Which patient with an anterior cruciate ligament rupture will need a surgical reconstruction?

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PROTOCOL SIGNATURE SHEET

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PROTOCOL TITLE '*Which patient with an anterior cruciate ligament rupture will need a surgical reconstruction?*'

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Laboratory sites	***NA***
Pharmacy	***NA***

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: It is unknown what the most optimal treatment is for the individual patient with an anterior cruciate ligament (ACL) rupture.

Objective: To evaluate the effectiveness (primary) and cost-effectiveness (secondary) of a treatment algorithm for patients with a complete ACL rupture compared to current used treatment strategy, over a follow-up period of 2 years. With the treatment algorithm faster recovery of functional outcome will be achieved compared to the current practice (superiority study). As a secondary outcome we expect that a faster recovery of functional outcome will lead to a faster return to work and sports. Hence, we hypothesize that the treatment algorithm will lead to lower societal cost.

Study design: Cluster randomized design, randomization will take place on hospital level. All patients will be followed for 2 years.

Study population: Adult patients with a complete primary ACL rupture.

Intervention (if applicable): intervention group: a treatment algorithm has been formulated, based on a previous performed systematic review, results of recently finished RCT, and an assigned ACL expert panel. Special attention is given to shared decision making.
Control group (usual care): treatment decision is made based on the experience of the orthopedic surgeon combined with the preference of the patient.

Main study parameters/endpoints: Recovery of physical functioning during 2 years assessed by the IKDC questionnaire. Besides, differences in medical consumption, absence from work or decreased productivity, and patient costs, will be assessed.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden is primarily time (visit of outpatient clinic, and to fill in questionnaires). There is no direct benefit from participation or group relatedness.

1. INTRODUCTION AND RATIONALE

An anterior cruciate ligament (ACL) rupture causes serious morbidity with large socio-economic impact(1). The overall incidence of ACL injury is 78 per 100.000 persons(2, 3). The group at risk, between 15-39 years old, shows an incidence of 85-91 in 100.000 people per year(2). The incidence of surgical ACL reconstructions is increasing, particularly in women as well as patients younger than 20 years and those 40 years and older. Patients with an ACL rupture may experience knee instability and are at risk for concomitant injuries of menisci, cartilage and collateral ligaments. This leads to decreased activity and poor knee-related quality of life. Moreover, medical expenses, patient costs and loss of productivity costs are impressive(4-6).
A patient with an ACL rupture can be treated nonoperatively (rehabilitation program) or by surgical ACL reconstruction. The primary goal of both treatment options is to restore knee stability without risk of concurrent knee injuries. Functional instability of the knee can be treated by ACL reconstruction, of which aproximately 8.000 are performed annually in the Netherlands. The Dutch guideline "Anterior cruciate ligament injury" was updated in 2018. In the current Dutch guideline, recommendation for treatment choice for the individual patient is mainly based on expert opinion, because strong scientific evidence is lacking. Consequently, no strong recommendations are given. As a consequence of this, the majority of patients diagnosed with an ACL rupture are currently advised to undergo surgical reconstruction. Whether surgical reconstruction is the most optimal treatment for the majority of all patients with an ACL rupture is debated.

Noyes reported in 1985 the "rules of thirds", indicating that some patients are capable to cope with an ACL ruptured knee and others do not. Potential copers are considered to be able to return to their pre-injury sports activity level without surgical reconstruction. Noncopers do not succeed in regaining adequate knee stability and are considered to be candidates for ACL reconstruction. Till date it is unknown which patient will be capable of restoring adequate knee stability, for sports and daily activities, by means of nonoperative management and who will require surgical reconstruction. Patients who will not be capable to restore adequate knee stability by means of physical therapy, will need a delayed surgical reconstruction. Consequently, these patients will have two rehabilitation periods, before (3-6 months) and after surgery (9-12 months). A treatment algorithm would be essential to identify the non-coping patients indicated for early surgical reconstruction after injury.
The current proposal covers one of the top-10 prioritized topics of the "Agenda Zorgevaluatie Orthopedie", and is supported by all relevant stakeholders. The members of the Dutch guideline ACL rupture are actively involved as project members of the proposal. Moreover, the

proposal is a follow-up project of a recent cost-effectiveness study of patients with an ACL rupture, in which early surgical reconstruction and a more conservative treatment strategy were compared (COMPARE study/ ZonMw 171102006).

