Optimizing GRAft SElection in ACL reconstruction - a randomized controlled clinical trial

Acronym: GRASE ACL

{1}

PROTOCOL CONTRIBUTORS

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PROTOCOL DETAILS

This protocol is developed according to SPIRIT guidelines [1] and the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [2].

The numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers.

The order of the items has been modified to group similar items, as recommended by the TRIALS journal [3].

SITE AND SPONSOR

{5b}

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TRIAL REGISTRATION

{2a, 2b}

ClinicalTrials.gov registration and protocol repository{2a,2b}: NCT05342441

The Regional Committee on Health Research Ethics – Capital Region of Denmark: H-19001194

FUNDING

{4}

Novo Nordic Foundation – Surgical Grant, 2021 Grant ID [NNF21OC007211

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(*Foundation name may not be publicly disclosed for administrative reasons; no conflicts of interest or ethics to declare*

Internal Copenhagen University Hospital, Amager-Hvidovre Research funds, 2022

TRIAL STATUS

Inclusion for the trial is currently at 147 patients per 08-08-25

VERSION

{3}

MAIN PROTOCOL REVISION HISTORY

Version	Date	
1.0	2019-01-07	• First draft submitted to ethical review board (Regional Committees on Health Research Ethics for The Capitol Region).
1.1	2021-09-17	• Second draft (full protocol with embedded statistical analysis plan) with approval identifiers from the Capital Region Data Protection Agency, Denmark and the Regional Committees on Health Research Ethics for The Capitol Region, Denmark (Identifyer: H-19001194)
1.2	2022-04-04	Registration submitted at ClinicalTrials.gov - registration identifier (NCT05174182).
1.4	2025-13-08-25	• Full protocol submitted as supplementary document to ClinicalTrials.gov registration

Table 1 – Overview of protocol versions.

CLINICAL TRIALS.GOV REVISIONS

Clinical trials version	Date submitted	Changes
2	2022-05-27	Study status: Study start altered from April 14th to May 9th
3	2023-09-20	Study status: Record verification
4	2025-04-15	Study status: Record verification Oversight: Product manufactured in and exported from the U.S noted at NO.
5		Full protocol including all ethically approved changes submitted. Primary Completion (Estimated): Altered to 2026-9-30 Enrollment (Estimated) **:** Altered to 160

Table 2 – overview of revisions to study registration at clinicaltrials.gov

REVISIONS TO REGISTRATION AT THE REGIONAL COMMITTEE ON HEALTH RESEARCH ETHICS – CAPITAL REGION OF DENMARK

Clinical trials version	Date submitted	Changes
2	2020-12-07	Administrative information: Title change Intervention: BPTB was added as third arm to the planned trial to justify the clinical application and relevance of the study. Power calculation: Power calculation: Updated to enable superiority analysis with three-way comparisons, resulting in 150 projected patients. Timeline: Extended by a year due to changed inclusion. Outcomes: Muscle morphologic changes altered from primary outcome to secondary outcome.
3	2022-05-05	Administrative information: Title change Timeline: Extended to 2027-12-30 due to Covid-19 delays and national nurse strike. Funding: Surgical Grant from Novo Nordic
4	2022-10-10	Recruitment strategy: Project team permission to review patients in the inpatient clinic for eligibility and inform responsible surgeon. Measurements: Collection of X-ray imaging as the clinical routine imaging was not sufficient.
5	2025-06-03	Inclusion: Number of included participants increased to 160 to ensure a minimum of 50 in each group, with the possibility of more in two others due to stratified randomization. Funding: Anonymous family foundation (*no conflicts of interest or ethics*)

Table 3 - Overview of revisions to study registration at the regional committee on health research ethics – capital region of Denmark

APPENDICES AND SUPPLEMENTARY

Appendix 1: Clinical knee examination protocol

Appendix 2: Biomechanical protocol

Appendix 3: Medical imaging protocols

Appendix 4: Bi-Weekly monitoring via text-messages (Danish)

Appendix 5: Ethical approval documents: Written participant information (Danish) {32}, Informed consent forms (Danish) {24}.

Abbreviations

GRASE ACL – Optimizing GRAft SElection in ACL reconstruction

SPIRIT – Standard Protocol Items: Recommendations for Interventional Trials

RoB 2 – Revised Cochrane Risk of Bias Tool for Randomized Trials

BPTB – Bone–Patellar Tendon–Bone (graft)

HT – Hamstring Tendons (graft)

QT – Quadriceps Tendon (graft)

ST/Gr – Semitendinosus and Gracilis (hamstring tendons used in graft)

ACL – Anterior Cruciate Ligament

ACLR – Anterior Cruciate Ligament Reconstruction

RCT – Randomized Controlled Trial

NKR – National Clinical Guidelines (Denmark)

RTD – Rate of Torque Development

PROM – Patient-Reported Outcome Measure

IKDC – International Knee Documentation Committee (evaluation form)

LSI – Limb Symmetry Index

RTD Rate of Torque Development

PICOT – Population, Intervention, Comparison, Outcome, Time (research framework)

PASS – Patient Acceptable Symptom State

KNEES-ACL – Knee Numeric-Entity Evaluation Score for Anterior Cruciate Ligament Injuries

ACL-RSI – Anterior Cruciate Ligament – Return to Sport after Injury (scale)

TSK-11 – Tampa Scale for Kinesiophobia

WORQ – Work Rehabilitation Questionnaire

HRQoL – Health-Related Quality of Life

EQ-5D – EuroQol 5-Dimensions

PRECIS-2 – PRagmatic-Explanatory Continuum Indicator Summary tool (version 2)

WP – Work Package

MVIC– Maximal Voluntary Isometric Contraction

EMG – Electromyography

PLRI – Posterolateral Rotatory Instability

MRI – Magnetic Resonance Imaging

ICRS – International Cartilage Repair Society (cartilage damage grading)

RoM – Range of Motion

CONSORT – Consolidated Standards of Reporting Trials

ITT – Intention-to-Treat

MCID – Minimal Clinically Important Difference

MDD – Minimal Detectable Difference

BMJ – British Medical Journal

GCP – Good Clinical Practice

LBK – Lovbekendtgørelse (Danish Consolidated Act – context: Patient Compensation Act)

ICMJE – International Committee of Medical Journal Editors

SORC-C – Sports Orthopedic Research Center – Copenhagen

KEYWORDS

Anterior Cruciate Ligament Reconstruction, Graft Selection, Randomized Controlled Trial, Patient-Reported Outcomes, Neuromuscular knee control

RECRUITMENT:

Start:	May 9th, 2022
Anticipated termination:	August 30th, 2025

BACKGROUND

{6a}

Rupture of the anterior cruciate ligament (ACL) is a common sports-related knee injury that primarily affects young, active individuals [4,5]. The ACL plays a crucial role in knee stability [6] and ACL rupture leads to pain, reduced function [7–11], and an increased risk of subsequent injuries and osteoarthritis [12–14], significantly impacting long-term quality of life [15,16].

ACL reconstruction (ACLR) is the primary surgical treatment to restore knee stability [17,18], enable return to physical activity, and mitigate the risk of subsequent injuries [19]. However, recovery is often prolonged, functional deficits can persist for years, and only around half of patients regain their pre-injury activity levels [20].

Graft selection plays a pivotal role in ACLR outcomes, as different options vary in tissue properties, graft integration, and donor site morbidity, such as pain and muscle strength deficits [21–23]. Surgeons base their decisions on expertise, patient-specific factors, and the clinical outcomes associated with each graft type [9]. However, the lack of consensus on the optimal graft type has led to significant variability in surgical practices among institutions.

CURRENT GRAFT CHOICES

{6b}

The primary graft options for ACLR are autografts, which are commonly harvested from the patellar tendon with bone plugs (BPTB), hamstring tendons (HT), or quadriceps tendon with or without bone plug (QT).

PATELLAR TENDON WITH BONE PLUGS (BPTB)

BPTB autografts were once considered the gold standard for ACLR due to several advantages, including ease of harvest, consistent graft size and strength, and rapid graft incorporation facilitated by bone-to-bone healing. These factors contribute to low graft failure rates and minimal post-operative laxity. However, donor site morbidity remains a significant drawback, with anterior knee pain reported in up to 52% of patients two years after surgery and reduced extensor strength often contributing to functional deficits [9].

According to the 2024 Danish ACL Reconstruction Registry, the use of BPTB grafts has declined, representing 3.4% of primary ACL reconstructions in 2023 compared to 9,2% in 2005-2022 [4].

HAMSTRING TENDONS (HT)

HT autografts, comprising the semitendinosus and gracilis tendons, are associated with reduced rates of anterior knee pain [21,24,25] and fewer complications involving the extensor mechanism compared to BPTB grafts [26]. However, donor site morbidity for HT grafts includes sensory deficits from saphenous nerve disruption and strength deficits in the harvested muscles, affecting knee flexion and internal rotation [27–29]. These deficits are of biomechanical concern, as the semitendinosus contributes to knee

stabilization and ACL protection [30,31]. Additionally, HT grafts have been linked to greater knee laxity and higher graft failure and revision rates than BPTB grafts [32–35].

Preparation techniques for HT grafts include doubling the semitendinosus and gracilis tendons (ST/Gr autograft) or using a quadrupled semitendinosus tendon, which aims to limit loss of hamstring strength [36]. While patient-reported outcomes between these methods and other techniques show no significant differences, outcomes on pain, hamstring strength, and knee laxity remain inconsistent, warranting further long-term studies [37].

In Denmark, HT was used in 66.5% of primary ACLR in 2023. The quadruple semitendinosus increased from 8.2% in 2005-2022 to 24.2% in 2024, while the use of doubled tendons slightly declined to 42.3% in 2024 from 69.9% in 2005-2022 [4].

QUADRICEPS TENDON (QT)

QT autografts have gained popularity due to robust graft size and tissue properties [38,39], reduced anterior knee pain compared to BPTB grafts [38,40–45], and the advantage of preserving hamstring function [46]. They also demonstrate comparable or superior outcomes in PROMs, knee stability, graft failure, and revision rates relative to HT grafts [38,40–45,47–53].

Introduced in 1979, QT autografts initially faced skepticism due to early studies reporting inferior outcomes for partial-thickness grafts, and additionally, early clinical outcomes from 2000 to 2010 were mixed, with concerns about postoperative pivot shift and prolonged knee extension weakness. However, subsequent research with larger cohorts and higher evidence levels have yielded more positive results [9,38]. In Denmark, QT grafts saw a temporary decline in use around 2020 due to reports of higher revision rates, later attributed to the surgical learning curve, as high-volume institutions reported revision rates comparable to other graft types [35,54,55].

Despite these advancements, QT autografts have certain limitation, including a higher risk of patellar fractures when harvested with a bone block [38], potential extensor weakness persisting up to two years postoperatively [56], and a limited amount of high-quality evidence supporting their use.

In 2023, QT autografts accounted for 18.1% of primary ACL reconstructions in Denmark in 2024 (9.3% were performed without a bone block [4]), which is an increase from the period between 2005-2022 (6%).

GAPS IN LITERATURE (NEED FOR A TRIAL)

The literature on QT grafts in ACLR remains in its early stages, with limited data from randomized controlled trials (RCTs). Most systematic reviews compare only two graft types at a time, thereby limiting the scope for comprehensive evaluations of all three principal autograft options. Additionally, heterogeneity in study design, follow-up durations, reported outcomes, and patient demographics further complicate direct comparisons. Consequently, the most recent Danish National Clinical Guidelines (NKR) were not able to provide definitive recommendations on the preferred graft [57].

Another gap in the literature is the limited focus on strength deficits by graft type. Flexion strength is more affected in HT grafts, while extension strength is more impacted in BPTB and QT grafts [58,59].

