excluded.

7.3.2 Secondary outcome analysis

Mean differences at other time-points are obtained as additional post-hoc tests from the model used for the primary analysis.

The analysis of secondary outcome variables will be performed analogously to the primary analysis.

A sensitivity analysis will be performed, repeating the primary analysis using multiple imputation to deal with patients that have no outcome measures apart from baseline. |

7.3.3 Prediction analysis |

A prediction model will be ran on the intervention group (rehabilitation with optional delayed ACL reconstruction). Based on 5 variables we want to assess whether it is possible to predict whether the patients in the intervention group will need surgery or not (binary outcome). The event of 'delayed surgery' was considered as binary outcome and not as time-to-event since the main question is to investigate whether it is possible to predict who will need a delayed surgery. The timing of the delayed surgery is less relevant as the timing is often influenced by several personal factors such as work, school, holiday and also by the availability of the surgeon etc.

A logistic regression model will be used and a backward selection procedure will be applied for model selection. The performance of the model will be quantified by the area under the ROC curve (AUC). Internal validation will be performed by means of a leave-one-out cross validation method to obtain a more realistic estimate of the model performance.

7.3.4 Explorative analysis

A similar method of analysis as described for the primary analysis (intention-to-treat) will be applied to the as-treated analyses.

7.3.5 Measures taken to minimize bias

The methodological shortcomings of the KANON trial as described in the Cochrane review by Monk et al. (9) will be addressed as follows:

1. Selection bias

Random sequence generation (computer generated, using block randomisation) will be performed and allocation will be concealed (sequentially numbered).

2. Performance bias

Given the nature of the trial, blinding of participants and personnel is not feasible. However, bias will be limited as much as possible by explaining the study to eligible patients by a neutral person, by explaining that both treatment arms are considered equal at this moment. Measures will be taken to ensure that the same uniform information is given in all centres.

3. Detection bias

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

4. Attrition bias

Incomplete outcome data because of post-randomization exclusion as in the KANON trial will be avoided by performing the MRI investigation before randomization, which is standard procedure in Belgium (In the KANON trial 14% of randomized patients were not included in the primary analyses because of MRI-findings and findings during surgery post-randomization)

7.4 Procedures to account for missing or spurious data

The primary analysis is based on longitudinal data including all time-points and hence includes all patients with at least one outcome measure apart from baseline. This approach has been shown to provide consistent estimates under missingness-at-random (MAR). MAR occurs when the missingness is not random, but where missingness can be accounted for by model variables or previous outcome measures. Hence, if missingness is group-related, the proposed analysis method corrects for possible resulting bias. Patients with no outcome measures apart from baseline, hence, patients that dropped out before 4 months, are excluded from the primary analysis. A multiple imputation approach will be applied as a secondary and sensitivity analysis, to study the impact of these cases. The imputation model will include group, time, the baseline outcome measurement and patient characteristics.

At each center, a study nurse will track patients and ensure in-time contact with the patient for scheduling the follow-up visits to prevent missing data. Reasons for missing data will be recorded in the eCRF.

7.5 Data collection for economic evaluation

This protocol has been designed that a later economic analysis is possible. The economic analysis is not a part of the trial and the decision to conduct such economic analysis will depend on the effectiveness results of the trial. The planned economic analysis is briefly described below, together with the variables that will be collected for this purpose.

It is hypothesized that a conservative treatment approach with optional delayed surgical reconstruction for an acute ACL injury is at short term superior to immediate surgical reconstruction in terms of patient reported outcome measures and faster return to normal activity levels (work, sports) for the patient at short term. At long term, clinical outcomes are hypothesized to be similar in both groups (49,50). Consequently, decreasing the number of required ACL surgeries and faster return to (work) activities may lead to considerable cost savings. The difference (*incremental*) between both treatment arms lies in the frequency of surgical procedures, associated adverse events and additional rehabilitation program after delayed surgery.

