



KU LEUVEN

CLINICAL TRIAL PROTOCOL

A pilot study to investigate the feasibility of conducting a randomized controlled trial that compares Immediate versus Optional Delayed surgical repair for treatment of acute Anterior cruciate ligament injury - IODA pilot trial

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Sponsor

University Hospitals Leuven (UZ Leuven)
Herestraat 49, B-3000 Leuven

Coordinating Investigator

Prof. Koen Peers

KCE Trials Number

INV18-1158

Clinical Trials Register:

NCT04408690

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.

CLINICAL TRIAL PROTOCOL HISTORY

CTP / Amendment #	Date	Reason for amendment
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LIST OF PARTICIPATING SITES

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SIGNATURES

Title: A pilot study to investigate the feasibility of conducting a randomized controlled trial that compares Immediate versus Optional Delayed surgical repair for treatment of acute Anterior cruciate ligament injury - IODA pilot trial

The undersigned confirm that the following protocol has been acknowledged and accepted and that they 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 Regulation 536/2014 as soon as applicable and any subsequent amendments, the ICH-GCP 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 on clinical trials on medicinal products for human use as soon as applicable, the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian law implementing the GDPR as soon as applicable, the Belgian Law of August 22nd 2002 on patient rights and the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical Trial without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the Trial publicly available through publication or other dissemination tools, in accordance with this protocol without any unnecessary delay and that an honest accurate and transparent account of the Trial will be given; and that any discrepancies from the Trial as planned in this protocol will be explained.

For and on behalf of the Study Sponsor (UZ Leuven), Chief investigator:	
Signature: 	Date:/...../.....
Name: Prof. Koen Peers Position: Head of the Department of Physical Medicine and Rehabilitation, UZ Leuven	
Statistician	
Signature:	Date:/...../.....
Name: Annouschka Laenen Position: Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat)	
PI of the University Hospital of Liège	
Signature: 	Date:/...../.....
Name: Prof. Jean-Francois Kaux Position: Head of the Department of Physical Medicine and Rehabilitation, CHU Liège	

For acknowledgement on behalf of the funder, KCE	
Signature: 	Date:/...../.....
Name: Position: Researcher KCE Trials	

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Statistician	Annouschka Laenen, annouschka.laenen@kuleuven.be

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LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
ACL	Anterior Cruciate Ligament
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Coordinating Investigator
CTP	Clinical Trial Protocol
DMC	Data Monitoring Committee
EC	Ethics Committee
FPFV	First Patient First Visit
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
LPLV	Last Patient Last Visit
PI	Principal Investigator (Participating Site)
PROM	Patient Reported Outcome Measures
REC	Research Ethics Committee
SAE	Serious Adverse Event
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

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

FUNDING AND SUPPORT

Funder	Kind of Financial or Non-Financial Support
BELGIAN HEALTH CARE KNOWLEDGE CENTRE, Administrative Centre Botanique (Doorbuilding) Boulevard du Jardin Botanique 55 B-1000 Brussels, Belgium	

ROLES AND RESPONSIBILITIES

PRINCIPAL INVESTIGATOR

The PI is responsible for the conduct of the Trial at his/her Participating Site, must protect the rights, safety and well-being of the participants and ensure adequate supervision of the conduct of the Trial at the Participating Site. If any tasks are delegated, the PI must maintain a log of appropriately qualified persons to whom he/she has delegated specified Trial-related duties. The PI must ensure that there is adequate and documented training for all Trial staff participating in the conduct of the Trial. It is the PI's responsibility to supervise the conduct of the Trial.

SPONSOR

UZ Leuven/KU Leuven as mentioned in KEY TRIAL CONTACT shall act as sponsor of the Study, as defined in the Law of 2004, and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2004. UZ Leuven/KU Leuven shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with the Study Subjects or the Regulatory Authorities as sponsor of the Study. UZ Leuven/KU Leuven acknowledges and agrees for the avoidance of doubt that KCE shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and UZ Leuven/KU Leuven shall make no representations whatsoever in this respect.

TRIAL STEERING COMMITTEE

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. The TSC will monitor trial progress, conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

The TSC consist of the Chief Investigator (Prof. Koen Peers), experts of the main institution (Prof. Filip Staes, Dr. Stijn Bogaerts and Dr. Pieter Berger), trial statistician (Annouschka Laenen), economic expert (Prof. Koen Putman), a representative of the other participating site (Prof. Jean-Francois Kaux), a representative of the sponsor (*Clinical Trial Center*), 2 patient representatives (Frederik Lenaerts and Steve Stroobants) and a representative of the funder. The TSC will meet on average 2 times per year or as necessary when adapted to the stage of the trial (set-up, conduct, analysis).

TRIAL MANAGEMENT GROUP

The day-to-day management and work of the study will be performed by the Trial Management Group (TMG) which is distinct from the TSC. The TMG has the responsibility to run the trial, monitor the trial and prepare the study report. The TMG will be lead by one project manager (Dr. Annemie Smeets).

DATA MONITORING COMMITTEE

The trial is categorised as a low risk intervention clinical trial (see justification in Appendix I) so no data monitoring committee is necessary.