Research often attributes poor outcomes to quadriceps deficits and hop-test performance without adequately addressing hamstring function or its relationship with quadriceps strength [60–62]. Given the critical role of hamstring activation in ACL protection during cutting movements[63], further research is warranted to elucidate its impact on reconstruction outcomes.

Rate of torque development (RTD), a measure of neuromuscular performance [64,65], is essential for assessing readiness to return to sport and reducing re-injury risk, as injuries frequently occur during the initial milliseconds of movement [64,66]. However, research linking RTD to graft choice remains limited. Studies on HT grafts suggest persistent RTD deficiencies [64,67], but no studies have directly compared HT grafts with other graft types [68]. The biomechanical changes caused by graft harvest and their impact on outcomes such as PROMs and knee function also remain poorly understood.

This study aims to address these gaps by analyzing a uniform cohort within the same timeframe, enabling direct comparisons across graft types. To date, only one RCT has compared all three major autograft options. The study included 75 patients and was powered to detect differences in knee laxity. It found no significant differences [69]. In contrast, this study is designed to assess more comprehensive outcomes, including International Knee Documentation Committee (IKDC) scores and RTD, providing critical data to optimize graft selection.

OBJECTIVES & HYPOTHESIS

{7}

The overall aim of the GRASE ACL trial is to investigate and compare the effect of graft selection in ACL reconstruction using a comprehensive holistic research approach. The trial is designed to ensure a full reporting of consequences and effects from a patient-reported, movement biomechanical, clinical and muscle morphological perspectives. To meet this ambition and owed to the scale of the trial, two primary objectives have been formulated to reflect different aspects of treatment efficacy. This dual approach captures both subjective recovery and objective functional performance.

The research questions answered by the objectives follow the PICOT model [70].

PRIMARY OBJECTIVES:

1: The primary objective 1 is patient-centered to evaluate the effect of graft selection on patient-reported outcome measures, primarily investigated as the International Knee Documentation Committee Evaluation Form score (IKDC).

The research question answered by this objective is:
Is ACL reconstruction surgery using the QT graft non-inferior to the BPTB- and ST/Gr grafts on patient-reported knee function 12 months postoperatively in adult men and women with primary ACL rupture.

This objective will be evaluated using a non-inferiority approach, with the hypothesis that the QT graft will show non-inferior IKDC scores at 12 months compared to the ST/Gr and BPTB grafts.

2: The primary objective 2 is centered in movement biomechanics to evaluate the effect of each graft on neuromuscular control of the knee, primarily investigated as the limb symmetry of rate of torque development (RTD-LSI) in isometric knee extension and knee flexion.

The research question answered by this objective is:
Is the consequences from graft harvest on neuromuscular control of the knee (RTD-LSI) greater in ST/Gr grafts than QT- and BPTB grafts 12 months postoperatively in adult men and women.

This objective will be assessed using a superiority approach, with the main hypothesis that the ST/Gr graft will show the lowest performance on RTD-LSI in knee flexion compared to the BPTB and QT grafts.

Secondary to this the differences between grafts in RTD-LSI in both knee extension and knee flexion is investigated is tested using pairwise comparisons.

SECONDARY OBJECTIVES

Compare effect of graft selection on secondary and exploratory patient-reported, clinical, and biomechanical outcomes of improvement and adverse effects at 12 months postoperatively

Compare effect of graft selection on secondary and exploratory patient-reported, clinical, biomechanical and medical imaging outcomes of improvement and adverse effects at secondary timepoints at 1 and 6 months, and at long-term follow-up after 24months (table 4-5).

Explore factors associated with effect moderation or mediation of primary or long-term secondary outcomes to determine who will potentially experience benefits or harm from different grafts.

TRIAL DESIGN, REPORTING, AND CONDUCT

{8}

This study is a single-center assessor-blinded randomized controlled trial with a three-group parallel design. Patients are randomly assigned to ACL reconstruction using either the BPTB, ST/Gr, or QT graft, with a 1:1:1 allocation ratio.

The reporting of the results will adhere to the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting [71].

To increase the transparency and validity, we have posted this protocol as a timestamped pre-print publication to the ClinicalTrials.gov repository before termination of patient inclusion and prior do data analysis as a supplementary to the registration.

FRAMEWORK

As described in objectives, the study was conducted with two parallel however, interdependent objectives.

Objective 1 was designed and powered from a non-inferiority framework as the QT graft represents the option least utilized historically, but in high growth in the clinical community (KILDE ÅRSRAPPORTER).

Objective 2 was designed and powered from a superiority framework. The ST/gr graft has shown higher risk of re-rupture in the literature. As it has been established that semitendinosus activity is protective of the ACL [31], the design and analysis plan reflect this association expressed in evaluation of RTD-LSI. The superiority framework in the statistical analysis further allows three-way comparisons, which is important as this objective is a new perspective in a surgical RCT investigating graft choice.

TWO-GROUP PARALLEL-ARM DESIGN

This design was chosen to include the three most utilized grafts in Denmark and internationally to give the study higher clinical relevance and validity for patients and clinicians.

It allows for three-way comparisons and, has higher external validity than other designs, and incurs fewer statistical issues [72].

PRAGMATIC FRAMEWORK:

Using the PRECIS-2 tool (PRagmatic-Explanatory Continuum Indicator Summary) for categorizing our trial, we found our design to be mostly pragmatic with a total score 37 of 45 [73]. Some domains, in terms of patient eligibility and follow-up are the least pragmatic (fig. 1).

Also, neuromuscular control may seem more explanatory in nature but is considered very relevant to patients in terms of evaluation of effect at 12 months before being cleared for sports participation.

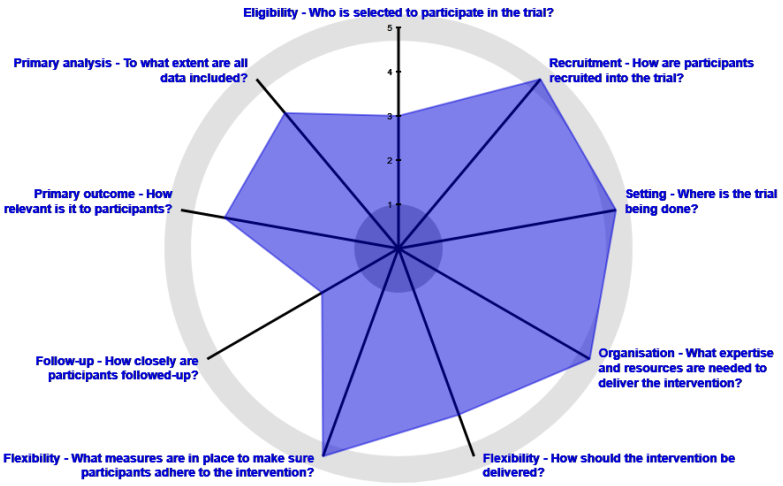

Fig. 1 - Visualization of the PRECIS-2 item scores of the GRASE ACL trial.

PATIENT AND PUBLIC INVOLVEMENT

The research questions, outcome measures, and study design were drafted by the research team based on clinical expertise and existing literature. Seven patients with previous ACL-R fulfilling the inclusion criteria were asked to complete the full set of questionnaires. The patients were subsequently interview about the amount of follow-up visits and the number and selection of PROMs. The study team plans to share the results with participants and relevant patient communities, ensuring that the findings are accessible and informative.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

STUDY SETTING

{9}

Data collection, including recruitment, surgeries, and follow-ups are conducted at the Arthroscopic Centre and HuMAn Lab, Amager-Hvidovre University Hospital, Capital Region, Denmark.

RECRUITMENT STRATEGY

{15}

Patients will be recruited consecutively from the operating list for ACL reconstruction at Amager-Hvidovre University Hospital (fig. 2). Recruitment strategies include direct outreach during and after preoperative consultations.

All patients signed up for ACL reconstruction during the study's timeframe will be screened for eligibility by the surgeon as first contact. If eligible and interested in receiving further information, the surgeon provides the written information and obtains consent for a project staff member to contact the patient for further information. The participant is given >48 hours consideration time before being contacted by project staff, at which time they can decline further information even they accepted it previously with the surgeon.

For patients who meet eligibility criteria but choose not to participate, the reasons for declining, will be recorded anonymously. This information will be used for post-hoc analyses to assess population characteristics and potential bias.

CONSENT

{26a, 26b}

Informed consent will be obtained from all participants by trained clinical personnel prior to any study-related procedures. The consent process will provide comprehensive written and oral details regarding the study's purpose, procedures, risks, and benefits, ensuring that participants can make an informed decision about their participation.

Patients are informed about their rights as study participants provided by the National Committee on Health Research Ethics. The consent forms, written in clear and understandable Danish, have been reviewed and approved by the Ethics Committee.

The patient is further informed of our data protection agreement stating that all information captured is confidential, and that their data will be stored according to current laws and regulations.

KEY ELIGIBILITY CRITERIA

{10}

INCLUSION CRITERIA

- Age 18-40 years.
- First-time ACL rupture.
- Injury sustained within the last 2 years.
- Activity level with a Tegner score ≥ 3 prior to ACL rupture.
- Personal goal of returning to an activity level of Tegner score ≥ 3.

EXCLUSION CRITERIA

- Concomitant knee ligament injury (apart from MCL grade I-II).
- Non-Danish speakers.
- BMI > 30.
- Previous severe injury to either knee.
- Prior severe injury to quadriceps, hamstrings, or patella tendon.
- Prior bone fracture involving the articular surfaces of the femur and tibia.
- Medical conditions preventing participation.
- MRI verified meniscus or cartilage damage according to criteria below.

EXCLUSION CRITERIA DURING INITIAL ARTHROSCOPY

- Medial or lateral meniscus resected to less than 50%.
- Meniscus treatment requiring more restrictive rehabilitation than usual care (e.g., root lesion or complete radial tear).
- Cartilage damage ≥ ICRS grade 3 involving more than 2 cm^2.

RATIONALE FOR POPULATION

The study includes adult patients with primary ACL rupture referred to surgical reconstruction.

The age between 18-40 was decided upon as young patient are most likely to sustain re-injurie after reconstruction [74], and this age group make up the largest representation of patients with ACL injuries in Denmark [75]. It was decided that the intervention was of a magnitude that it would not be ethical to accept informed consent from patients below the legal age in Denmark (<18). Previous ACL rupture, other severe injuries to either knee, and large concomitant meniscus, cartilage or bone injuries in the index knee would all exclude the patient from the study. These prior or concomitant injuries would interfere with the limb symmetry indices (healthy leg) and would most likely reduce the preoperative state and the outcome trajectory on the reconstructed knee.

Required activity level was set to follow the clinical practice, where surgery may be indicated due to work life requirements or sustained laxity and reduced control of the knee. To this end we allowed a two-year period from injury to surgery and previous attempts with conservative treatment.