Previous health-economic analyses of the KANON and COMPARE trial show conflicting conclusions (51–53). This may be explained by certain assumptions that are made in these analyses and their specific context. In the proposed trial, the Belgian context will be taken into account. More specific, following aspects from these previous analyses will be addressed as follows:

- **Surgical costs:** both immediate and delayed surgery cost the same per unit. Also the cost of revision surgeries will be taken into account.

- **Rehabilitation costs:** it is expected to have more rehabilitation costs as described by Mather et al. (52) and Kiadaliri et al. (51) in the optional delayed surgical group since patients who receive delayed surgery may need a rehabilitation program for the second time. Costs per rehabilitation session (according to the nomenclature) will be taken into account. Rehabilitation will be performed at a physical therapy practice chosen by the patient.

- The study of Mather et al. (52) focuses on the **risk of osteoarthritis and meniscal surgery** as additional cost. They report more meniscal surgery procedures in the optional delayed surgery group. Kiadaliri et al. (51) report also higher costs for meniscus operations in the optional delayed surgery group. However, the KANON trial showed no difference in development of osteoarthritis and number of meniscal operations between the immediate and optional delayed surgery group. This was also confirmed by a recent systematic review of Saueressig et al. (50); The additional costs for meniscal surgery and consequent rehabilitation should be investigated in more detail (we will perform an additional MRI at 3 years to investigate early cartilage degeneration and meniscus lesions).

- **Use of IMA (InterMutualistisch Agentschap) database and iMCQ (iMTA Medical Consumption Questionnaire):** given the substantial difference in health insurance in Belgium vs Sweden (KANON trial) and the Netherlands (COMPARE trial), this may be critical for correct conclusions. Most important are costs related to rehabilitation, the surgical procedures and productivity loss (e.g. average salary of working Belgian population). Permission from patients and the IMA will be asked to collect Individual data on health care consumption and reimbursement (health insurance and patients' share) for all insured patient, through the IMA database. However, to avoid missing data, a resource-questionnaire will be administered by the patient (the Institute for Medical Technology Assessment (iMTA) Medical Consumption Questionnaire (54)) and data on medical costs will be collected from the system of the participating centers.

- **Productivity loss:** Kiadaliri et al. (51) and Eggerding et al. (53) reported less productivity loss in the optional delayed surgery group. Despite the high costs related to productivity loss, this is not reflected in the cost-effectiveness analyses. Additionally, estimates according to disutility immediate after surgery is based on expert opinion in the analyses of Mather et al. (52). This may need more detailed investigation using a disease-specific questionnaire post-surgery. Productivity loss will be quantified with the iMTA Productivity Cost Questionnaire (iPCQ) (55).

- **Markov cohort decision model:** the state transition probabilities and model parameters will be adapted to the Belgian health care system and based on the findings of the proposed trial and other trials including the KANON and COMPARE trial. (e.g. cycle duration, health states, additional costs, risk of re-injury); in the analyses of Mather et al. (52) a major part of the modelling is based on expert opinions. As stated in the original manuscript, the connection of these experts to the AAOS this may lead to conflict of interest.

- Kiadaliri et al. (51) and Eggerding et al. (53) showed in the as-treated analysis that subjects treated with rehabilitation alone consumed fewer resources than the early ACL reconstruction group. This confirms the tremendous need for the **early identification of individuals who would benefit from a conservative approach** and is therefore one of the primary aims of the proposed project.

- **Baseline risk:** data of a real-world databases (IMA) will be used and combined with the relative treatment effect found in the trial to estimate the incremental benefit. Currently 6700 surgeries are performed each year in Belgium with an estimated cost of 2.1 million euros. However, to our knowledge, no data on indirect costs are available.

- The internationally recommended **EQ-5D-5L will be used** instead of the 36-Item Short Form Health Survey in the KANON Trial.

The health-economic analyses will consider the aspects below:

1) **time-horizon:** short- and long-term data will be considered.

- Mid-term (i.e. 1 year after injury), all patients in both groups should have returned to normal activity
- Long term (i.e. 3 years after injury), patients who received delayed surgery/had complications should have returned to normal activity; all patients are in a steady state

2) **Perspectives** to consider:

- **from a patient perspective:** direct and indirect medical costs for the patient will be collected by a modified version of the iMCQ (56). Additionally, adverse effects related to the surgical procedure will be registered. If consent is given, individual billing data will be collected through the IMA database.
- **from a societal perspective:** direct and indirect medical costs related to the health insurance, productivity loss and associated sickness benefit will be registered (IMA database and a modified version of the IPCQ).