TRIAL SYNOPSIS

Title of clinical Trial	A pilot study to investigate the feasibility of conducting a randomized controlled trial that compares Immediate versus Optional Delayed surgical repair for treatment of acute Anterior cruciate ligament injury - IODA pilot trial
Protocol Short Title Acronym	IODA pilot trial
Trial Phase (I, II, III, IV)	Phase III
Sponsor name	University Hospitals Leuven (UZ Leuven)
Coordinating Investigator	Prof. Koen Peers
Contact Address	Herestraat 49 – 3000 Leuven
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Contact Phone	+32 16 34 21 80
Principal Investigators and Participating Sites	- UZ Leuven (Prof. Koen Peers) - University Hospital of Liège (Prof. Jean-Francois Kaux)
Medical condition or disease under investigation	Acute anterior cruciate ligament (ACL) injury
Trial rationale of clinical Trial	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 explore the feasibility to recruit ACL deficient patients for a future definitive randomized controlled trial that 1) compares the effectiveness of conservative treatment with optional delayed surgical reconstruction (intervention group) versus immediate surgical ACL repair (control group) and 2) predict which patients will benefit from the conservative treatment.
Secondary objective(s)	1) To assess the feasibility of the protocol and 2) to assess the adherence of the participants to the treatment arm that they were allocated to.
Trial Design	A parallel, multicentric, pragmatic, pilot randomised controlled trial comparing immediate ACL reconstructive surgery (control group) with optional delayed surgery (intervention group).
Endpoints	1) 4 months after first patient first visit 2) When 5 patients per site have completed the 3 month follow-up visit
Intervention	Rehabilitation and optional delayed ACL reconstruction.
Control	Immediate ACL reconstruction and rehabilitation
Maximum duration of treatment of a Participant	6 months
Maximum duration of Trial	14 months

Anticipate First Patient First Visit (FPFV)	Q3 2020
Anticipate Last Patient Last Visit (LPLV)	Q1 2021

TRIAL FLOWCHART

Screened

Patients assessed for eligibility (V1)

Excluded:

- Not meeting inclusion criteria
- Declined to participate
- Other reasons

Enrolment

Patients randomized (V2)

Baseline assessment (V2)

Allocation

Allocated to intervention

= conservative treatment of ACL injury with optional delayed surgery

- Received allocated intervention
- Did not receive allocated intervention
→ specify reasons in eCRF

Allocated to control

= immediate surgical repair of ACL and post-surgical rehabilitation

- Received allocated intervention
- Did not receive allocated intervention
→ specify reasons in eCRF

Follow up

Follow-up assessments

- 3 months FU (V3)
- 6 months FU (V4)

- Lost to follow-up
- Discontinued intervention
→ specify reasons in eCRF

- Lost to follow-up
- Discontinued intervention
→ specify reasons in eCRF

Figure 1 Trial Flow chart

I Background and Rationale

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. Often 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) (Lie et al. 2019) and athletes who return to sport have a high chance to sustain a re-injury (Paterno et al. 2014).

In Belgium, standard care for ACL injuries is reconstructive surgery. It was believed for years that reconstruction of the ACL is necessary to restore mechanical knee stability in order to avoid long term disadvantages such as persistent knee instability and episodes of giving away, re-injury and PTOA and ultimately also a prerequisite for a safe return to sport (Thorstensson et al. 2009). However, evidence assessing treatment outcomes after surgical ACL reconstruction do not support these beliefs. Moreover, studies showed that about 21-48% of the patients who underwent an ACL reconstruction have degenerative changes (Øiestad, Holm, and Risberg 2018; Øiestad et al. 2009; Lie et al. 2019) and up to 29.5% suffer a new ACL injury within 2 years after return to sport (Paterno et al. 2012). Furthermore, Ardern et al. (Ardern et al. 2014) 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 necessarily imply restoring of normal knee joint function and protection to long-term disadvantages. Moreover it is unclear whether stabilising the knee joint surgically with a graft results in any benefit for the knee joint compared to conservative treatment.

Indeed, systematic reviews comparing operative and non-operative management of ACL rupture have found similar long-term outcomes, including physical activity levels, pain, symptoms, knee osteoarthritis and quality of life (Filbay et al. 2015). Studies indicate that exercise therapy is an essential part to help to improve knee strength and function. Even a short 5-week exercise therapy program leads to significant improvement in knee function early after ACL injury (Eitzen et al 2010). Rehabilitation of ACL injuries should progress goal-based rather than time-based and consist of a wide range of exercises (Van Melick et al. 2016).

The only randomized controlled trial (KANON trial) comparing early reconstruction plus exercise therapy, versus exercise therapy with optional delayed ACL reconstruction, found no difference in patient-reported, structural or functional outcomes at 2 and 5 years follow-up (R. Frobell et al. 2010; R. B. Frobell et al. 2013). The latter strategy substantially reduced the frequency of surgical reconstructions, with only 51% of the optional delayed cohort eventually going into surgery. (Frobell et al. 2010 and 2013). However, there are a few limitations associated with the KANON trial. First of all, the sample size was small and only limited to young active individuals (age between 18-35 year) which jeopardizes generalizability. Furthermore according to the GRADE methodology, the study is considered of low overall quality 3. In particular the high risk of performance and detection biases and the unclear risk of attrition bias, because of an imbalance in the post-randomisation exclusions, caused this low score.

Despite the lack of high quality evidence that surgical reconstruction is better than non-operative treatment, 6700 ACL reconstructive surgeries are performed in Belgium yearly. Inherent risks to an ACL reconstructive surgery are continued anterior knee pain, infection, bleeding, arthrofibrosis and