HEALTH CARE EFFICIENCY PROBLEM

In the recently updated Dutch guideline "Anterior cruciate ligament injury" recommendation for treatment choice for the individual patient are mainly expert opinion based. The guideline stated that ACL reconstruction can be advised to patients with symptomatic instability of the knee after ACL injury, which is not reduced after physiotherapeutic exercise program or after adjustment of activity(7). Looking at the number of ACL reconstructions in the Netherlands in the last 10 years, there is an increase of more than 60% (from 5.000 to 8.000). The general assumption is that the incidence of ACL ruptures is also increasing, but not as fast as the amount of surgical reconstructions. This suggests that the proportion of ACL reconstructions has also increased. A successful non-operative treatment is more cost-effective than a surgical reconstruction. A certain amount of patients are able to return to their pre-injury sports activity level without surgical reconstruction. On the other hand, some patients need a surgical reconstruction after non-successful physical therapy. These patients will need two rehabilitation periods besides the surgical reconstruction. So, it will be highly efficient to know the most optimal treatment for the individual patient with an ACL rupture as soon as the diagnosis has been made.

USUAL CARE

The recommendations of the Dutch guideline are stated above. Because of the absence of a clear treatment algorithm, the current daily practice is that a treatment choice is made based on the clinical experiences of the orthopedic surgeon combined with the preference of the patient. Patients are treated non-operatively under supervision of a physical therapist, or with an early surgical ACL reconstruction which is possible not indicated and also with delayed ACL reconstruction after physical therapy has been unsuccessful.

(SUB-)GROUP OF PATIENTS

Patients visiting the outpatient clinics of one of the participating hospitals with a recent ACL rupture are eligible for inclusion.

THE INTERVENTION TO BE INVESTIGATED

[redacted]

EXISTING EVIDENCE OF EFFECTIVENESS

We recently finished the 2-year follow-up of the COMPARE study (n = 167). In this study patients were randomized to an early surgical ACL reconstruction or non-operative treatment with optional (delayed) ACL reconstruction. Of the 82 patients who were randomized to the non-operative treatment with optional ACL reconstruction group, 50% underwent a delayed reconstruction during the 2 year follow-up. Recovery of physical functioning was similar for the early ACL reconstruction patients and those who were treated non-operatively. However, patients that underwent a delayed ACL reconstruction after unsuccessful physical therapy, had lower physical functioning scores at two year. Our RCT confirmed the results of a previous RCT (KANON study) of the group of Frobell (n = 121)(8, 9). They also showed that 51% of the initially non-operatively treated patients underwent delayed reconstruction. Both groups showed no statistically significant differences regarding the presence of radiological osteoarthritis, patient reported outcomes and the amount of meniscus surgery. A systematic review of Smith et al(10) concluded that there is insufficient evidence to base clinical decision-making with respect to treatment opinions for people following ACL rupture. A systematic review of Eggerding et al(11) showed there is limited evidence (1 study) that a combination of baseline characteristics could distinguish between those patients who needed ACL reconstruction and those who sufficed with nonoperative treatment.

Based on the current state of knowledge there is still no consensus on clinical decision-making of a patient with an ACL rupture. Thanks to our COMPARE study and the KANON study it will be possible to better support clinical decision-making.

GUIDELINE

The Dutch guideline "ACL injury" has been updated and approved by the Dutch orthopedic society in 2018(12). The recommendation for the most optimal treatment for the individual patient is mainly based on expert opinion. ACL reconstruction can be advised to patients with symptomatic instability of the knee after ACL injury, which is not reduced after physiotherapeutic exercise program or after adjustment of activity.

RELEVANCE FOR PRACTICE

Based on the current evidence and existing guidelines it is unknown for which patient nonoperative management will be successful and which patients will need early reconstructive surgery. Our ACL treatment algorithm will be helpful to distinguish these patients. An ACL treatment algorithm will diminish unnecessary surgery or delay of surgery. As a consequence of this less surgical complications on group level will be seen. The Dutch Orthopedic Association (NOV) supports this proposal as one of the key unanswered orthopedic treatment issues, which shows the need for improvement of care.