3) **Willingness to pay threshold and discount rate** should be determined according to the Belgian context.

4) **Costs calculation**

Following **direct measures (i.e. through the trial)** will be used to collect data for this purpose:

1) iMCQ will be used (56) to collect direct and indirect (medical) costs. Direct medical costs related to the surgical procedure are hospital stay, surgical costs, medical consults medication use and imaging. Indirect medical costs are transport costs and number of rehabilitation sessions. Additionally, adverse effects related to the surgical procedure will be registered (see above). The participant will be informed that individual billing data will be collected through the IMA database (our collaborator, KCE, has the legal mandate to access billing data).

2) Besides the chosen disease-specific patient reported outcomes, a **generic measure of health outcome** will be administered. The EQ-5D-5L will be used for this purpose. The EQ-5D-5L will be completed each assessment point to have an overview of short and long term beneficial effects.

3) **productivity loss**: the IPCQ, a questionnaire on sickness absences/number of days off work and employment rate will be used to calculate total of lost income due to absence from work (human capital approach).

→ With this information **the incremental cost-effectiveness ratio (ICER)** will be calculated as general outcome of economic benefit (cost-effectiveness) and **Quality-Adjusted Life-Years (QALY)** as outcome of enhanced quality of life (cost-utility analysis).

8 Data handling

REDCap will be used for data management. This online tool will be used for data capture, management and analysis. REDCap consists of a secure Health Insurance portability and Accountability Act compliant.

The study data will be transcribed on a regular basis by study personnel from the source documents onto the REDCap eCRF in a pseudonymised manner*, and transmitted in a secure manner to the Sponsor within the timeframe agreed upon between Sponsor and the sites.

All data relating to the study must be recorded in eCRFs prepared by the investigator. Data must be entered into eCRFs in English. Designated site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The pseudonymized study MRI is transferred to the sponsor through LiquidFiles. The sponsor will send a request to perform the transfer within 1 month after the study visit.

All subjective measurements (e.g. questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided. All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. Proper audit trails are available to demonstrate the validity of the trial data. A copy of the completed eCRFs will be archived at the study site. The CRF data is used to perform statistical analysis for the trial.

**pseudonymisation” means the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person. The participant’s name or other identifiers will be stored separately from the Trial data and replaced with a unique code to create a new identity for the participant |*

Data handling and data flows for the Trial are summarized below and will be described in more detail in the Trial-specific Data Management Plan (DMP).

8.1 Data Collection Tools and Source Document Identification

8.1.1 Operational aspects

Data collection, handling, processing and transfer for the purpose of this Trial will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures, as follows:

8.1.1.1 Data collection

Source Data will be collected and recorded in the Trial participant’s files/medical records.

If applicable, worksheets may be used for capturing some specific data in order to facilitate completion of the eCRF. Any such worksheets will become part of the Trial participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the Trial).

It remains the responsibility of the Investigator to check that all data relating to the Trial, as specified in the Trial protocol, are entered into the eCRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

eCRFs are provided by the Sponsor for each participant. The Trial data will be transcribed from the source records (i.e. participant’s medical file or Trial-specific source data worksheets) into an eCRF by Trial Staff. Transcription to the eCRF will be done as soon as possible after a participant visit and in a pseudonymized manner using a unique identifier assigned by the Sponsor.

The eCRFs will be available for review at the next scheduled monitoring visit (as applicable) and shall under no circumstances capture personal data such as but not limited to the participant or their relative(s) name, home address, contact details, full date of birth medical record number (e.g. UZ Leuven EAD number), social security number etc.

8.1.1.2 Data Validation

All data relating to the Trial must be prepared and validated by the Investigator. Any eCRF entries, corrections and alterations must be made by the Investigator or other authorized Trial staff.