re-rupturing of the ACL graft, occurring in approximately 5.2% (Lai et al 2018). Moreover, high economic costs are associated with surgical treatment of ACL injuries. In Belgium, for surgery alone a cost of 2.1 million was registered at the National Health Institute in 2017. Applying the results of the KANON trial in Belgium, considering an optional delayed approach would lead to a reduction of approximately 50% in ACL surgeries and a cost saving of around 1.45 million euros per year for the National Health Institute. This number does not take into account other health-related expenses such as rehabilitation, sick leave, etc. Additionally, consultation with patient groups confirmed the need of the proposed project and highlighted the advantages of a conservative approach in terms of better and faster clinical outcomes. This because, iatrogenic knee joint damage due to surgery is avoided, resulting in less pain and faster return to normal activities such as work and sports. Therefore, the current surgical treatment standards, which are highly influenced by the biased beliefs of patients and medical doctors towards surgery (Thorstensson et al. 2009), should be re-evaluated, and a non-operative approach with rehabilitation should be considered. This should be assessed through a randomized controlled trial that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical reconstruction of an acute ACL injury. Furthermore, future research should assess whether it is possible to discern which acute ACL ruptures need surgical treatment, versus which can be treated conservatively. Several patient-specific variables might influence if a patient will experience prolonged knee instability requiring delayed surgery. We hypothesize that MRI findings (Belle van Meer et al. 2014), PROMS (Filbay et al. 2017) but also psychological aspects such as self-efficacy and expectations and beliefs regarding conservative therapy (Warren R Dunn et al. 2016) are important predictors.

Before we start with a large, adequately-powered RCT that compares both treatment options, we will run a pilot study that assesses the feasibility to recruit ACL patients for such RCT. This seems necessary, as many patients still believe that timely surgery is a prerequisite for restoring knee function, for returning to sports and for preventing cartilage degeneration. These preferences for surgery might affect recruitment and adherence to the protocol. Therefore, we will perform a pilot study that demonstrates whether a large RCT is feasible with regard to 1) participant recruitment, 2) adherence to the treatment arm they were allocated to and 3) protocol feasibility. The findings of this pilot study will help deciding about progressing to a future definitive RCT.

If recruitment turns out to be feasible, the data of this pilot study will be used in the definitive, full trial. The patients participating in this pilot trial, will be asked to continue with the full trial that will have a longer follow-up period.

2 Assessment and management of risk

The trial is categorised as a low risk intervention clinical trial (see justification in Appendix I: Risk assessment of the trial intervention(s)).

3 Trial Objectives and Design

An overview table of the different objectives and endpoints can be found on page 19 (Figure 2).

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

3.1 Primary objective

The primary objective of this pilot trial is to demonstrate the feasibility to recruit patients that agree to be randomized.

The primary objectives of the trial are as follows:

- To assess how many eligible patients **accept** to participate in the RCT that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical reconstruction of an acute ACL injury.
- To explore why eligible patients are not willing to participate in an RCT that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical reconstruction of an acute ACL injury.
- To assess the percentage of all ACL patients in 2 Belgian hospitals that are **eligible** to participate in an RCT that compares the effectiveness of immediate surgical repair versus conservative treatment with optional delayed surgical reconstruction of an acute ACL injury (the inclusion criteria can be found on page 20).
- To determine whether certain inclusion or exclusion criteria were too open or too restrictive.

3.2 Secondary objective

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

The secondary objectives of the trial are as follows:

- To investigate the number of patients that received the allocated treatment
- To investigate the number of patients that cross-over between groups (e.g. number of patients that received the other treatment then allocated)
- To explore why patients crossover between groups
- To determine the amount of drop-outs during follow-up
- To explore why patients drop-out after randomization
- To assess for each questionnaire and functional test, the number of patients that completed these assessments.
- To explore why patients did not complete an assessment.

3.3 Primary endpoints

A first interim analysis will be performed 4 months after the last study site has been initiated, in order to assess the feasibility of recruitment. We will assess the number of patients with an acute ACL injury that has been screened, the number of patients that was eligible to participate and the number of patients that signed the informed consent (=primary objective).

Furthermore we will explore the reasons why eligible patients decided to not participate in the study.

Finally, we will investigate whether the inclusion and exclusion criteria are too narrow/wide.

A recruitment of at least 50% of the expected recruitment rate is necessary to continue with the study (see page 37: Sample Size Determination & planned recruitment rate).

3.4 Secondary Endpoints

A second analysis will be performed when at least 10 patients of each site have returned for Visit 3. At this time point we will assess the secondary objectives, namely 1) adherence to the protocol and 2) protocol feasibility.

	Primary endpoint	Secondary endpoint
Primary objective	Feasibility of recruitment - Number of recruited patients (>29 /4months) - Reasons for not participating	
Secondary objectives		Feasibility of protocol - Completion of questionnaires and functional tests Adherence to allocated treatment arm - Number of patients that did not received allocated treatment arm

Figure 2. Overview of the objectives and endpoints

3.5 Trial Design

A parallel, multicentric, pragmatic randomised controlled pilot trial comparing immediate ACL reconstructive surgery (control group) with optional delayed surgery (intervention group) will be performed. (see Flow Chart on page 14).

The study will run simultaneously in 2 Belgian university hospitals. Participants will be recruited at the department of Orthopaedics and department of Physical Medicine and Rehabilitation of the participating sites.

If recruitment turns out to be feasible, the patients participating in this pilot trial, will be asked to continue with the full trial that will have a longer follow-up period. To allow for use of the data, the variables that are considered necessary for evaluation of the research question in a large RCT will be collected during this PILOT study.

4 Trial Population / Eligibility Criteria

4.1 Inclusion criteria

Patients eligible for inclusion in this trial have to meet **all** of the following criteria:

1. Rotational trauma to a previously uninjured knee within the preceding 4 weeks
2. Medical diagnosis of ACL insufficiency including MRI (both partial and complete ruptures)
3. Minimum of 18 years

4.2 Exclusion criteria

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

1. Patient has 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. Any disorder, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
4. Female who is pregnant **or plans to become pregnant in the first 3-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...).