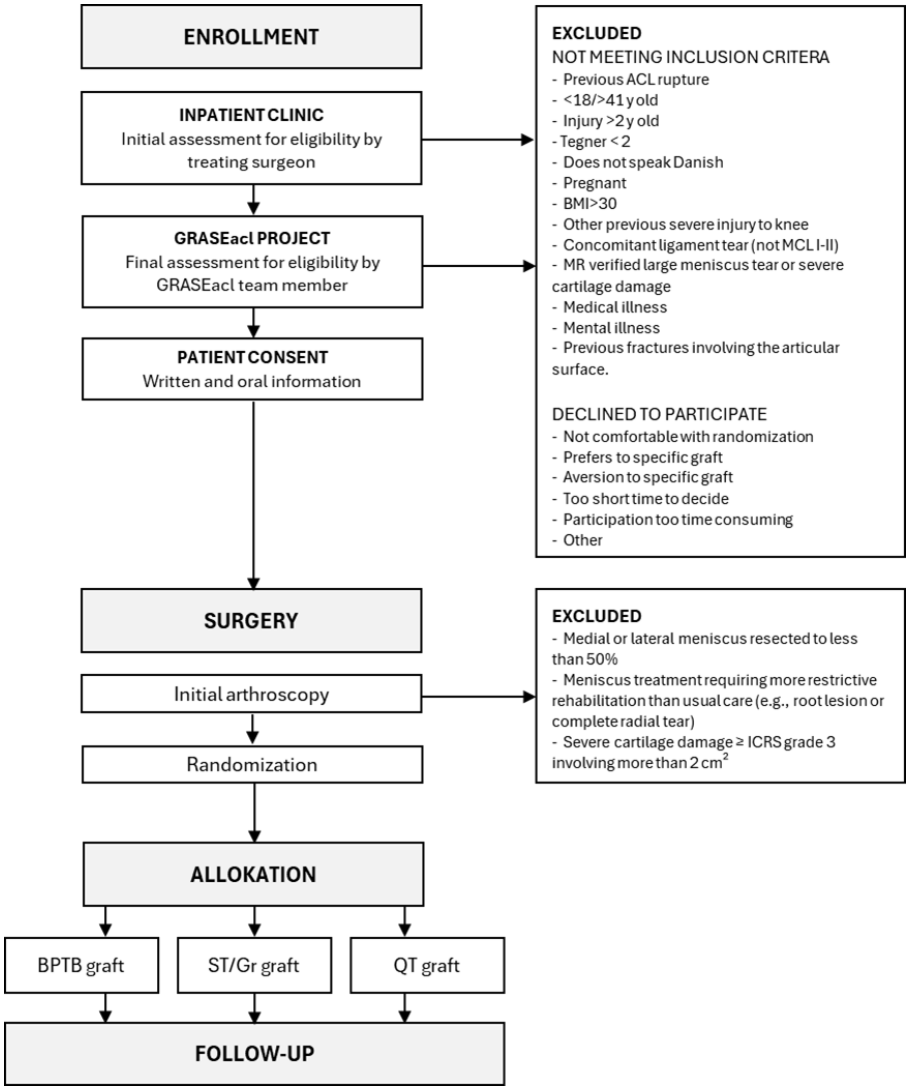

fig. 2 – Inclusion flow

ALLOCATION

{16a, 16b, 16c}

Participants will be allocated to graft type following a sequence generated using a computer-based randomization schedule with permuted blocks of three and six in randomized order (REDCap). Small blocks have been permuted to avoid skewed allocation towards the end on inclusion, where a minimum allocation has been determined according to sample size. Stratification factors include biological sex and age to ensure balanced groups.

Allocation is concealed using opaque, sealed envelopes, managed by an unblinded project associate who will provide the envelope to the surgeon. The envelope may only be unsealed in the operating room when the final perioperative exclusion criteria are assessed.

SAMPLE SIZE

{31c}

As the trial has been designed with two primary objectives, a sample size calculation has been performed on both primary objectives which are described below. The final sample size has been scaled for the primary outcome requiring the most patients. To allow for potential dropout and maintain robust analysis, the study plans to recruit 50 patients for each group. To ensure this, inclusion will continue until 50 patients have been included in each group.

PRIMARY OBJECTIVE 1

The literature suggests a minimal clinically important difference (MCID) between 7-13 points [76,77] with a standard deviation of 12 points [76]. To test non-inferiority between groups (A vs. C, A vs. B, and B vs. C) with a non-inferiority margin of 7 points and a standard deviation of 12 points, a sample size of 37 participants per group is required. This sample size ensures 80% power to detect that no group is worse than the others within the predefined margin at a significance level of 0.05.

LSI-RTD OUTCOME

A local unpublished pilot study showed a minimal detectable difference (MDD) of 12% with a standard deviation of 17%. Although the minimal clinically important difference is unknown, the MDD of 12% guides the analysis. Detecting an effect size of 0.71 (12/17) with 80% power and significance level 0.0167 (Bonferroni correction for multiple testing) requires 44 participants per group.

BLINDING

{17a}

Outcome assessors are blinded to group allocation, to reduce bias. Prior to each patient visit, elastic sports tape will be placed over the areas where possible incisions would be placed depending on which graft is used to conceal the donor graft site. It is not possible to blind the assessor to injured and healthy knee due to the nature of the injury making it perceptibly obvious.

UNBLINDING

{17b}

Blinding of patients and surgeons is not feasible or ethical due to the nature of the intervention. However, the surgeon is not involved in any postoperative assessment of the participants, and the patients are instructed not to reveal to the assessor, what graft has been used for the reconstruction.

A project associate may discuss cases with clinical personnel when necessary for clinical decision-making, but these discussions will not involve the outcome assessors. Unblinding is necessary for clinical reasons, scientific logistics and monitoring of termination of inclusion.

The unblinded project associate is responsible for inclusion of perioperative information from the patient medical chart. The unblinded treating surgeon is involved in clinical knee outcomes prior to randomization and perioperative registration of graft characteristics after randomization is revealed.

INTERVENTIONS

{11a}

ACL reconstruction is performed as usual care with the deviation from the randomization process and that two specialized surgeons (regardless of seniority) will be present for each procedure to maintain consistency and reduce variability.

PREOPERATIVE PREPARATION

The surgical procedures will be performed by a team of specialized and experienced surgeons from the Arthroscopic Center at Hvidovre Hospital, ensuring standardized procedures across patients. The procedure begins with standard preoperative preparation, including time-out to confirm the surgical plan and administration of prophylactic antibiotics. Under anesthesia, the knee is evaluated to confirm positive Lachman and pivot shift tests, ensuring no signs of combined instability.

SURGICAL PROCEDURES

{11a, 11b}

Diagnostic arthroscopy is initiated using two anterior portals, with systematic inspection of the knee. Cartilage and meniscus conditions are evaluated and managed as appropriate. Meniscal lesions are either left untreated, resected, or repaired to restore stability. The ACL is confirmed to be ruptured.

If the patient does not present with any exclusion criteria during this initial arthroscopy, the randomization will be performed, and the ACL reconstruction will continue according to the assigned graft type. In case of adverse effects with graft preparation, the surgeon was allowed to deviate from assigned graft, but the patient remained included per intention to treat.

BPTB GRAFT

The central 10 mm of the patellar tendon with 20-30 mm bone plugs from the tibia and patella are harvested. Both the femoral and tibial tunnels are anatomically placed in the native footprint of the ACL [78]. The graft is secured proximally with a Milagro screws (DePuy Synthes) and, after preconditioning and in 30deg of flexion, with a Milagro screws (DePuy Synthes) distally.

ST/GR GRAFT

Harvest of gracilis and semitendinosus tendons via a 4-5 cm incision at the pes anserinus, prepared as a four-strand graft. Both the femoral and tibial tunnels are anatomically placed in the native footprint of the ACL [78]. The graft is secured with resorbable RIGIDFIX® Curve Cross Pin System (DePuy Synthes) proximally and, after preconditioning and in 30deg of flexion, with a Milagro screws (DePuy Synthes) distally.

QT GRAFT

Harvest of the central portion of the quadriceps tendon through a 4-5 cm transversal incision at the upper pole of the patella. A 10-12 mm wide and 6 mm deep graft is taken. No bone is harvested. Both the femoral and tibial tunnels are anatomically placed in the native footprint of the ACL [78]. The graft is secured with resorbable RIGIDFIX® Curve Cross Pin System (DePuy Synthes) proximally and, after preconditioning and in 30deg of flexion, with a Milagro screws (DePuy Synthes) distally.

IMMEDIATE POSTOPERATIVE CARE

Following fixation, graft tension and stability are confirmed, ensuring no impingement. The joint is thoroughly irrigated, subcutaneous tissues are closed with resorbable sutures, and the skin is sutured intracutaneously with nylon. Ropivacaine is administered intra-articular and in the portals for pain management. Sterile dressing and cooling bandage are applied.

POSTOPERATIVE PLAN AND REHABILITATION

{11c, 11d}

Analgesics are prescribed via the electronic prescription system. Sutures are removed 10–14 days postoperatively at the nurse's outpatient clinic, and clinical follow-up with the operating surgeon is scheduled at 3–4 months.

The patient is referred to the rehabilitation program offered as usual care immediately postoperatively. The patient is not required to follow usual care but is allowed to seek private alternatives. The adherence to rehabilitation is tracked bi-weekly in terms of hours completed supervised and home-based for descriptive purposes.

The regional rehabilitation plan guiding usual care in rehabilitation after ACL reconstruction [79] emphasizes full weight-bearing and unrestricted range of motion from day one, daily mobility exercises, and progressive strength and stability training. It includes criteria- and time-based milestones, such as cycling at 6 weeks, jogging at 16 weeks, and gradual return to sport-specific training after 9–12 months. Supervised sessions are supplemented by home-based training programs. Return to sports involving physical contact and cutting maneuvers is not recommended until after 12 months.

STUDY PERSONAL

This study is conducted as a single-center study to ensure uniform clinical procedures and postoperative care. Orthopedic surgeons from the Arthroscopic Center, Department of Orthopedic Surgery, Hvidovre Hospital are affiliated with the project. All participating surgeons have substantial experience in anterior cruciate ligament (ACL) reconstruction. In the year leading up to project initiation, a comprehensive training program will be implemented for all surgeons to ensure balanced use of ST/GR grafts, BPTB grafts, and quadriceps tendon (QS) grafts. This approach is intended to ensure equal proficiency across techniques and to minimize the risk of experience-related bias.

Clinical outcome collection is performed by PI, Per Hölmich (not performing ACL reconstructions in the trial) and a project assigned surgeon (not assessing own patients). Each surgeon performs both 6 and 12 months follow up on the same patient. This is only deviated from if the risk of missing data due to logistics and scheduling occurs.

OUTCOMES

{12}

This protocol describes a large clinical trial using a holistic research approach with outcomes assessed based on four work packages with assigned outcome measures. The trial time points are baseline, 1, 6, 12 and 24 months. In addition, a bi-weekly tracking via SMS was performed (appendix 4). Follow-up at 12 months was decided as primary time frame as this corresponds to the point in time in usual care that the patient is released from clinical follow-up unless adverse effects have occurred prolonging the rehabilitation. Follow-up was decided to continue to 24 months, as this is the time point classified as medium term in surgical follow-up [80]. Additionally, the Hospital policy is to advice the patients to refrain from full sports participation until 12 months, making the time from 12 to 24 months most relevant in terms of the ability to return to sport. A full overview of outcomes is provided in table 4. The timepoints of which the outcomes assigned to each outcome is obtained is presented in table 5 in participant timeline

WORK PACKAGES

Trial outcomes have been designed with four main work packages, inspired by domains highlighted in the Panther consensus on ACL injury clinical outcomes[81] and Panther Symposium ACL Injury Return to SportConsensus[82]. Each work package will provide outcomes to answer different research questions and objectives, which will be outlined in detail in the statistical analysis plan. Relevance and purpose of each work package is described below.

WORK PACKAGE 1: PATIENT-REPORTED OUTCOMES

Patient reported outcomes measures (PROM) are key to capturing the patients' perception of effect and possible persistent impairments following ACL reconstruction. According to the recommendations of the Panther statement [81], relevant domains to report using patient-reported outcome measures are subjective knee function outcomes, psychological measures, health related quality of life (HRQol) and return to sport, which are all covered in work package 1 and will be elaborated on below.

In addition to the recommended domains, a work life outcome measure was added under a participation domain along with return to sport. Given the age and activity level of the population, work life function, may influence patient satisfaction and perception of function and symptoms to the same or larger degree as sports participation.