Proper audit trails must be available to demonstrate the validity of the Trial data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e. who made the correction/addition, when and why), without obliterating the original data entry information.

8.1.1.3 Data Management

The Trial Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A Data Management Plan

(DMP) will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed and, as applicable, the role and responsibilities of the Data Safety Monitoring Committee (DSMB)

8.1.1.4 Data Transfer

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the Trial-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Trial must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor (see 8.1.2. legal requirements).

8.1.2 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR) and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, and will maintain a Trial Master File (TMF)/Investigator Site File (ISF) containing all Trial documents as specified in ICH-GCP E6(R2) Chapter 8 entitled “Essential Documents for the Conduct of a Clinical Trial”, and as specified by applicable regulatory requirement(s).

The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the European General Data Protection Regulation). The receiving party will be bound by contractual agreement to keep the transferred data confidential at all times and to only process the data for the purpose of the Trial. To this end, appropriate Data Transfer Agreements (DTAs) will be established.

8.2 Audits and Inspections

The Investigator will permit direct access to Trial data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such (e)CRFs, source records and other Trial related documentation (e.g. Investigator Site File, the Trial Master File, pharmacy records, etc.) must be kept current, complete and accurate at all times.

8.3 Monitoring

In accordance with ICH-GCP E6(R2) the Sponsor is responsible for monitoring the Trial to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the Trial procedures have been followed as shown in the approved protocol, and that relevant Trial data have been collected and reported in a manner that assures data integrity. To this end Source Data will be compared with the data recorded in the eCRF. A risk-based approach will be applied to determine the extent of

monitoring activities and monitoring of the Trial will be performed by qualified individuals (independent from the site Trial staff), as applicable.

Monitoring of the Trial will be conducted periodically by Trial monitors of CTC of UZ Leuven (independent from Trial staff).

The Sponsor and Investigator/Participating Site will permit direct access to the Trial data and corresponding Source Data, and to any other Trial related documents or materials to verify the accuracy and completeness of the data collected. More details about the monitoring strategy are described in the Trial specific Monitoring Plan (MP).

8.4 Archiving

As specified in ICH-GCP E6(R2) section 8.1 Addendum, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Trial Documents (including but not limited to Source Documents, completed and final (e)CRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Trial.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Trial.

The Sponsor is responsible for archiving Trial specific documentation (such as but not limited to the Trial protocol, any amendments thereto, the final Clinical Study Report (CSR) and the Trial database) according to ICH-GCP E6(R2). Source data and site-specific Trial documents (such as but not limited to the original signed ICFs) will be archived by the participating site(s) according to local practice, and for at least 25 years following termination of the Trial. Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

9 Ethical and Regulatory Considerations

9.1 Ethics Committee (EC) review & reports

Before the start of the Trial, this protocol and other related documents (e.g. ICF, advertisements, IB, etc.) will be submitted for review to the EC and to the relevant CA for Trial authorization. The Trial shall not commence until such approvals have been obtained and until other relevant essential Trial documents, such as duly signed contract agreements, evidence of adequate Trial financing etc. are in place.

It is the responsibility of the CI to produce the Annual Progress Report (APR) and submit to the EC/CA within 30 days of the anniversary date on which favourable opinion to start the Trial was given, and annually until the Trial is declared ended.

The CI shall notify the EC/CA of the end of the Trial. Should the Trial be temporarily suspended or, ended prematurely, the CI will notify the EC/CA and include the reasons for suspension/premature termination within 15 days of the decision. The CI will submit a final report with the results of the study, including any publications/abstracts, to the EC/CA within 1 year of trial termination or within 6 months for paediatric Trials.

9.2 Peer review

This study protocol was peer reviewed by the Belgian Health Care Knowledge Centre and an independent expert (Prof. Filip Staes, dept. of Rehabilitation Sciences of KU Leuven). Peer review was conducted by this expert to the professional and scientific standards expected for clinical studies.

9.3 Regulatory Compliance

The Trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical Trials in the EU as provided for in Directive 2001/20/EC or EU Regulation 536/2014, as applicable, and any subsequent amendments, as well as in compliance with ICH-GCP E6(R2) guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended), and with the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

9.4 Protocol / GCP compliance

The Trial must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Trial participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the Trial data are credible, reliable and reproducible.