4.3 Expected Duration of the Trial

4.3.1 Full trial duration

Time point	Event
Month 0	Contract signature
Month 1	Final protocol EC submission
Month 2-3	Data base ready
Month 4 – 6	First patient first visit
Month 8 – 10	Interim analysis Decision to continue the pilot trial if recruitment is >50% of expected recruitment
Month 12	Last patient randomized Database lock for analysis of secondary objectives
Month 14	Final report ready Decision on progression to definitive RCT

Table 1: Expected duration of the trial

4.3.2 Table of trial procedures for a single patient

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

Table 2: Trial procedures for a single patient

* a detailed description of all assessments can be found in 6.4 Visit schedule and assessments on page 29; [#] the following PROMS will be assessed at V2-V4: KOOS, IKDC, Modified Tegner score + sport participation, EQ-5D-5, IPQ-R; ¹Optional delayed surgery can occur after randomization; ²Immediate surgery has to be performed within 12 weeks after injury

4.4 Screening failures

Patients not meeting the inclusion criteria will be referred back to the orthopaedist or medical doctor for standard care of the ACL injury.

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 orthopaedic surgeon.

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 (Wilk and Arrigo 2017; Melick et al. 2016; Cavanaugh and Powers 2017). The rehabilitation consists of three phases and progression is based on goal-based criteria, not on strict time points (see Table 3, page 25). 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.

	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 program

5.1.2 Indications for 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, Frobell et al 2010). Optional delayed surgery can occur between randomization and visit 4. 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 kept in the trial for intention-to-treat analysis but excluded for per protocol analysis. 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 centra. All details of the surgery will be noted down in the patient register. The following information of the surgery will be copied to the eCRF as it might be used for exploratory analysis: graft type, lateral augmentation or not, treatment of concomitant injuries.

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 above). However, depending on the 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.

5.3 Consent withdrawal

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 will always be respected without prejudice to further treatment. This will be documented by the PI in the patient's medical record. The PI will take into account the consequences of such withdrawal concerning the use of personal data / study data.

5.4 Lost to Follow-up

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.

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.

6 Trial Procedures

6.1 Recruitment

We will recruit ACL patients from 2 participating centres, over a period of 4 months. The following centres will participate:

- UZ Leuven (Prof. Koen Peers)
- University Hospital of Liège (Prof. Jean-Francois Kaux)

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. This visit is not yet to be considered a trial-related visit.

During the second consultation (V1) 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 not to miss potential candidates there will be a weekly check of the planning of both the orthopaedic and physical medicine department at each centre and a reminder to the treating physicians will be sent in case potential candidates are scheduled for an appointment.

Furthermore we will put posters and distribute brochures in the waiting rooms of the participating centres to promote the study and convince patients to participate in the study. All potential candidates will be personally approached by their medical doctor. The promotion material will thus only be used to promote the study and not for direct recruitment.

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). This will be anonymously recorded. The following categories will be used for recording: medical reasons, beliefs that surgery is necessary, beliefs that no surgery is necessary, time-issues and fear of surgery.

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.

All consultations with the medical doctors and also the MRI for diagnosis are standard care and will thus be paid by RIZIV/INAMI and the patient. The extra MRI at 3 months will be covered by the study budget.

6.2 Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at his site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided and documented on the delegation log.

Prior to signing the informed consent the PI, and/or delegate will discuss about the nature and objectives of the trial and possible risks associated with their participation with the potential participant. An information leaflet and consent document (approved by the EC and in compliance with GCP, local regulatory requirements and legal requirements) will be used to explain the trial. The potential participant will have the opportunity to ask questions during these contacts. A contact phone number and e-mail address will be provided so the potential participant can contact the study team for additional questions.

Informed consent will be obtained prior to randomization and data collection from the medical records and specific data collection for the purposes of the trial that are out-with standard routine care at the participating site.

The right of a participant to refuse participation without giving reasons will be respected.

The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person understands the purpose and nature of the research, understands what the research involves, its benefits (or lack of benefits), risks and burdens and understands the alternatives to taking part. This person is able to retain the information long enough to make an effective decision. Where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

General good practice in research (and the basis of legal frameworks) requires that persons incapable of giving legal consent should be given special protection. They will not be included in this trial.

6.3 Trial Randomisation

1. Randomisation

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 variable block randomisation) will be performed and allocation will be concealed. A 1:1 allocation ratio will be used.

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

Stratification by centre will be applied (variable block size).

2. Blinding procedures

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

Data collectors and data analysts will be blinded to the extent possible. Outcomes will be collected in the same way in both groups, 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.

6.4 Visit schedule and assessments

All assessments are described in detail below. 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 4 (page 32).

6.4.1 Baseline data

○ Demographics (V2)

- BMI (Height & weight), age, leg dominance
- Lifestyle factors that might predict worse ACL reconstruction/recovery outcomes: smoking, education (W R Dunn et al. 2015), 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 (Sturgill 2009). 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 no possible to move). The intra-rater reliability of this grading scale was proved moderate with a kappa value of 0.75 (Sturgill 2009).
- 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 (Filbay et al. 2017).
- Giving away, knee instability
Both the pivot shift test and the Lachman test will be performed to assess passive knee joint stability (Benjaminse, Gokeler, and van der Schans 2005).

During the Lachman test the examiner apply an anteriorly directed force on the tibia to displace the tibia anteriorly relatively 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 (Roemer et al. 2014). 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 (Belle van Meer et al. 2014).

○ **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 (Roos et al. 1998). The KOOS has been validated and is used for patients undergoing ACL reconstruction (Ageberg and Forssblad 2010; Roos and Lohmander 2003).

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 ACL patients report most problems on the subscales Sport/Rec and QOL, and only small problems with pain, symptoms and ADL function, the subscales Sport/Rec and QOL are recommended to follow-up ACL patients (Ingelsrud et al. 2018; Roos et al. 2019). 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 (Collins and Roos 2012). The minimal

detectable change is 7-7.2 for the KOOS QOL and between 5-12 for the other subscales (Collins and Roos 2012).