Patient Acceptable Symptom State (PASS) which is a dichotomous PROM assessing whether patients consider their knee function acceptable (yes/no), was added as a global satisfaction measure summing up patient perception across domains reported.

SUBJECTIVE KNEE FUNCTION

International Knee Documentation Committee (IKDC) score at 12 months was selected as primary outcome for objective 1 of the trial.

IKDC is considered GOLD STANDARD, as a validated patient-reported outcome measure used to assess symptoms, function, and sports activity in individuals with various knee conditions, including ACL injuries, meniscal injuries, and osteoarthritis[83]. Scores range from 0 to 100, where higher scores indicate better function.

Knee Numeric-Entity Evaluation Score for Anterior Cruciate Ligament Injuries (KNEES-ACL) is a condition-specific PROM designed for individuals with ACL injuries. It consists of seven subscales assessing daily activity limitations, psychological burden, symptoms, perceived weakness, instability, sports-related behavior, and physical sports participation. Responses are assigned numerical values (0–3 or 0–4), with total scores for each subscale ranging from 12 to 24. As all participants are ACL-reconstructed, a 0.7-point differential item functioning adjustment is applied to the "perceived weakness" subscale for scores in the range of 9–20, and a 1-point reduction is applied to the "instability" subscale for patients 6–12 months postoperatively [84,85].

Donor Site-Related Functional Problems Following ACLR Score is a PROM assessing donor-site morbidity following ACL reconstruction with autografts. The questionnaire consists of 16 items, each scored on a 0–6 verbal rating scale, where 0 indicates never/not at all and 6 indicates always/totally (ref).

PSYCHOLOGICAL MEASURES

ACL-Return to Sport after Injury (ACL-RSI) is patient-reported PROM assessing psychological readiness to return to sport, with scores ranging from 0 to 100, where higher scores indicate greater readiness.

Tampa Scale for Kinesiophobia (TSK-11) is a patient-reported PROM assessing fear of movement and re-injury, with scores ranging from 11 to 44, where higher scores indicate greater fear of movement.

PARTICIPATION

Return to sport ability is reported with a PROM assessing pre-injury sport level, return to sport status and experienced barriers of return to sport. The questionnaire is modified from a questionnaire developed for patient with femoroacetabular impingement-syndrome[86,87] based on themes and terminology from the return to sport consensus statement[82].

Return to work ability is reported with a PROM assessing the patients' ability to return to their specific work function and workload in terms of pain, sick leave status and an estimation of workability. The questions were adapted from the validated WORQ questionnaire[88] and the published SeniorWorkingLife - push and stay mechanisms for labor market participation among older workers[89] with counseling from the National Research Centre for the Working Environment.

As an addition, patients report their return to work and return to sport status through biweekly SMS-track surveys during the first postoperative year with questions adapted from the main questionnaires.

Participation in rehabilitation (adherence and barriers) is similarly registered through biweekly SMS-track surveys.

HEALTH RELATED QUALITY OF LIFE

EQ-5D™ is a generic health-related quality of life (HRQoL) PROM evaluating five domains: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. Each domain is assessed on a 5-point verbal rating scale, where 0 indicates no problems and 5 indicates extreme problems or inability to perform the activity. Permission to uses EQ-5D has been obtained (Registration ID: 74677)

WORK PACKAGE 2: MOVEMENT BIOMECHANICS & NEUROMUSCULAR CONTROL

The movement biomechanical work package was designed to meet the criteria highlighted in the consensus for return to sport to include quality of movement, strength, range of motion, balance, and neuromuscular control of the lower extremity and body in the evaluation (KILDE). Muscle strength and balance has been investigated in prior RCT's on graft choice. Neuromuscular control and quality have however been overlooked in this randomized context. To this end it has been necessary to classify several of these outcomes "explorative" (Table 4). Domain investigated in WP 2 are neuromuscular control, strength, movement quality and performance.

NEUROMUSCULAR CONTROL

Isometric Rate of Torque Development was measured (appendix XX) and is reported as Limb Symmetry Index (RTD-LSI). RTD measures the ability to generate torque rapidly during isometric contractions (Nm/s), which is a key indicator of neuromuscular function and ACL protection. RTD for both injured and non-injured leg is assessed using isometric dynamometry in the biomechanics laboratory and expressed as RTD in the injured leg in percentage of the non-injured leg. RTD has been selected as primary outcome contrary maximal muscle strength which has been evaluated extensively. RTD has been shown to been impaired to a larger degree than maximal strength and is emphasized as an important function to evaluated following ACL reconstruction [68,90].

The primary outcome for objective 2 is the Rate of Torque Development Limb Symmetry Index (RTD-LSI) at 12 months knee flexion. This was chosen based on the evidence that hamstring activation and hamstring function is important to protect the ACL [91], and that young patients with ST/Gr have a larger incidence of re-rupture in larger cohort studies[92]. RTD-LSI in knee flexion at 12 months was prespecified as a secondary outcome solely as this was not included in the power calculation. It is considered an outcome crucial to answer objective 2 in full.

STRENGTH

Maximum Voluntary Isometric Contraction Limb Symmetry Index (MVIC-LSI) I performed to evaluate maximal quadriceps and hamstring strength (Nm) through standardized isometric dynamometry (Metitur, FI) (APPENDIX 2).

3-D MOVEMENT ANALYSIS

Instrumented 3-D movement analysis was performed to report on the domains: movement quality, performance and neuromuscular control. Full protocol is added in appendix 2. Outcome variables from the movement analysis are outlined in table 4:

As emphasized in the panther consensus[81,82], variability in test batteries investigating movement quality and neuromuscular control remains. The protocol was designed based on test previously reported in the literature with a variation of one-leg jumps for comparison between the healthy and reconstructed leg for LSI quantification. The jump tasks were selected to include simple jumps with vertical and horizontal propulsion and landings as well as combination jumps with transitions from landing to propulsion in both vertical and horizontal direction[93]. The following jump tests are assessed:

Single-leg horizontal jump, Single-leg vertical jump, single-leg horizontal to vertical jump, single-leg 90 degrees rotation jump, counter-movement jump, single-leg triple-jump for distance, cross-over triple jump for distance and 6 timed one-leg jump.

All jump tasks are assessed using 3D motion capture analysis (Vicon motion systems, Oxford, UK) with the clinical gait-model 2.3 lower limb marker set for reporting movement kinematics. Simultaneous capture of ground reaction force is captured on AMTI force plates (OR6-7, Watertown, MA, USA) to report movement kinetics. Finally, synchronized surface electromyography measurements were collected to report neuromuscular control of thigh muscles and hamstrings (appendix 2). Performance in jump tasks (height, distance) were calculated from 3-D motion capture and force platform data (table 4).

WORK PACKAGE 3: CLINICAL ASSESSMENT and MEDICAL IMAGING

WP 3 was designed based on usual care and recommendations from the panther consensus on clinical assessment. Clinical assessments and medical imaging are key for determining the clinical efficacy and effectiveness of each treatment, but WP3 is similarly designed to identify modifiable and non-modifiable predictors of good and poor outcomes in WP 1 and WP 2. Domains reported in WP3 are objective knee function, adverse events, perioperative outcomes, Muscle morphology & anatomical predispositions. Detailed protocols for medical imaging are added in appendix 3.

OBJECTIVE KNEE FUNCTION

Clinical knee stability assessments are performed by an experienced orthopedic surgeon blinded to allocation reporting:
The Rolimeter test measures anteroposterior tibial translation (mm) to assess ACL stability; The pivot shift test evaluates rotational knee stability, graded 0 to 3 (0 = no shift, 3 = severe shift); Passive Range of Motion (RoM) in knee extension and knee flexion in degrees; The dial Test in 30 and 90 degrees of knee flexion to evaluate posterolateral rotatory instability (PLRI); Medial and lateral laxity to evaluate the integrity of collateral ligaments and the joint effusion test to evaluate presence of inflammation.

PERIOPERATIVE DETAILS & ADVERSE EVENTS

Prespecified perioperative details are extracted from medical records: including surgeon, concomitant injuries, meniscal tears below exclusion criteria level and treatment, graft length and diameter[94], tunnel placement, and surgical duration.

Prespecified adverse events are recorded via medical records, including infection, arthrofibrosis, meniscal injury, graft rupture, and revision surgery.

Postoperative X-rays are reviewed to assess tunnel placement.

MUSCLE MORPHOLOGY & ANATOMICAL PREDISPOSITIONS.

Magnetic resonance imaging (MRI) scans are performed on the thigh muscles of both legs to report symmetry indices of muscle length of semitendinosus[95] and cross-sectional area of biceps femoris, semitendinosus, gracilis, vastus medialis, vastus medialis and rectus femoris[96].

Postoperative X-rays are reviewed to report lateral tibial slope of the reconstructed knee[97].

	Instrument / Test	Domain	Outcome Variables / Scores	Assessment & Validity
Work Package 1: Patient-reported function				
Primary outcome				
WP 1	International Knee Documentation Committee (IKDC)	Subjective knee function	Total IKDC score (0–100)	Validated PROM. Gold standard for follow up after ACL reconstruction[83].
Secondary outcomes				
WP 1	Knee Numeric-Entity Evaluation Score for Anterior Cruciate Ligament Injuries (KNEES acl)	Subjective knee function	7 subscales with total score ranging from 12-24.	Condition-specific validated PROM[84,98].
WP 1	EQ-5D	Health-related quality of life	Domain scores (1–5)	Validated HRQoL PROM[99]
WP 1	TSK-11	Psychologic effects	Total score (11–44)	Validated fear-of-movement PROM[100]
WP 1	ACL-RSI	Psychologic effects	ACL-RSI score (0–100)	Validated psychological readiness scale[101]
WP 1	PASS	Global satisfaction	dichotomous outcome (yes/no)	Validated PROM on acceptable knee function[102].
WP 1	Return to Sport	Participation	Self-reported ability to return to *participation and* performance in pre injury sport (primary and secondary), and level (*Elite, competitive, leisure)*. Self-reported barriers (Pain, donor-site pain, laxity, swelling)	Modified patient reported outcome measure based on a return to sport consensus statement from 2015[86,87]
WP 1	Donor Site-Related Functional Problems Following ACLR Score	Subjective knee function	16 items, each scored on a 0–6 rating scale. (0=never/not at all)	Validated donor-site morbidity PROM[103]
WP 1	Return to Work	Participation	Self-reported work-ability Knee related sick leave	Modified patient reported outcome measure with questions adapted from validated surveys [88,89].
Explorative outcomes				
WP 1	SMS-based tracking	Rehabilitation compliance	Adherence to rehabilitation (time) Pain interference with rehabilitation (yes/no) Knee related medical assistance beyond standard follow-up (yes/no)	Custom patient reported registration
		Subjective knee function	Knee function (numeric scale Sports participation ability (numeric scale) Workability (numeric scale) pain level (numeric scale)	Pain scores and numeric scales adapted from IKDC