The Investigator and Trial team acknowledge and agree that prospective, planned deviations or waivers to the protocol are not permitted under applicable regulations on clinical studies. However, should there be an accidental protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Deviations should also be reported to the EC as part of the EC's continued review of the Trial (e.g. through the ASR, APR, etc.). Protocol deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such recurring protocol deviations could potentially be classified as a serious violation of ICH and/or the protocol.

It is understood that "a serious violation" is likely to affect to a significant degree:

- the safety or physical or mental integrity of the Trial participants; or
- the scientific validity of the Trial

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Trial, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the EC at the Trial site should be informed according to local procedures and regulations.

9.5 Data protection and participant confidentiality

The Trial will be conducted in compliance with the requirements of the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR including the Belgian Privacy Act of 30 July 2018 on the protection of privacy in relation to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR. (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9.6 Insurance

The Participating Site, the Investigator and Sponsor shall have and maintain in full force and effect during the term of this Trial, and for a reasonable period following termination of the Trial, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

Art 29 of the Belgian Law relating to experiments on human persons dated May 7th, 2004 applies. Prior to the start of the Trial, the Sponsor shall enter into an insurance contract in order to adequately cover Trial participants from Belgian sites in accordance with art. 29 of the said law.

9.7 Amendments

Unless for urgent reasons as specified in ICH-GCP E6(R2) section 4.5.4, amendments must not be implemented prior to EC and/or CA review and/or approval, as applicable.

In accordance with the Belgian law of May 7th 2004 regarding experiments on humans, the Sponsor may develop a non-substantial amendment at any time during the Trial. The EC will provide a response in accordance with timelines defined by applicable regulations. It is the Sponsor's responsibility to assess whether an amendment is substantial or non-substantial for the purpose of submission to the EC.

Amendments to the Trial are regarded as 'substantial' when they are likely to have a significant impact on the safety or physical or mental integrity of the clinical Trial participants, or the scientific value of the Trial.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

9.8 Post-Trial activities

According to the latest version of the Declaration of Helsinki: "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process" and that "in clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions."

10 Research Registration, Dissemination of Results and Publication Policy

The Declaration of Helsinki (latest version) and European and Belgian regulations require that every research Trial involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Trial.

In addition, the CI will fulfil their ethical obligation to disseminate and make the research results publicly available. As such the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, Sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

Publications will be coordinated by the CI. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

For multicentre Trials, it is anticipated that the primary results of the overall Trial shall be published in a multicentre publication.

Participating Sites are not allowed to publish any subset data or results from the Trial prior to such multicentre publication.

Any publication by a Participating Site must be submitted to the Sponsor for review at least thirty (30) calendar days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

11 Intellectual Property

Any know how, inventions, methods, developments, innovations, discoveries and therapies, whether patentable or not, arising from the Trial or made in the performance of the Trial protocol ("Inventions") shall vest in the Sponsor. The Participating Site, its employees and Investigator(s) shall promptly disclose to the Sponsor any such Inventions. Parties have expressly agreed that any and all Trial data as collected and prepared in the performance of the Trial protocol shall be the sole property of Sponsor unless otherwise agreed in the clinical trial agreement.

12 Joint Commission International (JCI)

In order to ensure the same quality and safety standards in patient care for clinical research as commonly applied by the Sponsor in its regular activities, and in accordance with JCI standards, the Sponsor shall comply with the following obligations: (a) the Sponsor will use trained and qualified employees or contractors to manage and coordinate the Trial; (b) the Sponsor will ensure that multi-center Trial reporting is reliable and valid, statistically accurate, ethical, and unbiased. (c) the Sponsor will not grant incentives, other than standard compensations and reimbursement of costs, to Trial participants or to participating site's staff that would compromise the integrity of the research; (d) the Sponsor is responsible for monitoring and evaluating the quality, safety, and ethics of the Trial and will respect the participating site's policies and processes when performing such monitoring and evaluation activities; (e) the Sponsor will protect the privacy and confidentiality of the Trial participants in accordance with all applicable laws.