- **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. (B van Meer et al. 2013) 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 (Roos and Lohmander 2003). We decided to include both questionnaires as we are interested in both short-term changes and long-term changes.
- **Modified Tegner Score**
This scale will be used to grade the **activity level** of the patients (Tegner and Lysholm 2017). 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.
- **Customized Sport participation questionnaire**
Besides the Tegner Score, a customized questionnaire will be used to obtain more detailed information about sport participation. This questionnaire includes the following questions:
 - frequency of training
 - level of sport (competition?)
- **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) (Moss-Morris et al. 2002). Evidence exists that patients' expectations are an important indicator for success of non-operative treatment (Dunn et al., 2015). 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 (Hartigan et al. 2013).
- **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	30 min	Radiologist	X		X
PROMS		total: 35 min				
KOOS	V2-V4	5 min	SN			X
IKDC	V2-V4	10 min	SN			X
Modified Tegner score + sports participation	V2-V4	5 min	SN			X
IPQ-R	V2-4	5 min	SN			X
Tampa Scale for Kinesiophobia	V2-4	5 min	SN			X
EQ-5D-5L questionnaire	V2-V4	5 min	SN			X
Functional tests		total: 30 min				
Single leg hop for distance	V3-V4	10 min	SN			X
Quadriceps and hamstrings strength	V3-V4	20 min	SN	X	X	
Adverse events	V3-V4		PI + SN	X		X
Return-to-work & return to pre-injury activity level	V3-V4	total: 10 min	SN			X
Rehabilitation	V3-V4	total 5 min	SN			X

Table 4: Overview of the timing and duration of every assesement

6.4.2 Follow-up Visits

All baseline assessments will be repeated during the follow-up visits, except for the MRI which is only performed at 3 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 3 months follow-up visit)**

- ACLOAS

- **PROMs**

- KOOS

Besides the standard KOOS questionnaire, we will also administer seven anchor questions (Ingelsrud et al. 2015; 2018; Roos et al. 2019) 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 (Ingelsrud et al. 2015). For MIC, predictive modelling will be used to estimate the smallest change in KOOS score that seems important by the patient (Ingelsrud et al. 2018).

- IKDC subjective
- Modified Tegner Score
- 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 (Noyes, Barber, and Mangine 1991). This test is often used to decide on return-to-sport, with an LSI > 90% as criterium for readiness for return-to-sport (Kyritsis et al. 2016). Furthermore, performance on this test is correlated with re-injury risk after ACL reconstruction (Grindem et al. 2016).

- Isokinetic strength of the quadriceps and hamstrings

Isokinetic strength of the quadriceps and hamstrings will be measured on an isokinetic dynamometer (Biodex or Cybex). 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 (Grindem et al. 2016; Kyritsis et al. 2016). In addition, the hamstrings maximal eccentric strength at 30°/sec will be measured. This will allow us to calculate the mix ratio (e.g quadriceps concentric at 240°/sec divided by hamstrings eccentric at 30°/sec).

○ **Adverse events**

The following adverse events will be registered 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: modified Exercise Adherence Rating Scale (EARS)**

The EARS questionnaire enables the measurement of adherence to prescribed rehabilitation exercises (Newman-Beinart et al. 2017). This questionnaire has 3 sections (A, B, C).

- Section A asks about the prescribed exercises and the frequency of exercising. The developers of the questionnaire (Newman-Beinart et al. 2017) recommend to adapt this section to suit the needs of the study. Therefore, we adapted this section by providing a list with standard exercises of ACL rehabilitation.
- Section B is a validated section that consists of 6 items that evaluate the adherence to the prescribed exercises.
- Section C consists of 10 items that might hinder or improve exercise adherence.

6.4.3 Withdrawal

Patients may voluntarily discontinue from the treatment for any reason at any time. If a patient decides to discontinue from the treatment, the PI must make a reasonable effort (e.g. telephone, e-mail, letter) 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.

It is always within the remit of the physician responsible for a patient to withdraw a patient from a trial for appropriate medical reasons, individual adverse events or new information gained about a treatment.

Withdrawal of consent (discontinuation of trial participation)

A patient's wishes with respect to his or her data must be respected.

The patient may withdraw consent at any time during the study. For the purposes of this trial, withdrawal is defined as: willingness to get surgery without medical reasons or refusing the surgery without medical reasons. The patient would like to withdraw consent from study and is not willing to be followed up for the purposes of the trial at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the trial analysis).

The details of withdrawal will be clearly documented in the patient's medical records and in the eCRF.

Lost to follow-up

If a patient is lost to follow-up, every effort should be made to contact the patient's primary physician (GP) to obtain information on the patient's status. Similarly, if a patient's care is transferred to another clinician, every effort should be made so that follow-up information can be obtained.

6.4.4 End of trial

The end of the trial is defined at the time that the last patient has performed the last visit. The sponsor will notify the main EC of the end of a clinical trial within 90 days of its completion.

7 Safety Recording and reporting

The risk of adverse events occurring as a consequence of the intervention in this trial is unlikely therefore safety reporting will be limited to the safety reporting that is necessary in routine care.

The participant will be asked to report any adverse event related to the study-specific intervention to the study team. These reported events will be documented by the investigator in the source documents. The following minimum information should be recorded for each adverse reaction (AR) by the reporting investigator:

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

The sponsor will keep detailed records of all AEs reported to him by the investigators' and to perform an evaluation with respect to seriousness, causality and expectedness.

When reporting adverse events to the sponsor, the investigator will protect confidentiality by excluding the names of individual subjects, personal identification numbers (e.g. social security numbers) or addresses. The unique code number assigned to the trial subject will be used in the report and the investigator retains the code to facilitate data verification by the sponsor and any medical follow-up which may be warranted. The name of the investigator reporting the adverse events will be stated.