Work Package 2: Movement Biomechanics & neuromuscular control				
Primary outcome				
WP2	Isometric Rate of Torque Development – knee extension	Neuromuscular control	Limb symmetry of-Rate of Torque Development in knee flexion (%)	Standardized dynamometry, validated LSI method[104]
Secondary outcomes				
WP 2	Isometric Rate of Torque Development – knee flexion	Neuromuscular control	Limb symmetry of-Rate of Torque Development in knee extension (%)	Standardized dynamometry, validated LSI method[104]
WP 2	Maximal Voluntary Isometric Contraction	Strength	LSI-MVIC (%)	Standardized dynamometry
Explorative outcomes				
WP 2	One-legged jump tasks (Appendix 2)	Movement quality	3D kinematics: LSI in landing angles of knee, hip and ankle RoM during landings and propulsion	Validated instrumented method for movement analysis and load evaluation[31,91]
WP 2		Movement quality	3D kinetics: LSI in joint moments, power and work during landings and propulsion	
WP 2		Performance	LSI on jump height, distance, time and reactive strength index	Validated return to sport metrics [105]
WP 2		Neuromuscular control	Surface electromyography: Magnitude of EMG response (% of max) during landing and propulsion Timing of EMG response before and during landing.	Validated injury risk evaluation[91]
Work Package 3: Clinical assessment and Medical imaging				
Secondary outcomes				
WP3	Clinical knee exam	Objective knee function	Rolimeter (mm) Pivot Shift (0-3 grading)	Blinded orthopedic testing with standardized tools[32,52]
Explorative outcomes				
WP3	Clinical knee exam	Objective knee function	Dial Test (degrees), Range of Motion (degrees), medial and lateral laxity (yes/no), joint effusion (yes/no).	Standard postoperative clinical examination of the knee joint.
WP3	Patient medical file	Adverse event	Re-rupture, revision surgery, medical complications	Prespecified log
WP3	Patient medical file	Perioperative information	Graft size, adverse events, knife time.	Prespecified log
WP3	Magnetic Resonance Imaging (MRI)	Muscle morphology	Muscle length (mm), Cross Sectional Area (mm^2)	Blinded MRI analysis, validated anatomical landmarks and methods
WP3	X-ray imaging	Perioperative information	tunnel placement	Blinded assessment, Calibrated radiographic imaging
WP3		Anatomical predisposition	Lateral tibial slope	

Descriptive features of populations sample				
Exploratory and descriptive outcomes				
	Inclusion interview and patient file logging	Patient features and anthropometrics	Age, Height, Weight, Biological sex	Custom patient reported registration
		Preinjury participation	Primary and secondary sport, hours and level of participation. Occupational level	
		Injury information	Time from injury to surgery, Injury situation (mechanism), Preferred leg.	

Table 4 – Overview of work packages and all corresponding outcomes and instruments in the GRASE ACL trial.

DATA COLLECTION AND MANAGEMENT

PARTICIPANT TIMELINE

{13}

Participants will be followed from preoperative assessment to 24 months post-surgery (Table 5). Assessments include patient-reported outcomes (PROMs), clinical evaluations, biomechanical testing, and imaging, scheduled to optimize participant convenience and minimize burden. Follow-ups are scheduled for 1, 6, 12 and 24 postoperatively.

	Enrollment	**Surgery**	**Follow-ups**			
Timepoint (mo.)	**-1**	**0**	**1**	**6**	**12**	**24**
ENROLLMENT						
Eligibility screen	x					
Informed consent	x					
Baseline demographics & descriptive features of population sample	x					
INTERVENTION						
ACL reconstruction surgery		x				
Surgical details		x				
Allocation		x				
ASSESSMENTS						
WP 1 Patient-reported						
IKDC	x		x	x	x	x
KNEES-ACL	x		x	x	x	x
Donor Site-Related Functional Problems				x	x	x
PASS				x	x	x
EQ-5D	x		x	x	x	x
ACL-RSI				x	x	x
TSK-11	x		x	x	x	x
Return to Sport questionnaire				x	x	x
Return to Work questionnaire			x	x	x	x
Bi-weekly sms-based tracking			x			
WP 2 Biomechanical						
RTD-LSI				x	x	
MVIC-LSI				x	x	
Jump performance				x	x	
3D kinematics/kinetics				x	x	
Muscle activity (EMG)				x	x	
WP 3 Clinical						
Objective Knee stability	x			x	x	
Passive RoM	x			x	x	
Adverse events (from records)						x
WP 4 Medical Imaging						
MRI of thigh muscle				x		
Postoperative X-rays				x		

Table 5 – Time points of assessment and participant timeline from enrollment until 24 months post-surgery.

PLANS FOR ASSESSMENT AND COLLECTION OF OUTCOMES

{18a}

Patient-reported outcomes (PROMs) will be collected electronically via e-mail link in REDCap (Research Electronic Data Capture), a secure, web-based platform hosted by Region Hovedstaden. REDCap contains options for valid values, range checks, data validation, branching, scheduling, and stop-rules to increase data quality. Questionnaires administered are described in WP1 in the outcomes section.

Clinical assessments, including knee stability tests, will be performed by blinded clinicians at standardized follow-up time points, and registered in the patient medical file (EPIC Hyperspace®) (appendix 1). Prespecified clinical and surgical details will be extracted from medical records, and adverse events will be documented throughout the study in secured folders with logged access.

SMS-based surveys (SurveyXact) will be used for biweekly data collection on pain, rehabilitation compliance, healthcare utilization, return to sport, and return to work during the first postoperative year.

To ensure consistency and data integrity, all assessors will undergo standardized training, and detailed data collection protocols will be available upon request.

Biomechanical outcomes will be assessed using isometric dynamometry, 3D motion capture (Vicon Motion Systems, Oxford, UK)), and surface electromyography (EMG) in the Motion Analysis laboratory. The full laboratory protocol is attached in appendix 2.

Data on Non-Participants

Non-sensitive baseline data and reasons for opting out will be recorded anonymously for eligible individuals who decline to participate. This information will be utilized in analyses to evaluate population characteristics and identify potential selection biases.

Managing Allocation Deviations

It is possible, though predicted to be very rare, that some participants deviate from their assigned graft due to intraoperative complications. In these instances, data collection will continue as planned to facilitate intention-to-treat analyses.

Managing Protocol Deviations

Participants will adhere to standardized postoperative care, including follow-up with their surgeon and receive physiotherapy according to Danish guidelines, with additional care provided as needed. Any adverse effects, additional treatments, or interventions will be closely tracked and documented to assess their impact on study outcomes.

STRATEGIES FOR ENSURING FOLLOW-UP COMPLIANCE

{18b}

Adherence to intervention protocols and follow-up assessments will be promoted and monitored through multiple strategies to maximize participant retention.

We will continue data collection irrespective of adherence to rehabilitation and follow-ups. In cases of re-injury a clinical evaluation of safety determines if the biomechanical protocol is performed.

Data collection will only discontinue if participants explicitly wish to withdraw from the study and not attend further visits. In such cases, we will offer participants the option to only complete electronic patient-reported questionnaires and/or partial clinical and biomechanical follow-up with focus on obtaining primary outcomes. However, every reasonable effort will be made to retain all participants and collect all outcomes for every patient enrolled in the study.

Survey participation will be actively tracked, with reminders sent via email, text messages, and phone calls to non-responders.

- Biweekly SMS Surveys: If a participant does not complete an SMS survey, a reminder will be sent 2 days later. Data collection is permitted within 1 week before the response is considered missing.
- 1-Month Survey: Sent 4 days before follow-up time point. Participants who do not complete the survey will receive reminders every 4 days, up to three times. If still unanswered, a phone call will be made. A 14-day delay is permitted before the data point is considered missing.
- Hospital Follow-Up Visits (6 and 12 months): Participants will receive a confirmation text message 1 month and 2 days before their scheduled visit. Scheduling is flexible, and data collection is permitted within a 30-day window before or after the follow-up time point.
- 6- and 12-Month Surveys: Sent 21 days before the follow-up time point. If participants have not completed their surveys before the hospital visit, they will be asked to complete them on an iPad during their visit. A 30-day delay is permitted.
- 24-Month Survey: Sent 30 days before the follow-up time point. Participants who do not complete the survey will receive reminders every 5 days, up to three times. If still unanswered, a phone call will be made. A 60-day delay is permitted.
- MRI Scan at 12 months: The scan can be scheduled within a 30-day window before or after the designated time point.

DATA MANAGEMENT

{19}

The study directors will manage and curate data in collaboration with the blinded statistician.

REDCap users (study personnel) will have access to all instruments and data within the REDCap project to maintain blinding to group allocation, outcomes, and contents of interventions. Digital consent forms are stored in REDCap. Other hardcopy data will be stored in locked steel cabinets in a locked room and will be stored for 3 years after completion of the long-term follow-up of the study.

Data from biomechanical analysis holds video material with the consent of each participant. Data from these analyses is processed in NEXUS versions XXX (VICON systems), but stored in logged, secure drives only accessible by study personnel.

DATA PROTECTION & CONFIDENTIALITY

{27,33}

This study complies with the General Data Protection Regulation (GDPR) and Danish Data Protection Law. Region Hovedstaden is the data controller responsible for processing personal data, with oversight from the Danish Data Protection Agency (Jr. no. VD-2018-524).

All personal and health data will be securely stored within Region Hovedstaden's IT infra-structure, with strict confidentiality measures in place. Personal and health data are stored in a secure, password-protected database with regular backups, and only authorized research personnel will have access to de-identified study data. Identifiable information will be re-moved or encrypted to ensure privacy. Study data will be retained for 10 years in accordance with regulatory guidelines. External data processors, such as SurveyXact and University College Copenhagen, are involved in handling pseudo-anonymized data for project-related analysis.

Participants have the right to access their personal data, request corrections or deletions (subject to legal research exemptions) and withdraw consent at any time without affecting their medical care. If a participant withdraws consent, no new data will be collected, but previously gathered data will be retained for research integrity.

STATISTICAL ANALYSIS PLAN

Final version of the statistical plan has been specified per 30-06-25, and follows the pre-SPEC framework of statistical analysis strategies in clinical trials [106].

Demographic parameters will be presented for each graft group. Continuous variables will be summarized as mean with standard deviation (SD) or median with interquartile range (IQR), depending on the distribution. Categorical variables will be presented as frequencies and percentages.

Analysis will follow an intention-to-treat (ITT) approach. To check the robustness of the primary intention-to-treat analysis, per protocol analysis on primary outcomes will be performed.

Statistical models specified below will be set up by a statistician in R with a dummy allocation to ensure full blinding in the statistical analysis. R codes will be available upon request.

STATISTICAL MODELS and HANDLING OF MISSING DATA

{20c}

For continuous data, a t-test will be used. Assumptions of normality will be evaluated using QQ-plots and histograms. If variances are not homogeneous, Welch's t-test will be applied. For non-normally distributed data, the Mann-Whitney U-test will be employed.

Adjusted analysis will be done by expanding t-test using mixed effect linear regression models.

To not introduce unnecessary bias in regression models, possible covariates will however only be included if doing so changes the primary estimate meaningfully, as we expect equal distribution of these pre-specified covariates given the sample size and randomization process. The linear models will be evaluated for linearity, multicollinearity, homogeneity of variance, distortion of outliers, homoskedasticity, correlation of variables, distribution of residuals using histograms. If these model assumptions are not met nonparametric bootstrap estimation and tests will be used instead.

Missing data will be imputed by multiple imputation, with imputation models based on available variables believed to be predictive of the missing measures. All available variables will be included in the imputation models, unless a specific reason is given for exclusion.

STATISTICAL METHODS FOR PRIMARY AND SECONDARY OUTCOMES

{20a, 20b}

PRIMARY OBJECTIVE 1

Three distinct hypotheses on patient-reported effect of graft choice will be tested for change in the IKDC score 12 months after surgery:

QT (Group A) is non-inferior to BPTB (Group B).
QT (Group A) is non-inferior to ST/Gr (Group C).
BPTB (Group B) is non-inferior to ST/Gr (Group C).

Each hypothesis will be tested using a non-inferiority two-sample t-test, with non-inferiority margin of 7 points, which is considered a clinically relevant difference based on prior studies [76,107]. As the three hypotheses are independent, no adjustment for multiple comparisons will be applied to the p-values.