PATIENT PARTICIPATION

In absence of an adequate patient association, we formed a panel of patients with an ACL rupture to think along with and comment on our study. A participation plan has been formulated in which for each phase of the project the patient participation is stated.

ANTICIPATED COST-EFFECTIVENESS

In general, young and active patients will suffer a considerable economic burden in absence from work related to their knee injury. The total costs of a surgical procedure are estimated at €7280: surgical procedure costs (€5000 per patient), rehabilitation costs (9 months twice a week physiotherapy á €30 ≈ €2280), and costs due to absence from work (≈ 27 days*8 hours*€34,75/hour = €7500). The total costs of a non-operative treatment are estimated to be lower because of absent surgical costs, and generally a rehabilitation twice as short (€1140) and shorter absence from work (≈ 14 days*8 hours*€34,75/hour = €3900). Patients that will receive a delayed operation are the most expensive group (medical costs: €8420 and productivity loss: €7500). The actual situation is that 80-90% of the patients with an ACL rupture will be treated with a surgical reconstruction. We expect that the treatment algorithm will result in fewer patients receiving a surgical reconstruction compared to the current practice (50% instead of 80%). The estimated yearly total medical cost-saving could potentially be: estimated fewer surgical procedures of 3000 (8000-5000 ACL reconstructions) * 6140€ = 18.420.000€ yearly in the Netherlands. The gain in productivity costs is: 3000 ACL reconstructions * 3610€ = 10.830.000€. The yearly total gain will potentially be 29.250.000€.

IMPLEMENTABILITY

Aim is to implement the results of this study in an update of the Dutch guideline. The results will be presented to the different professional associations of orthopaedic surgeons, trauma surgeons, general practitioners, sports physicians and physiotherapists and on several (inter)national scientific conferences. They also will be published in international peer-review journals.

DIVERSITY

Given the few exclusion criteria and broad representation of hospitals our population will represent the Dutch situation of patients with an ACL rupture. This population will typically consist of more younger and active patients varying in ethnic and socio-economic background.

OPEN ACCESS

A Data Management Plan will be written that will contain detailed information regarding data gathering, data analysis, data storage during and after the research project. Naturally we plan open access to the results by peer-reviewed publications and scientific presentations.

2. OBJECTIVES

Nowadays the majority of the patients with an ACL rupture will go for a surgical reconstruction. Whether this is the most optimal treatment for each patient is debated. Some patients are able to return to their pre-injury sports activity level without surgical reconstruction. On the other hand, some patients need a (delayed) surgical reconstruction after physical therapy has been unsuccessful. We formulated a treatment algorithm based on a previous performed systematic review, results of recently finished RCT, and an assigned ACL expert panel. The aim of the current project is to evaluate the effectiveness and cost-effectiveness of this treatment algorithm for patients with a complete primary ACL rupture compared to current used treatment strategy, over a follow-up period of 2 years. The current treatment strategy (control group) is based on the recently updated guideline "anterior cruciate ligament injury".

HYPOTHESIS

The hypothesis is that the treatment algorithm will lead to earlier identification of both treatment options, this means those patients indicated for a surgical reconstruction and those that will be able to cope based on an exercise program. Consequently, we expect that overall fewer patients will receive a surgical reconstruction compared to the current practice. Furthermore, we expect that less patients need later surgery after revalidation has failed. Hence, we hypothesize that with the treatment algorithm faster recovery of functional outcome will be achieved compared to the current practice (superiority study). Recovery of functional outcome will be evaluated at multiple time points during two year follow-up, and will be expressed as change in International Knee Documentation Committee (IKDC) score (subjective form) compared to baseline. As secondary outcome we expect that a faster recovery of functional outcome will lead to a faster return to work and sports. Hence, we hypothesize that the treatment algorithm will lead to lower societal cost.