After the trial has been completed or terminated, all recorded adverse events will be listed, evaluated and discussed in the final report.

Reporting to the Ethics Committee

The sponsor will assess whether any relevant safety information that becomes available during the study should be reported ad hoc to the EC.

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

8 Statistics and Data Analysis

8.1 Bias

The methodological shortcomings of the KANON trial as described in the Cochrane review by Monk et al (2016) will be addressed as follows:

1. Selection bias

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

2. 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.

3. 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)

8.2 Sample Size Determination & planned recruitment rate

Since this is a pilot study to assess the feasibility to recruit patients, a sample size calculation was not performed.

Our hypothesis is that 50% of all eligible ACL patients in both sites will sign the informed consent. An overview of the monthly ACL reconstruction rates of both sites can be found in Table 5 on page 38. The last column represents the average patient number in both sites of the past 3 years. This number will be used to calculate the projected recruitment rate. The number of patients that were treated conservatively are not represented in the table as it is not possible to have data on this. It can be assumed that the total number of eligible patients will be higher.

Four months after both sites are open for recruitment, we will perform an interim analysis to evaluate the recruitment progress. At this point, if the recruitment rate is lower than 50% of what can be expected (e.g. 50% of the ACL patients will sign the ICF) based on the mean data of the last 3 years, we will stop the trial.

	2017		2018		2019		Average (last 3 years)		
	UZ Leuven	CHU Liège	UZ Leuven	CHU Liège	UZ Leuven	CHU Liège	UZ Leuven	CHU Liège	Sum
January	9	13	17	11	9	7	12	10	22
February	10	6	7	9	8	6	8	7	15
March	10	9	16	7	10	4	12	7	19
April	2	11	5	10	10	16	6	12	18
May	10	10	5	2	7	5	7	6	13
June	5	16	8	9	8	6	7	10	17
July	9	18	11	13	6	13	9	15	23
August	8	13	13	8	5	1	9	7	16
September	15	11	9	6	11	20	12	12	24
October	6	13	5	5	12	15	8	11	19
November	14	17	12	12	4	6	10	12	22
December	13	4	3	18	12	not available	9	11	20

Table 5: Overview of ACL reconstruction in the past 3 years

For example, if the study has started in both sites in August, participants will be recruited until the end of November. In these 4 months, we expect that in total 80 patients with an acute ACL injury will come to one of the sites, and that 50% of these patients will sign the informed consent (n=40). If the interim analyses shows that we were not able to recruit at least 50% of this projected recruitment rate (n=20), we will stop with the trial.

8.3 Analytical methods

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

All other outcomes/assessments (such as the PROMS, functional tests and MRI) will not yet be analysed. The pilot trial is underpowered to perform analyses on these outcomes. However, as we progress to the full study (that will have enough power), the data of the participants of the pilot trial will be transferred if the participant agrees.

8.3.1 Primary outcome analysis

The primary outcome analysis is to determine the recruitment rate 4 months after the first patient entered the study.

More specifically we will count the number of patients that agree to participate in the trial and compare this to:

- The expected recruitment rate:

Based on the KANON trial, we expect that 50% of the patients with an acute ACL rupture, will agree to participate in the trial. The expected recruitment rate is thus calculated by taking 50% of the average number of ACL patients that visited one of both participating centers in the respective month during the last 3 years (see table 5).

- The total number of patients with an acute ACL rupture that visit one of both participating centra.

The results of this pilot trial will be used to decide on progression to a future definitive RCT in more centers:

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

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

8.3.2 Secondary outcome analysis

The secondary outcome analysis will assess feasibility of the protocol. We will assess, for every questionnaire and functional test, how many patients completed these assessments. **More specifically we will calculate per assessment the percentage of patients that completed this assessment.** Furthermore we will explore why certain assessments are not fulfilled if necessary.

Second, we will assess non-adherence to the allocated treatment. The number of patients that discontinued the intervention or crossed-over to the other group, will be calculated 8 months after the first patient entered the study.

Furthermore the main reasons for non-adherence will be listed.

8.4 Procedures to account for missing or spurious data

The 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 3 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 dedicated person 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.

8.5 Data collection for potential future full trial

Based on the Full Research Proposal that was developed prior to the PILOT trial, the data that are collected in this trial will be used for analysis of the endpoints in a potential future full trial.

Patients will be asked to sign a new informed consent to document they agree that their data will be used for this analysis and to agree to continue further evaluation beyond visit 4 should the potential full trial aim to investigate this.

9 Data handling

REDCap will be used for data management. This online tool will be used for data capture, management and analysis.

9.1 Data collection tools and source document identification

Source Data

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

Source Documents

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation

checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

Source data will be collected and recorded in the study participants files/medical records. They will be kept on a secured location at all times. The collection and processing of source data (from subjects enrolled in this study) will be limited to those data that are necessary to fulfill the objectives of the study. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place. Personnel whose responsibilities require access to personal data agree to keep the data confidential.

Documentation of source data is necessary for the evaluation and validation of clinical findings, observations and other activities during a clinical study. Source documentation serves to substantiate the integrity of study data, confirms observations that are recorded and confirms the existence of study participants. Furthermore source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the investigator. The investigator will maintain complete and accurate documentation for the study. All source documents will be reviewed by the clinical team to ensure that they are accurate and complete.