To provide additional insight into the effects and safety of graft types, secondary outcomes will be analyzed as follows:

- KNEES-ACL score at 12 months will be assessed using a non-inferiority approach, with a non-inferiority margin of 8 points. As no established threshold exists in the literature, this margin is chosen conservatively based on expert consensus and comparisons with other knee-specific PROMs [98].
- Donor-site related functional problems, PASS, EQ-5D, rolimeter measurements and pivot shift at 6 and 12 months will be analyzed using a superiority approach with three-way comparisons.

Adjusted analysis will be done by expanding t-test using linear regression models. Confounding effects will be evaluated by including and removing the following covariates in statistical model.

Possible confounders include:

- Patient-related factors: sex, BMI, age, physical activity prior to injury, time from injury to surgery, and tibial slope, and surgeon.
- Concomitant injuries: Meniscal and chondral injuries and treatment.
- Knee function prior to surgery: Range of motion (ROM), Rolimeter, pivot shift, medial and lateral laxity tests, and dial test results.
-

To explore mechanisms underlying treatment effects, the following variables will be reported:

- Surgical details: Graft size and tunnel placement.
- Healthcare Utilization: Number of additional physician consultations during the first postoperative year, tracked biweekly via SMS surveys (SurveyXact).
- Follow-up knee examination at 6 and 12 months: Passive ROM, medial and lateral laxity, and dial test results.
- Pain Assessment: Patient-reported pain scores, using the same two pain-related questions as in the IKDC questionnaire, collected biweekly during the first postoperative year via SMS surveys (SurveyXact).
- Complications and adverse events: Including infections, arthrofibrosis, meniscal lesions, graft failure, and other relevant events, recorded via medical records.

PRIMARY OBJECTIVE 2

A superiority approach will be applied to assess differences between groups on RTD-LSI in knee flexion at 12 months postoperatively. A composite hypothesis of differences between groups will be tested, consisting of two pairwise comparisons:

- QT (Group A) versus ST/Gr (Group C).
- BPTB (Group B) versus ST/Gr (Group C).

For RTD-LSI in both knee flexion and knee extension a superiority approach will be applied to assess differences between groups. A composite hypothesis of differences between groups will be tested, consisting of three pairwise comparisons:

- QT (Group A) versus BPTB (Group B).
- QT (Group A) versus ST/Gr (Group C).
- BPTB (Group B) versus ST/Gr (Group C).

Each pairwise comparison will be analyzed using a two-sample t-test. To control for the potential inflation of type I error due to multiple testing, the max-t/min-p test for multiple comparisons will be applied[108].

The secondary outcome MVIC-LSI in knee flexion and knee extension will be analyzed using the same method.

Mixed effect linear regression models will be used to analyze the effect of RTD-LSI on 1: Kinetic and kinematic outcomes during one-leg landing and propulsion, 2: Performance in isolated horizontal, vertical and horizontal to vertical jumps and 3: Subjective knee function in terms of IKDC and KNEES at 12 months.

Adjusted analysis will be done by expanding t-test using linear regression models. Confounding effects will be evaluated by including and removing the following covariates in statistical models.

Possible confounders include:

- Patient-related factors: sex, BMI, age, physical activity prior to injury, injury mechanism, and time from injury to surgery.
- Concomitant injuries: Meniscal and chondral injuries and treatment.
- Pain domain of KNEES-ACL at 12 months.

To explore mechanisms underlying treatment effects, the following variables will be reported:

- Knee function prior to surgery: Range of motion (ROM), Rolimeter, pivot shift, medial and lateral laxity tests.
- Donor Site-Related Functional Problems Following ACLR Score at 12 months.
- Complications and adverse events recorded via medical records.

METHODS FOR ADDITIONAL ANALYSES

Additional analyses and trial reports are pipelined for the full trial answering the additional objectives outlined previously.

Additional analyses will investigate differences between the three graft choices according to a superiority framework, and adhere to the same missing data handling, assumption testing and control for the potential inflation of type I error as specified above.

INTERIM ANALYSES

{21b}

No interim analyses or stopping rules are planned to preserve statistical power. The three treatment options employed can be classified as usual care, thus safety concerns are very low.

RISK OF BIAS

A risk of bias analysis was performed prior to final inclusion according to the RoB 2 framework [2]. Bias arising from the randomization process, bias due to deviations from intended interventions were reported as low risk domains as randomization was very controlled and performed simultaneous with completed interventions.

Bias in measurement of outcomes and bias in selection of reported result were reported as low risk domains as all outcomes were selected in accordance with recommendations in clinical and scientific consensus groups, and outcome reporting and statistical analyses plans were pre-specified.

Bias due to missing outcome data was reported with some concerns of bias. To meet this concern, the patients' reason for possible dropout our missing an assessment was registered. In addition, several strategies for retention of participants and adherence to trial outcome assessments were designed.

PLANS TO GIVE ACCESS TO THE FULL PROTOCOL, PARTICIPANT LEVEL-DATA AND STATISTICAL CODE

{31c}

Full methodological protocols for biomechanical assessment and medical imaging are attached to this current protocol.

Statistical code and participant-level dataset will be available upon demand, to the extent that it does not compromise Danish Data Protection Law.

ETHICS AND DISSIMENATION

RESEARCH ETHICS APPROVAL

This trial will be conducted in compliance with the principles of Good Clinical Practice (GCP) as set out by the International Conference on Harmonization (ICH) and the Declaration of Helsinki. This study has received approval from the Scientific Ethics Committee for the Capital Region (Journal-no.: H-19001194). Any significant protocol amendments will require re-approval by the relevant ethics committees.

RISK AND SAFETY CONSIDERATIONS

Biomechanical evaluations may cause temporary muscle soreness or fatigue, particularly after strength or dynamic movement tests. Additionally, there is a slight risk of strain during physical tasks, but participants will be closely supervised to reduce this risk. To reduce risks, it was attempted to plan the clinical examination prior to biomechanical examination to ensure integrity of the new ACL. For patients with low function, the demanding tasks combining landing and propulsion were avoided.

MRI scans, while non-invasive, may lead to discomfort due to the enclosed space, noise, and duration of the procedure. A postoperative X-ray will be performed, involving minimal radiation exposure. Comprehensive safety protocols are in place to monitor and address any potential adverse effects throughout the study.

HARMS

{22}

Adverse events and unintended effects will be closely monitored throughout the trial by the designated non-blinded personnel. Any serious adverse events will be reviewed by clinical personnel and promptly reported to the relevant ethics committees. Participants who experience adverse effects related to the trial interventions will receive appropriate medical care according to local clinical guidelines. Participants are encouraged to report any health issues during the study, and they will be immediately informed if any new side effects or risks are identified during the trial.

COMPENSATION TO PATIENTS

No participants will receive reimbursement for their travel expenses related to participation in the study, nor will participants be offered compensation of any kind. During treatment at Hvidovre Hospital, the participants will be covered under the Danish Patient Compensation Act (LBK no 995 of 14/06/2018, chapter 3 §19) (In Danish: Patienterstatningen), which is a scheme that deals with compensation claims of patients treated in the public health system in Denmark who has sustained an unintended or unexpected injury or harm.

DECLARATION OF INTERESTS

The principal investigators and collaborators involved in this trial declare no financial or other conflicts of interest that could potentially influence the study outcomes. Any future competing interests will be disclosed in relevant publications and reports.

DISSEMINATION PLANS

{31a}

The results of the trial will be shared through peer-reviewed journal publications, conference presentations, and updates to ClinicalTrials.gov. Key findings will also be communicated directly to participants who have expressed interest in receiving study results, as indicated when they signed the consent form, as well as to relevant healthcare professionals. There are no publication restrictions, allowing for full transparency and broad dissemination of the findings. Primary trial reports are listed below.

PRIMARY TRIAL REPORTS

- *Optimizing GRAft SElection in ACL reconstruction (GRASE ACL): effect of graft choice on patient reported knee function and knee stability.*

Reporting the primary outcome corresponding to objective 1 – the patient centered perspective supported by secondary outcomes previously outlined in the statistical plan.

- *Optimizing GRAft SElection in ACL reconstruction (GRASE ACL): effect of graft choice on rate of torque development and the consequences to dynamic control of the knee.*

Reporting the primary outcome corresponding to objective 2 – the biomechanical perspective supported by secondary outcomes and analyses previously outlined in the statistical plan.

ADDITIONAL TRIAL REPORTS

Further publications based on data from the trial will be conducted and should adhere to the pre-specified main statistical plans outlined for in METHODS for additional analyses with full transparency on outcome status presented in this current protocol on disseminated outcomes.

TENTATIVE ADDITIONAL DISSEMENATIONS ON THE PRIMARY TIMEPOINT (12mos)

- *Influence of graft selection on return-to-work ability following ACL reconstruction*.

The primary objective is to investigate the effect of graft selection on workability reported in the workability questionnaire and additionally biweekly SMS-tracking.
The secondary objective is to evaluate probable clinical and patient-reported barriers and facilitating factors of work ability will be analyzed.

- *Influence of graft selection on readiness for safe return to sport 12 months after ACL reconstruction*.

The primary objective is to investigate the effect of graft selection on the physical readiness to return to sport evaluated with a return to sport battery evaluating performance in return to sport one-leg jump tasks and LSI-MVC in quadriceps.
Barriers and facilitating factors to physical readiness from neuromuscular, clinical and psychological outcomes to return to sport 12 months after reconstruction will be analyzed

Secondary objective is to evaluate the psychological and biomechanical readiness for safe return to sport. This will be analyzed as the effect of graft selection on known kinetic, kinematic and EMG predictors for re-rupture, as well as psychological readiness measured as the ACL-RSI and TSK-11.

AUTHORS' CONTRIBUTION

{31b}

Authorship will be determined based on the International Committee of Medical Journal Editors (ICMJE) guidelines. All plans for additional dissemination of trial results must be presented and reviewed by the scientific group to avoid bias in data selection and slicing of data. No professional writers will be employed in preparing the study's publications.

COMPETING INTERESTS

{28}

Some of the authors have previously published in this area and have designed the experimental intervention being tested and are therefore prone to self-citation incentives and confirmation bias. Thomas Kallemose is paid for statistical consultation and performing blinded analyses. There are no other conflicts of interest to declare.

OVERSIGHT AND MONITORING

SCIENTIFIC TRIAL STEERING COMMITTEE AND DATA MONITORING COMMITTEE

{5c, 5d, 21a}

The Sports Orthopedic Research Center – Copenhagen (SORC-C), specifically PhD-fellows Merete Brink Speedtsberg and Cecilie Køllner Olsen and Professor Per Hölmich (Main Supervisor and Medical Advisor) and Professor Mette Zebis (Co-supervisor) has initiated and will manage the trial.

Along with Jesper Bencke, they also form the steering- and writing committee, which will oversee the trial and decide on authorships and assume stewardship of the data for publications from the two phd's. Further publications and post hoc use of trial data must be approved by Professor Per Hölmich (Main Supervisor and Medical Advisor) and Professor Mette Zebis (Co-supervisor). No specific data monitoring committee is convened.

Frequency and plans for auditing trial conduct

{23}

No trial audit is planned.

Plans for communicating important protocol amendments to relevant parties

{25}

Amendments to the trial will be reported to the review board (Regional Committees on Health Research Ethics for The Capitol Region), and the amendments will be reported with justifications in the main report.

All protocol amendments must be approved by the trial scientific committee and when affecting statistical and data management aspects amendments Statistician Thomas Kallemose must be consulted.

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Appendix 1 – Clinical knee examination

Clinical knee examination

6 months ☐

12 months ☐

Has the patients scars been covered?