RESEARCH QUESTIONS

Primary:

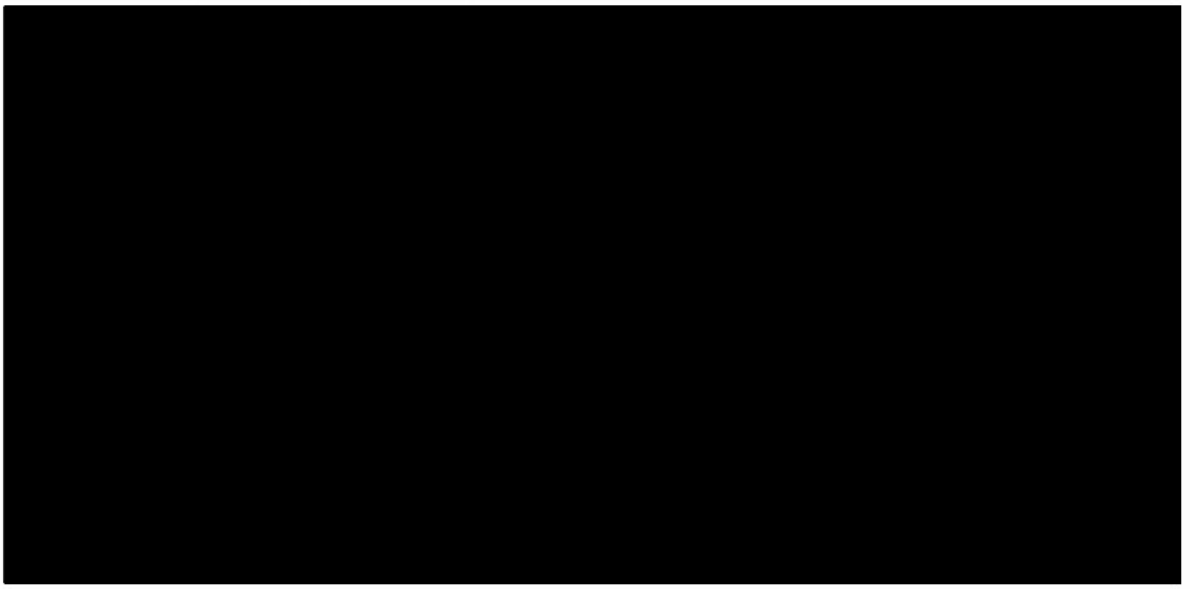
1) Is the treatment algorithm for patients with a complete primary ACL rupture superior to the current practice regarding recovery of functional outcome during two year of follow-up?

Secondary:

2) Will this treatment algorithm lead to lower societal costs compared to the current practice?
3) Does this treatment algorithm lead to less surgical ACL reconstructions?

3. STUDY DESIGN

Treatment algorithm (prior to study start)



Cluster Randomized Controlled Trial

The present proposal has a cluster randomized design, and its main concern is a comparison of the cost-effectiveness of two treatment decision strategies for patients with an acute ACL rupture, namely the current used surgeon based choice and ACL treatment algorithm embedded in the shared decision process. To avoid dilution between both treatment decision strategies, randomization will take place on hospital level, meaning that all patients referred by one hospital the treatment choice will be based on the same treatment decision strategy. This will be done to overcome that the treatment choice of a participating orthopedic surgeon will be influenced by knowledge of the algorithm, in case the Hospital is allocated in the control group. The treatment algorithm will be implemented by training of the orthopedic surgeon, and by the use of a specific intervention incorporation the algorithm application. Patients will be followed for 2 years. The following hospitals will participate in this trial: Erasmus MC (Rotterdam), Haaglanden MC (Den Haag), Martini hospital (Groningen), Máxima MC (Eindhoven), St. Antonius hospital (Utrecht), Noordwest hospital group (Alkmaar), and Tergooi hopsitals (locatie Hilversum).

A detailed economic evaluation will be performed evaluating costs and effects.

4. STUDY POPULATION

4.1 Population (base)

All adult patients with an ACL rupture, visiting an orthopaedic surgeon of one of the participating hospitals will be invited to participate.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria: aged 18 year or older, with a complete primary ACL rupture (confirmed by MRI and physical examination), maximum of 6 weeks of physical therapy, and willing to comply with the study protocol.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study: multi ligament trauma indicated for surgical intervention, presence of another disorder that affects the activity level of the lower limb, pregnancy, and insufficient command of the Dutch language.