Case report forms

CRFs are provided for each subject in electronic format through RedCap. The study data will be transcribed on a regular basis by study personnel from the source documents onto an eCRF in a pseudonymised manner*, and transmitted in a secure manner to the Chief Investigator within the timeframe agreed upon between Chief Investigator and the sites. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets (including but not limited to copies of the eCRF) will become part of the study participant's source documentation. 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 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. Solely the Investigator and his/her Trial staff will be able to link the data to an identifiable person; the codelist must be retained in a secured place on site and can under no circumstances leave the site or be accessed by unauthorized persons.*

9.2 Data handling and record keeping

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator will take measures to prevent accidental or premature destruction of these documents.

If data need to be transferred, this will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the Belgian Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and the European Data Protection Act). Receiving party will agree to keep the transferred data confidential at all times. Data will not be transferred outside of the EEA.

9.3 Access to data

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

Electronic CRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities. The accuracy of the data will be verified by review of the source documents.

9.4 Archiving

As specified in ICH-GCP section 8.1 Addendum the Sponsor and Investigator/Participating Site should maintain a record of the location(s) of their respective Essential Documents (including but not limited to Source Documents, completed and final 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 after the Trial.

The Sponsor is responsible for archiving Essential Documents part of the TMF (such as but not limited to protocol, potential amendments, copy of (e)CRF, final report and database) for at least twenty (20) years¹. Essential Documents part of the ISF (such as but not limited to the originally signed ICFs) will be archived locally on site according to local practice, guidelines and Sponsor's instructions. Archived data may be held on electronic record, provided that a back-up exists and that hard copies can be obtained, if required. Destruction of Essential Documents will require authorisation from the Sponsor.

¹ Will be considered as twenty five (25) years once EU Clinical Trial Regulation 536/2014 is applicable.

I0 Monitoring, audit and inspection

Monitoring of the Trial will be conducted periodically by Trial monitors (independent from Trial staff). The Sponsor and Investigator/Participating Site will permit direct access to the Trial data and to the corresponding Source Data and documents to verify the accuracy of these data. The Trial will be monitored to ensure that the Trial is being conducted in compliance with GCP and current legislation, verify, among other procedures, that written informed consent has been obtained correctly, that the Trial procedures have been followed as shown in this protocol, and that the data have been recorded, for which the Source Data will be compared with the data recorded in the (e)CRF. More details about the monitoring strategy for this Trial are described in the Trial specific Monitoring Plan

For all details about monitoring, see trial Monitoring Plan (*will be defined in a later stage*).

11 Ethical and regulatory considerations

11.1 Ethics Committee (EC) review & reports

The study will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. Before the start of the study, this protocol, the informed consent forms and other related documents e.g. advertisements and information letters, will be submitted for review to the REC. The study shall not commence until such approvals have been obtained.

Any subsequent protocol amendments will be submitted to the REC. No substantial amendment that require review by REC will be implemented until the REC grants a favorable opinion for the study.

The study can and will be conducted only on the basis of prior informed consent by the study participants, or their legal representatives, to participate in the study. Extensive discussion of risks and possible benefits of participation will be provided to the patients and/or their families. The participating site shall obtain a signed informed consent form for all study participants prior to their enrolment and participation in the study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The participating site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

All correspondence with the REC shall be retained in the Trial Master File/Investigator Site File.

The Chief Investigator acknowledges that it is his responsibility to produce annual progress reports (APR) and he will do so by submitting to the REC within 30 days of the anniversary date on which the favorable opinion was given, and annually until the study is declared ended.

The Chief Investigator shall notify the REC of the end of the Study. Should the study be ended prematurely, the Chief Investigator will notify the REC and include the reasons for the premature termination. The Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

11.2 Peer review

This study protocol was peer reviewed by certain independent experts. Peer review was conducted by expert referees to the professional and scientific standards expected for clinical studies.

- Prof. Filip Staes, dept. of Rehabilitation Sciences of KU Leuven
- Dr. Stijn Bogaerts, dept. of Physical medicine and rehabilitation of UZ Leuven
- Dr. Pieter Berger, dept. of orthopaedics of UZ Leuven

11.3 Public and Patient involvement

Six Patient representatives are recruited through the Univeristy Hostpials Leuven and completed two patient surveys on the relevance of the proposed project, the design of the research, motivational and practical issues concerning undertaking the research.

In the future, they will be involved in development of the informed consent, recruitment material and dissemination of findings.

11.4 Regulatory Compliance

This study protocol and the conduct of the study in general is in compliance with applicable law, including but not limited to the Belgian law of May 7th 2004 regarding experiments on the human person and any relevant amendments.

11.5 Protocol compliance

The Chief Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

It is acknowledged and agreed that prospective, planned deviations or waivers to the protocol are not allowed under applicable regulations on clinical studies and must not be used. However, should there be an accidental protocol deviation, such deviation shall be adequately documented on the source documents and on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Protocol deviations which are found to frequently recur, will require immediate action. Chief Investigator acknowledges that such recurring protocol breaches could be potentially classified as a serious violation (as defined under section 11.6).

11.6 Notification of serious violation to GCP and/or the protocol

It is understood that “a serious violation” is likely to effect to a significant degree

- the safety or physical or mental integrity of the participants of the study; or
- the scientific value of the study

The Sponsor shall be notified immediately upon becoming aware of a serious violation during the study conduct phase.

11.7 Data protection and patient confidentiality

The study will be conducted in compliance with the requirements of the Belgian Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and the European Data Protection Act. Any collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with the aforementioned personal data protection laws.

Any personal data shall be treated as confidential at all times including during collection, handling and use, and that 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 data protection legislation. 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.

The personal data of study participants will be encoded, which means that they can only be related to an identifiable person by means of a unique code. The unique code will only be in the possession of the members of the study team who are in direct contact with the study participants. In no event will the coded personal data include personal identifiers, including any Study participant's initials. Such coded personal data can only be traced or linked back by said study team members, and said study team members shall treat these codes as strictly confidential.