Yes ☐

No ☐

Reconstructed knee

Left ☐

Right ☐

Medical pain relief within the last 24 hours

Yes ☐

No ☐

Objective measures	Left	Right	Notes
Pivotshift Grade 0 (equal/absence) Grade 1 (+glide) Grade 2 (++clunk) Grade 3 (+++gross)			
Rolimeter (mm)			
Dialtest (30/90) Grade 0 (0-5 degrees) Grade 1 (6-10 degrees) Grade 2 (11-19 degrees) Grade 3 (≥20 degrees)	/	/	
Knee effusion (yes/no)			
RoM (EXT/FLEX)	/	/	

Appendix 2 – Biomechanical Protocol

Preparations BEFORE the participant arrives:

Lab:

a. Print the test form – Fill in possible information (12 months – transfer Metitur settings)

b. Check participant's status for cutting sport at 12-month test

c. Draw lots for right/left (dice – even = right, odd = left)

d. Prepare for EMG: electrodes + alcohol wipes + skin scraper

e. Prepare GRASE markers

f. Prepare the test track

g. Prepare for strength measurements: handheld dynamometer, strap, and suction cup for the floor

Metitur

Calibration of the Metitur is done once a month – see calibration protocol

Plug in the chair and computer and connect USB from chair to computer

Switch on at the back of the chair

Adjust the chair (at 12 months)

Creating a participant

a. Open the program – Good Strength (check connection)

b. Select Project: GRASE_HOVEDPROJEKT

c. Select examiner

d. Select Channel: Knee

e. Create/Select participant under system data

    i. S.I.C: ID_GRASE

    ii. First name: ID

    iii. Last name: GRASE

Vicon

Camera Calibration (Note: check 100Hz) (Mask Cameras; Calibrate; Set Volume Origin etc.)

Zero-Level Force Plates

Only keep the EMG receiver turned on when EMG is being recorded.

Creating a participant

a. Open VICON → research DB – GRASE ACL

b. Create new subject folder – Participant ID

c. Create new session in subject folder: Session name “6 months / 12 months”

d. Create new subject from Labeling Skeleton

    i. Model: GRASE.marts23.TEST2

Procedure – Preparation WITH the participant

Welcome + brief introduction to the program

Anthropometry measurements

a. Height – (with shoes – ideally same shoes at 6 and 12 months)
b. Weight – (with shoes)
c. Inter-ASIS distance (from ASIS to ASIS)
d. Leg length (ASIS to medial malleolus)
e. Knee width (lateral to medial epicondyle of the femur at 30° knee flexion)
f. Ankle width (lateral to medial malleolus)
g. Thigh circumference 10 cm above the upper edge of the patella
h. Lever arm:
i. Mark a line 7 cm proximal to the lateral malleolus
ii. Measure lever arm (7 cm proximal to the lateral malleolus to the lateral epicondyle of the femur). For tall participants, measure a shorter lever arm for use in the Metitur for the few participants whose lever arm is longer than 39.5 cm.

Fill out the test form + anthropometric measures in “subject” in Vicon.

EMG placement – Quadriceps

a. Palpate the muscle belly of VL, RF, and VM to find the most prominent point.
b. Mark with surgical marker, scrape, and clean with alcohol.
c. Place EMG electrodes in the following order:

EMG channel	Muscle
1	Left VL
2	Left RF
3	Left VM
5	Right VL
6	Right RF
7	Right VM

Adjust Metitur chair

See Metitur adjustment protocol
At the computer: Enter chair settings into the test form + any EMG changes

Standardized Warm-Up

TEST PROCEDURE

RTD + MVC + EMG MVC Quadriceps

Performed in the following order:
RTD extension – RTD flexion
MVC extension + EMG – MVC flexion

REPEATED for left and right sides – side determined by random draw

At the computer – note in test sheet if there are errors in a trial + prepare sock for EMG
Measure 1× leg length from the center of platform 1 for the jump test

Rate of Force Development (RTD)

Select Muscle Group: Knee Extension/Flexion Right/Left 60°

A. Test trials without recording

INSTRUCTION:

Fast and powerful/strong extension or flexion
Hold for 1–2 sec – do NOT hold until MVC
NO countermovement

B. Test trial with recording (up to 3 if necessary)
Measurement → New measurement
Measurement type: RFD 1 trial

INSTRUCTION:

Fast and powerful/strong extension or flexion
Hold for 1–2 sec – do NOT hold until MVC
NO countermovement

Start test → Zero level
Countdown 3-2-1 (delayed from the screen)
Visual error correction and repeat if needed

C. RTD measurement – 6× 1–2 sec with 30 sec pause

At the computer: VICON TRIALTYPE: "EMG_MVC"
Prepare Vicon filename: "RFD_QUAD_inj01" or "RFD_QUAD_heal01"
Start recording on count "1"
Mark as "good left" or "good right"

INSTRUCTION:

Fast and powerful/strong extension or flexion
Hold for 1–2 sec – do NOT hold until MVC
NO countermovement

Strong verbal encouragement during the test

D. MVC
Select Muscle Group: Knee Extension/Flexion Right/Left 60°

Test trial without recording

INSTRUCTION:
Strong – maximal extension/flexion

Hold for 4–5 sec – may be built up gradually
NO countermovement

E. Test trial with recording (up to 3 if necessary)
Measurement type: RFD 1 trial

INSTRUCTION:
Strong – maximal extension/flexion
Hold for 4–5 sec – may be built up gradually
NO countermovement

F. MVC – 3× 4–5 sec with 30 sec pause

At the computer: VICON TRIALTYPE: "EMG_MVC"
Prepare Vicon filename: "MVC_quad_inj01" or "MVC_quad_heal01"
Start recording on count "1"
Mark as "good left" or "good right"

Measurement type: GRASE_MVC
Check correct pre- and pause-settings
GIVE ALL INSTRUCTIONS (as in test trial)
Start test → Zero level
Countdown 3-2-1 (delayed from the screen)
Strong verbal encouragement during the test

G. Remove QUAD sensors carefully

MVC External Rotators

A. External Rotational Muscle Strength with Handheld Dynamometer
Participant sits at the end of the bed with knees and hips in 90 degerees.

INSTRUCTION:
Trunk upright (must not lean sideways)
Maximal force development – may be built up gradually
A fist is placed between the participant's knees to prevent hip abduction
Handheld dynamometer placed on the inside of the lower leg (on the marked line)

1–2 practice trials to 80%

3 MVCs in external rotation performed with 30 sec pause between trials

At the computer: Note measurements in test sheet

HAMSTRINGS – EMG MVC

A. EMG placement

a. Palpate the muscle belly of BF and ST at the most prominent point
v. Mark with surgical pen, scrape, and clean with alcohol
b. Place EMG electrodes in the following order:

EMG channel	Muscle
9	Left BF
10	Left ST
11	Right BF
12	Right ST

B. EMG MVC Hamstrings – 3x left and right

a. Patient in Prone position with 10° knee flexion

INSTRUCTION:
Maximal force development – may be built up gradually
1–2 test trials at 80% MVC
3 MVCs in flexion performed with 30 sec pause between trials

3D Recordings

Isolated jumps

All single-leg jumps are performed on both legs with starting leg decided by random draw.

A. Marker placement

CGM2.3 – 6 pelvis markers
Put elastic sock on thigh to minimize artifacts.

B. Static Measurement – 100 Hz

Instruction in static position (motor cycle pose)
TRIALTYPE: “Static”
Run Autoinitialize – step by step
Save trial

SWITCH TO 200 Hz AND TRIAL TYPE DYNAMIC

C. RoM trial

a. Participant performs 5 full extensions-flexions of each knee

D. Horizontal 1-leg jump

Filename: OLJ_inj01 or OLJ_heal01

3 valid trials performed per side

INSTRUCTION:

Take-off from FP1
Maximal horizontal hop
Valid if landing is controlled (no moving the foot, no support from other leg or hands)
Practice trials are given as needed

At the computer:

Mark as “good left” / “good right”
Check that heel marker is in volume

If not, note jump length from toe to toe

E. Vertical 1-leg jump

Filename: VOLJ_inj01 or VOLJ_heal01
3 valid trials performed per side

INSTRUCTION:

Take-off from FP1
Stand 1–2 sec before take-off for baseline
Maximal vertical hop – center of mass, not just the leg
Valid if landing within force plate

Practice trials are given as needed

At the computer:
Mark as “good left” / “good right”

F. Horizontal to Vertical Jump
Filename: HVJ_inj01 or HVJ_heal01

3 valid trials performed per side

INSTRUCTION:
Take-off from 100% mark
Land on FP1 with immediate maximal vertical take-off
Valid if landing within force plate
Practice trials are given as needed

At the computer:

Mark as “good left” / “good right”

G. Landing from Medial Rotation Hop
Filename: MRH_inj01 or MRH_heal01

3 valid trials performed per side

INSTRUCTION:
Take-off from 100% mark
Land on FP1 with 90° medial rotation
Valid if landing within force plate at 90 degrees on the take off postition and held for 2 sec. (no moving the foot, no support from other leg or hands).
Practice trials are given as needed

At the computer:
Mark as “good left” / “good right”

H. Countermovement Jump

Filename: CMJ01

3 valid trials performed

INSTRUCTION:

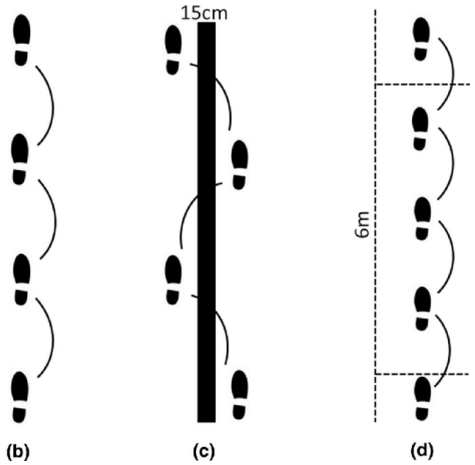
Participant with one foot on each force plate.
Stand still for 2 sec
Perform CMJ (starts from a standing position and initiates a downward movement, which is immediately fol- lowed by an upward movement leading to takeoff)
Valid if landing in balance with one foot on each force plate.

Functional Hop Test Cluster

RECORDED IN VICON

Start position adjusted to give a chance of hitting the force platform – but not required and not instructed to the patient.

2 valid trials performed on each side starting with healthy leg



A. Triple Hop for Distance (b)

Filename: THD_inj01 or THD_heal01

2 valid trials performed on each side

INSTRUCTION:

3 consecutive hops as far as possible

Valid if landing is controlled (no moving the foot, no support from other leg or hands)

Distance marked at the toe

Practice trials on each leg as needed

At the computer:

Mark as “good left” / “good right” if there is a strike on the force platform

Note if the landing foot is in volume.

B. Crossover Hop for Distance
Filename: CHD_inj01 or CHD_heal01

INSTRUCTION:

3 consecutive hops as far as possible crossing the midline

Valid if landing is controlled (no moving the foot, no support from other leg or hands)

Distance marked at the toe

Practice trials on each leg as needed

At the computer:

Mark as “good left” / “good right” if there is a strike on the force platform

Note if the landing foot is in volume.

C. 3. Single Leg 6 meter Timed Hop
NOT RECORDED in VICON

INSTRUCTION:

Single-leg Hop 6 meters for time

Self-selected jump frequency and length.

No requirement for controlled landing (just pass the 6 meter mark)

Time starts at take-off – ends when jump leg passes the 6 meter mark.

Practice trials on each leg as needed

D. Side Cut (cutting maneuver)

At 12 months – only for participants in handball and soccer

Filename: SC_inj01 or SC_heal01

3 valid trials on the force platform for each leg

INSTRUCTION:

Run towards the trash bin at high speed

Cut on the force platform

Practice trials on each leg as needed

At the computer:

Mark as “good left” / “good right” if there is a strike on the force platform

GRASE ACL – Metitur settings

a. LEG SUPPORT ANGLE (B): The knee joint angle is adjusted to 60 degrees of knee flexion, measured with a goniometer by the tester (Figure 6). This is read on a fixed measuring tape under the chair and entered into the computer (B).

b. The ankle is fixed with a belt strap, which is adjusted to the mark 7 cm proximal to the lateral malleolus (Figure 8).

c. LEG LEFT/RIGHT PLACEMENT: The degree of hip adduction and abduction is adjusted to ensure comfort for the test subject (approximately hip-width).

d. Belt fixation is applied distally on the femur and around the pelvis.