4.4 Sample size calculation

Our primary research hypothesis is that with the treatment algorithm faster recovery of functional outcome will be achieved compared to the current practice (superiority study). Recovery of functional outcome will be evaluated at multiple time points during two year follow-up, and will be expressed as change in IKDC score (subjective form) compared to baseline. The standard deviation (SD) of the IKDC after 24 months of follow-up has been reported to be 10.7(21). We aim to find a clinically relevant additional effect of the algorithm to usual care. Therefore, our hypothesis is that the potential additional effect size should be minimally 0.5 (6 points). For the intra cluster correlation coefficient we used an ICC of 0.10 which is reported for hospital processes. Based on a difference of 6 points, SD of 10.7, an ICC of 0.10 (randomization on hospital level), a power of 85%, an α of 0.05, and 8 participating hospitals; 25 patients per hospital need to be included (200 patients in total). To accommodate a 10% dropout rate, 28 patients per hospital are required, resulting in a final sample of 224 patients (8 hospitals * 28 patients per hospital).

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

a) Index group (see figure in appendix):
In the intervention specific attention is given to shared decision making, which takes into account that not only the outcome of the decision is important (determination), but also the process of coming to a decision (deliberation)(13, 14). At the initial consult, the ACL rupture will be clinically diagnosed. Also additional patient specific information will be collected essential for the ACL treatment algorithm. The patient will receive the consultation card "ACL treatment". Between the 1st and 2nd consult the patient is asked to read the consultation card. At the 2nd consult the outcome of the ACL treatment algorithm will be given and the information of both treatment options as described at the consultation card will be discussed. The final treatment choice will be made by shared decision making. The treatment preferences of the patient will be evaluated thrice; directly after the first consultation, after reading the consultation card before the 2nd consultation and as the final treatment decision. Also the treatment preference of the physician will be evaluated directly after the 1st consult.
b) Control group:
Usual care in which the treatment decision is made based on the experience of the orthopedic surgeon combined with the preference of the patient. In this group the patient does not get the consultation card "ACL treatment" and the physician does not have the ACL treatment algorithm.

5.2 Use of co-intervention

NA

5.3 Escape medication

NA

6. INVESTIGATIONAL PRODUCT

NA

6.1 Name and description of investigational product(s)

6.2 Summary of findings from non-clinical studies

6.3 Summary of findings from clinical studies

6.4 Summary of known and potential risks and benefits

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labelling of Investigational Medicinal Product

6.8 Drug accountability

7. NON-INVESTIGATIONAL PRODUCT

NA

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Difference between both groups in recovery of physical functioning as assessed by International Knee Documentation Committee (IKDC) questionnaire during 24 months follow-up(18). The IKDC is a valid and responsive outcome measure for patients with an ACL rupture.

8.1.2 Secondary study parameters/endpoints (if applicable)

- Return to sport activity and level of sport activity: Tegner score.
- Knee pain: number rating scale (NRS)
- Knee specific outcome score (Knee Injury and Osteoarthritis Outcome Score (KOOS))
- Satisfaction with treatment
- Kinesiophobia: Tampa scale
- General quality of life: EQ-5D-5L
- total costs: intramural and extramural medical costs (iMCQ) and productivity loss (iPCQ);
- adverse events
- physical examination, stability tests of the knee: Lachman, anterior drawer and pivot shift tests
- Surgeons fidelity to intervention, shared decision process.

8.1.3 Other study parameters (if applicable)

At baseline measurement we will inventory baseline characteristics (age, sex, ethnicity, body mass index (BMI), educational status, marital status, living arrangements, employment status and musculoskeletal comorbidities, other co-morbidity).

8.2 Randomisation, blinding and treatment allocation

To avoid dilution between both treatment decision strategies, randomization will take place on hospital level, meaning that all patients referred by one hospital the treatment choice will be based on the same treatment decision strategy. Randomization will take place before start of the inclusion period, and will be done by the use of a computer generated randomization list. The randomization will be stratified for academic versus non-academic Hospital.