Only anonymized personal data will be disclosed to KCE or, where specifically requested by KCE, coded personal data. In no event shall any of the reports, documents, information disclosed to KCE include data that may be linked to the specific identity of a study participant. The Sponsor shall make sure that the key to personal identities of all persons to whom the data relates is kept in a separate and secure place in compliance with applicable data privacy legislation and shall not be disclosed to KCE or unauthorized persons.

All study related data and documents will be stored for twenty five(25) years, in accordance with Belgian legislation.

11.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The chief investigator and PIs at each site and committee members of the overall trial management have no competing interest.

11.9 Indemnity

The Sponsor shall throughout the duration of the study effect and maintain with a reputable insurance company a policy or policies of insurance providing an adequate level of cover in respect of all risks which may be incurred by the Sponsor arising out of the Sponsor's performance of the study, including the insurance that is required to be taken out as sponsor of the study as set out in the Law of 2004.

The terms or the amount of cover of any insurance shall not relieve the Sponsor of any liabilities under the clinical trial agreement.

11.10 Amendments

In accordance with the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor may make a non-substantial amendment at any time during a study. If the Sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 28 days of receipt of the notice. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

11.11 Post-trial care

The latest version of the Declaration of Helsinki states that "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."

11.12 Access to the Study Data by KCE and similar institutes in the EU

The study results will be owned by the party who generates them. Sponsor will have access to the study data. At the end of the study, KCE will receive from Sponsor specific study data. This will only be anonymous study data or, where requested by KCE, coded personal data are made available to KCE.

The study data shall not be provided to a third party without the prior written approval of KCE, which approval KCE shall not unreasonably withhold or delay and which KCE may subject to specific conditions in order to ensure that the provision of said study data does not have a negative impact on

the further performance of the study, the rights granted to KCE under the research agreement and/or the benefit of the Study for the patients and/or the public payers.

12 Dissemination Policy

12.1 Dissemination policy

The results of the study shall be owned by the party who generates them.

The results of the study owned by Sponsor and/or (where applicable) any collaborator shall be disseminated as soon as possible, by disclosing them to the public by appropriate means, including in scientific publications (in any medium). Sponsor shall inform and discuss its dissemination strategy with KCE in advance.

The final Study report should be made available for review by KCE before the results are disseminated. KCE shall be notified prior to any dissemination (including publication) (whether in oral, written or other form) of the foreground IP or results or study data or of matters arising from the study. The Chief Investigator shall send one draft copy of the proposed dissemination to KCE at least ten (10) days for an abstract and thirty (30) days for a manuscript before the date intended for dissemination. For the avoidance of doubt, this obligation continues after the end of the study. KCE may object within thirty (30) days of receiving notification, if, in its reasonable opinion, the dissemination (or the timing thereof) is not in the public interests. In the event Chief Investigator or (where applicable) any collaborator intends not to protect the results of the study it needs to formally notify KCE thereof before the dissemination takes place, Sponsor shall ensure that any dissemination is scientifically correct, objective and unbiased (taking into consideration the primary endpoint(s)).

In the event of a multicentre study, Sponsor nor its collaborators shall independently publish or otherwise disclose any findings resulting from the study before publication of the main multicentre publication.

Any dissemination shall acknowledge KCE's financial support and carry a disclaimer as KCE may require in accordance with the clinical trial agreement.

Open access will be ensured (free of charge, online access for any user) to all peer-reviewed scientific publications relating to the results of the study owned by it and/or the collaborators. In particular, Sponsor shall: (i) As soon as possible and at the latest on publication, deposit a machine readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications; moreover Sponsor must aim to deposit at the same time the research data needed to validate the results of the study presented in the deposited scientific publications; and; (ii) Ensure open access to the deposited publication, via the repository at the latest on publication (if an electronic version is available for free via the publisher) or, within six (6) months of publication in any other case.

12.2 Authorship eligibility guidelines and any intended use of professional writers

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 multi-centric Trials, it is anticipated that the primary results of the overall Trial shall be published in a multi-centre publication.

Participating Site is not allowed to publish any subset data or results from the Trial prior to such multi-centre publication,

Any publication by Participating Site will be submitted to the Sponsor for review at least thirty (30) 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.

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APPENDICES

Appendix I: Risk assessment of the trial intervention(s)

Risks associated with trial interventions

☒ **A** $\equiv$ Comparable to the risk of standard medical care

☐ **B** $\equiv$ Somewhat higher than the risk of standard medical care

☐ **C** $\equiv$ 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.

Report completed by: Name: _____
_____ Date: ____/____/____

Signature:

Report validated by Investigator: Name: _____
_____ Date: ____/____/____

Signature:

Appendix II: Data Processing Annex (DPA)

Definitions:

- “Protocol” means the document entitled “Comparison of Immediate versus Optional Delayed surgical repair for treatment of acute Anterior cruciate ligament injury through a parallel, multicentric, pragmatic randomised controlled trial - IODA trial” containing the details of the academic study as developed by the Sponsor as approved by the relevant ethics committee.
- “Sponsor” means Universitaire Ziekenhuizen 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:
 - the European Data Protection Directive (95/46/EC) and upon its entry into force the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation (“GDPR”);
 - 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 pseudonimized 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 Protocol and only for the purposes of providing the data processing tasks set out in the Protocol.
2. 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.
3. 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.
4. 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.
5. 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.
6. The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to 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 Data Processor, the findings as described under 8) (ii) below to the Data Controller.

7. 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.
8. 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.
9. Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 8) (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.
10. 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).
11. The Data Processor must promptly reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 8) (ii) above and (b) any requests from Data Participants under Chapter III of the GDPR (upon its entry into force), 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. 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 8) (ii), and all

necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

12. 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.
13. 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.
14. 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.