Figure 5: Starting position in the Metitur Good Strength (MGS) for measuring the Rate of Force Development of the hamstring muscles.

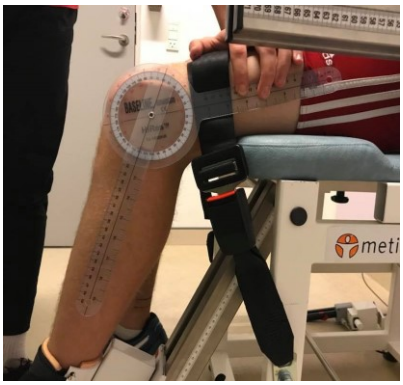


Figure 6: The standardized distance from the edge of the chair to the popliteal fossa, along with the measurement of the knee joint angle (60 degrees) in the MGS.

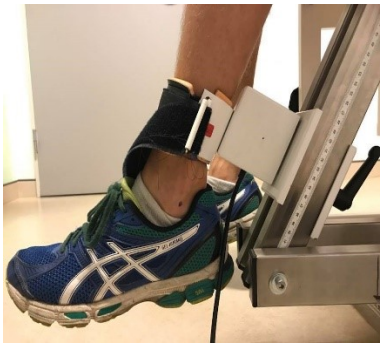


Figure 8: Ankle fixation with a belt strap at the marking for the lever arm in the MGS.

Appendix 3 – Medical imaging protocol

GRASE acl MRI-protocol

Scan

Leg length is measured before the first scan (by HBL) in two ways:

From ASIS (anterior superior iliac spine) to the medial ankle malleolus

From ASIS to the fibular head

At each examination, the following scans must be performed:

2 × axial PD-FS, 5/100% (5/5 mm) with 35 slices each (a total of 70 slices)

1 × coronal T1, 4/10% (4/0.4 mm) with 50 slices

For scanning, a vascular coil (Espree) is placed distally, and a body coil (Avanto) is placed proximally.

Both legs are scanned simultaneously, and therefore the FOV (field of view) must be 500 × 500 mm (max).

The scans are performed on an Avanto 1.5 T.

The FOV must be positioned so that scanning covers from the upper edge of the fibular head and proximally (upwards).

Image Processing

When measuring the change in length of the semitendinosus (semi-T), compensation must be made for any pelvic tilt. This is verified by determining the position of the medial joint space bilaterally on the coronal scan.

GRASE acl X-ray protocol

Examination guide tibial slope:
Acquire a true lateral projection, encompassing the proximal two-thirds of the tibia, to enable measurement of the angle between a line perpendicular to the mid-diaphyseal axis and the tangent to the medial tibial plateau.

Should the images be forwarded?
Images must be available in SP, Xero Viewer, and PACS.

Should patient data be anonymised?
No.

Are accompanying documents required?
No.

Are there specific requirements for the report?
No.

How often should the examination be performed?
Once per patient with suspected anterior cruciate ligament (ACL) injury.

Appendix 4 – SMS-Survey questions

Questions for SMS-track

1 – In the past 2 weeks, have you visited a doctor or physiotherapist because of pain or discomfort in your operated knee?

0 = No, 1 = Yes

2 – How often have you had pain in your operated knee in the past 2 weeks?

Never 0 1 2 3 4 5 6 7 8 9 10 All the time

2a – How severe has your knee pain generally been in the past 2 weeks?

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable pain

(Does not appear if they answered 0 or 1 in question 2.)

3 – How much rehabilitation have you completed for your ACL surgery in the past 2 weeks?

Minutes with a physiotherapist or other health professional present:

Minutes doing home exercises:

3b – Do you perform other knee-specific training or exercises (preventive/maintenance)?

0 = No, 1 = Yes

3c – Have pain or discomfort in your operated knee prevented you from completing your rehabilitation or knee-specific training exercises in the past 2 weeks?

To a very high degree / To a high degree / To some degree / To a small degree / Not at all

4 – How would you rate your maximum current physical/athletic/sporting function level?

Cannot be physically active 0 1 2 3 4 5 6 7 8 9 10 Function level as when it was at its best

4b – Have pain or discomfort in your operated knee prevented you from returning to your sport?

To a very high degree / To a high degree / To some degree / To a small degree / Not at all

5 – In the past 2 weeks, have you been on sick leave from work or education because of your ACL injury?

Yes / No / I am not employed or in education

5b – How would you rate your current physical work ability in the past 2 weeks?

Unable to work at the moment 0 1 2 3 4 5 6 7 8 9 10 My work ability is as when it was at its best

5c – Have pain or discomfort in your operated knee limited you in your work or education in the past 2 weeks?

To a very high degree / To a high degree / To some degree / To a small degree / Not at all

(Do not appear if they answered "I am not employed or in education" in question 5.)

Appendix 5 – Written information and Consent form

Participant Information for Participation in a Scientific Study

Study Title: GRASE ACL – Optimizing GRAft SElection for ACL Reconstruction

We would like to invite you to participate in a scientific study carried out by the Arthroscopic Center Hvidovre, the Gait Laboratory, and the Functional and Imaging Diagnostic Unit at Amager & Hvidovre Hospitals, in collaboration with University College Copenhagen. The study is initiated by Chief Consultant and Professor Per Hölmich.

Before you decide whether to participate, it is important that you fully understand the purpose of the study and what participation will involve. We therefore ask you to read this participant information carefully.

You will also receive detailed verbal information about the study from a member of the research team. If you have any questions that remain unanswered after reading this document, you are welcome to contact the research group using the contact details provided on the last page.

If you decide to participate, you will be asked to sign an informed consent form. You are entitled to take time to consider your decision before signing.

Participation is voluntary. You may withdraw your consent at any time without giving a reason, and this will not affect your further medical care.

If you develop illness or sustain an injury to your musculoskeletal system that prevents you from completing the project's tests or could otherwise influence the final results, we may need to withdraw you from the study. This will not affect your continued treatment. There are no anticipated reasons why the entire project would be terminated.

Purpose of the Study

The purpose of this study is to compare three different surgical techniques for reconstructing the anterior cruciate ligament (ACL). All three techniques are approved and used in standard clinical care. We aim to determine which method provides the best function and fewest problems during and after rehabilitation, as well as to investigate the underlying reasons.

A total of 150 participants aged 18–40 years will take part in the study.

Study Plan

If you wish to participate and have signed the informed consent form, you will be randomly assigned to one of three groups, differing by the tendon used to create the new ACL – either from the hamstring muscles, the quadriceps tendon, or the patellar tendon.

Before surgery, the operating surgeon will perform a standard clinical knee examination, and you will be asked to complete questionnaires regarding pain, self-perceived knee function, and fear of movement/exercise. These questionnaires will be repeated at 6, 12, and 24 months after surgery, along with additional questions about your ability to return to sports.

At 6 and 12 months after surgery, you will undergo the same knee examination. In addition, you will complete a biomechanical test involving 3-D motion capture and surface EMG muscle activity measurements while performing physiotherapy-based tests, change-of-direction movements, and muscle strength tests. You will also undergo an MRI scan.

All assessments will take place at Hvidovre University Hospital. We aim to schedule them on the same days as far as possible to minimize your time commitment. Completing the questionnaires is expected to take 1–1.5 hours, the clinical knee examination 30 minutes, the biomechanical test 2 hours, and the MRI scan 1 hour.

After 12 months, the main part of your participation will end, and you will be offered feedback on your tests. You will, however, remain in the project until 24 months after surgery, when we will ask you to complete a selection of the same questionnaires again.

During the study, we will request access to relevant notes in your medical record concerning your ACL injury, surgery, and postoperative progress. You will also be asked to answer two text messages per month during your rehabilitation, briefly asking about your knee function.

Overview of Assessments:

Assessment	Preop	1 mo after	6 mo after	12 mo after	24 mo after
Clinical knee exam				½ hr	½ hr
Questionnaires	1 hr		1 hr	1 hr	1 hr
Biomechanical test				2 hr	2 hr
MRI scan					1 hr
SMS replies				Bi-weekly	

Benefits of the Study

The results may contribute important new knowledge for further optimizing ACL reconstruction techniques. This could potentially guide the development of individualized rehabilitation protocols depending on graft choice. The results may also help establish future surgical decision-making criteria to reduce the risk of complications and re-injury.

For you personally, participation means closer follow-up during rehabilitation, with more frequent assessments and individual feedback on selected tests from the study. SKRIFTLIG

Side Effects, Risks, Complications, and Inconveniences

None of the assessments involve invasive procedures (such as biopsies or blood samples). MRI scanning is non-invasive and uses magnetic fields and radio waves; there are no known harmful effects.

Standard X-rays will be taken. According to the Danish Patient Handbook, this will expose you to an amount of radiation equivalent to a few days of natural background radiation from the atmosphere, and is therefore considered negligible.

After coordination and balance tests, you may experience mild temporary muscle soreness. However, no tests will be used that are not already applied in standard rehabilitation evaluation.

The study will also require your time for assessments and travel to/from Hvidovre Hospital.

There may be risks we are not yet aware of. You are therefore asked to report any health problems you experience during the study. If we discover any new side effects not mentioned here, you will be informed immediately, and you will be asked to decide whether you wish to continue.

Financial Information

The project is based at the Orthopaedic Surgery Department, Amager and Hvidovre Hospitals. The collaborating partners are all experienced in their respective fields, ensuring high research quality. All project staff are fully funded by Hvidovre Hospital and the Novo Nordisk Foundation to carry the project through to completion.

Access to Study Results

The results will be published in academic journals and presented at conferences. They will also be communicated to orthopaedic surgeons and physiotherapists in Denmark and internationally.

At the end of the project, a summary written for study participants will be prepared.

We hope this information has given you sufficient insight into what participation will involve and that you feel prepared to make your decision. Please also read the enclosed material *"The Rights of the Research Participant in a Health Science Research Project"*.

If you would like more information, please feel free to contact:

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Cecilie Køllner Olsen Email: cecilie.koellner.olsen.01@regionh.dk Phone: 24 89 91 15

Kind regards, on behalf of the GRASE ACL Project Merete Brink Speedtsberg & Cecilie Køllner Olsen

Research Project Title: GRASE ACL: Optimizing GRAft SElection in ACL Reconstruction

Declaration by the Participant:

I have received written and oral information, and I know enough about the purpose, method, benefits, and disadvantages to agree to participate.

I understand that participation is voluntary, and that I may withdraw my consent at any time without losing my current or future rights to treatment.

I consent to participate in the research project and have received a copy of this consent form as well as a copy of the written project information for my own use.

Participant's Name: _____

Date: _____ **Signature:** _____

Would you like to be informed about the results of the research project and any possible consequences for you? YES _____ (tick) NO _____ (tick)

May the project use video and image material of you for teaching purposes and communication of the project results? YES _____ (tick) NO _____ (tick)

Access to Medical Records:

I have received written and oral information about what information will be obtained from my medical records, and I consent to the project staff having access to my records from today's date, as well as contacting me once a year for five years to obtain renewed consent for access to my records regarding the current injury.

Participant's Name: _____

Date: _____ **Signature:** _____

Declaration by the Person Providing the Information:

I declare that the participant has received verbal and written information about the research project. In my opinion, sufficient information has been provided for the participant to make a decision about participating in the study.

Name of Person Providing Information: _____

Date: _____ **Signature:** _____