8.3 Study procedures

Eligible patients visiting an orthopedic surgeon of one of the participating hospitals will be informed about the study and invited to participate by the physician. Besides, the patient will receive written information. If they are willing to participate, they will be screened for eligibility. Randomization as reported before will take place at hospital level. When the patient conforms to the inclusion criteria and gives written informed consent, the study procedures can be started. If the patient is not willing to participate, the treatment decision will be made as usual (see described control group, page 16).

In table 1 an overview (appendix) of all measurements is given. At baseline we will collect baseline characteristics. Knee specific outcome measures will be used to evaluate symptom level (NRS-pain, KOOS), and recovery of physical functioning (IKDC score). Level of sport activity will be assessed by Tegner scale. All these outcomes are widely used and validated for patients with an ACL rupture. Patients will be asked to fill in questionnaires (web-based system, Gemstracker).

The efficacy of the shared decision making process will be evaluated by the level of 9-Item Shared Decision Making Questionnaire (SDM) for both patients and doctors(19), and decision quality (measured with Decisional Conflict Scale (DCS))(20). Also in the control group the deliberation and determination of shared decision making will be evaluated with these instruments.

EQ-5D-5L use is recommended for the assessment of quality of life in trauma patients, especially for economic assessments. The patients' EQ-5D-5L health states will be converted into utility scores using the Dutch tariff. The EQ-5D will be used for the cost-utility analysis.

Costs for health care and production loss will be measured using a questionnaire that is based on the Medical Consumption Questionnaire (iMCQ) and Production Consumption Questionnaire (iPCQ), validated by the Institute of Medical Technology Assessment (Erasmus University, Rotterdam, The Netherlands). iMCQ includes details on medical specialist care,

physical therapy, hospitalization, nursing home, home care, and other costs directly associated with diagnosis, treatment and rehabilitation. iPCQ includes details on work resumption and production losses.

Delivering an intervention as intended, also referred to as fidelity, is positively associated with better outcomes. Surgeons' fidelity will be measured with a self-developed Therapy Adherence Measurement (TAM). The development of the TAM will be guided by characteristics as described in the literature. First, the purpose of this fidelity measurement was established, after which essential elements of shared decision making will be identified an included in the measure. In order to analyse fidelity, 2-3 consultations (of one intervention hospital) will be video recorded and analysed using a semi-structured observation protocol.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

8.5 Replacement of individual subjects after withdrawal

No.

8.6 Follow-up of subjects withdrawn from treatment

Following usual care evaluations.

8.7 Premature termination of the study

NA

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

NA

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);

2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC *<reporting via webportalToetsingOnline is only applicable for investigator initiated studies>*:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

NA

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

NA

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

The difference between groups in course of recovery of physical functioning as assessed by International Knee Documentation Committee (IKDC) questionnaire during 24 months follow-up will be used as primary outcome. Patients will be analyzed according to the intention-to-treat principle. The primary analyses will be performed by using mixed models (IKDC at the various time points as dependent and intervention as fixed and hospital as random independent variable). Differences in course of recovery of physical functioning will be tested by the interaction between intervention and time. If necessary, adjustments for unbalanced covariates will take place.

10.2 Secondary study parameter(s)

Difference between groups in return to sport activity, knee pain, satisfaction with treatment, kinesiophobia, and quality of life will be used as secondary outcomes. The analyses will be performed by using linear or binary mixed models for repeated measures.

COST EFFECTIVENESS ANALYSIS (CEA)

An economic evaluation will be conducted from a societal perspective in accordance with the Dutch guidelines(22) in which medical costs and loss of productivity costs will be considered. The time horizon will be 2 years to include all relevant costs and effects.

Both a cost-effective (CEA) and cost-utility (CUA) analysis will be performed. Direct intramural and extramural care costs will be calculated (e.g. operation, physiotherapy, hospital days, costs of side effects, wound infections) and indirect non-medical costs (e.g. productivity losses). Data on medical resource use will be collected from the electronic hospital information systems, based on the iMTA Medical Consumption Questionnaire (iMCQ).