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APPENDICES

Appendix 1: Clinical trial protocol history

Appendix 2: Data Processing Annex

Appendix 3: Risk assessment of the trial intervention

Appendix I: Clinical trial protocol history

Original CTP version:	I.6 dated 30/01/2023 14/06/2023
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Amendment #1:	V3 dated 14/06/2023
Modifications made / Reason for amendment:	
7.2	Adding UZ Brussel as participating site + removing CHC Montlegia as participating site (CHC was not longer interested and had no SIV)
4.5	Detailed description of what to do when a patient does not undergo the allocated treatment (=cross-over).

Amendment #2:	<CTP version nbr> dated 14/06/2023
Modifications made / Reason for amendment:	
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>

Appendix 2: Data Processing Annex (DPA)

Definitions:

- “Protocol” means the document entitled |Protocol_IODA full trial_v1.6 |containing the details of the academic Trial as developed by the Sponsor and approved by the relevant Ethics Committee.
- “Sponsor” means University Hospitals Leuven (UZ Leuven).
- Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 (“Data Processor”) for the Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 (“Data Controller”).
- “Applicable Law” means any applicable data protection or privacy laws, including:
 - a) the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation (“GDPR”);
 - b) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;
- “Personal Data” means any information relating to an identified or identifiable natural person (“Data Participant”), including without limitation pseudonymized information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1. The Data Processor is instructed to process the Personal Data for the term of the Trial and only for the purposes of providing the data processing tasks set out in the Protocol. The Data Processor may not process or use Personal Data for any purpose other than a Data Participant’s medical records, or other than provided in the instructions of the Trial protocol, including with regard to transfers of personal data to a third country or an international organization, unless the Data Processor is required to do so according to Union or Member State law.
2. Data Processor shall at all times maintain a record of processing of Personal Data in accordance with Applicable Law and if the Data Processor considers an instruction from the Data Controller to be in violation of the Applicable Law, the Data Processor shall promptly inform the Data Controller in writing about this.
3. The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.
4. The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:
 - (i) accidentally or unlawfully destroyed, lost or altered,
 - (ii) disclosed or made available without authorization, or
 - (iii) otherwise processed in violation of Applicable Law.
5. The appropriate technical and organizational security measures must be determined with due regard for:
 - (i) the current state of the art,
 - (ii) the cost of their implementation, and
 - (iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.
6. Taking into account the nature of the processing, the Data Processor shall assist the Data Controller, by means of appropriate technical and organizational measures, insofar as this is possible, in fulfilling its obligation to respond to requests from Data Participants pursuant to laws and regulations in the area of privacy and data protection (such as, the right of access, the right to

- rectification, the right to erasure, the right to restrict the processing, the right to data portability and the right to object)
7. The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.
 8. The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to the Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with the Data Processor, the findings as described under 10) (ii) below to the Data Controller.
 9. The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.
 10. The Data Processor must without undue delay in writing notify the Data Controller about:
 - (i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,
 - (ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or
 - (iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the Data Participants or from third parties.
 11. Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 10) (ii)(a) above will contain at least the following information:
 - (i) the nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Participants concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);
 - (ii) the likely consequences of the Personal Data breach;
 - (iii) a proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.
 12. The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).
 13. The Data Processor must promptly and reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 10) (ii) above and (b) any requests from Data Participants under Chapter III of the GDPR, including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests.
 14. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where

the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 10) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

15. The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.
16. Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.
17. The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA.

Appendix 3: Risk assessment of the trial intervention

Risks associated with trial interventions

☒ **A** ≡ **Comparable to the risk of standard medical care**

☐ **B** ≡ Somewhat higher than the risk of standard medical care

☐ **C** ≡ Markedly higher than the risk of standard medical care

Justification: The only intervention that will occur is the randomisation to either immediate surgery or conservative treatment with optional delayed surgery for acute ACL injury. Both treatment options are currently applied in daily clinical practice and do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.

Both treatments are supported by published scientific evidence on the safety and efficacy.