For the calculation of medical costs, we will use charges as published in Dutch guidelines as a proxy of real costs(22). The unit price of the surgical ACL reconstruction and the intensive exercise program will be calculated with the micro-costing method. Productivity costs are assumed to be substantial and will be registered in detail by the iPCQ.

The economic evaluation of the ACL treatment algorithm for patients with an ACL rupture compared to usual care will be calculated as the incremental cost-effectiveness ratio (ICER). The primary effect outcome measures will be difference in recovery of physical functioning as assessed by IKDC for the CEA and quality adjusted life years (QALY) for the CUA. QALYs will be measured for a 2 year period, based on the Dutch tariff for the EQ-5D.

In order to account for the possible clustering of data, analyses will be performed using linear multilevel analyses(23). Accounting for the possible clustering of data (*e.g.*, at the hospital level) is very important, as most economic evaluations fail to do so, whereas ignoring the possible clustering of data might lead to inaccurate levels of uncertainty and inaccurate point estimates.

The sensitivity analysis will assess the robustness of the results to changes in costs and effect parameters. Bootstrapping with 5000 replications will be used to estimate 95% confidence intervals around cost differences and the uncertainty surrounding the ICERs. This will be graphically presented on cost-effectiveness planes and acceptability curves using the net benefit framework(24). Cost-effectiveness acceptability curves show the probability that the intervention is cost-effective in comparison with usual care for a range of different ceiling ratios thereby showing decision uncertainty. For the time horizon of 24 months, discounting is not necessary.

BUDGET IMPACT ANALYSIS (BIA)

The BIA will be performed following principles for good practice(25). Results of the economic evaluation will be linearly extrapolated over a period of 5 years to estimate the financial consequences of wide-spread implementation of the ACL treatment algorithm within ACL patients in the Dutch healthcare system. Furthermore, national incidence data will be used. Analyses will be performed for the societal-, Budgettair Kader Zorg (BKZ)-, health insurer's- and health care perspective. Within the BKZ perspective we will estimate the effect on the medication budget and specialized medical care budget. The intervention's effectiveness of this study will be extrapolated by a Markov model. Different scenario's will be considered in the BIA; a) usual care, b) scenario in which the ACL treatment algorithm is implemented in 100% of the patients, and c) scenario with gradual implementation (e.g. 80%) over time. The proportion and characteristics of the target population will be estimated using Dutch epidemiological data. For each perspective different prices will be used. In the societal and health care perspective standard prices will be used(22). For the BKZ and health insurer's perspective tariffs established by the Dutch Healthcare Authority (Nederlandse Zorgautoriteit) are used. Sensitivity analysis will be done on parameter uncertain parameters (e.g. % implementation, and optimization of the ACL treatment algorithm) and structural uncertainty (assumptions in the framing of the BIA).

10.3 Other study parameters

NA

10.4 Interim analysis (if applicable)

NA

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th version, date, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts .

11.2 Recruitment and consent

Eligible patients seen at the outpatient clinic of one of the participating hospitals, because of an ACL rupture and fit to the inclusion and exclusion criteria, will be informed about the

study and invited to participate by the physician. Besides the patient will receive written information.
If the patient is interested the physician will check whether the patient fits to the inclusion and not to the exclusion criteria. If the patient fits and sign the informed consent form they will receive the baseline questionnaire by email.

11.3 Objection by minors or incapacitated subjects (if applicable)

NA

11.4 Benefits and risks assessment, group relatedness

NA

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

NA

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Personal data of the participating patients that will be collected during the study, will be changed by a study number. This number will be used for all study documentation, and all study reports or publications. The key of this study number will be handled by an independent researcher. All data will be stored during the study period, and if the patient give informed consent for a total of 15 years.

12.2 Monitoring and Quality Assurance

The study will monitored according to the monitoring plan (document K).

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

NA

13. STRUCTURED RISK ANALYSIS

NA

13.1 Potential issues of concern

NA

a. Level of knowledge about mechanism of action

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

d. Selectivity of the mechanism to target tissue in animals and/or human beings

e. Analysis of potential effect

f. Pharmacokinetic considerations

g. Study population

h. Interaction with other products

i. Predictability of effect

j. Can effects be managed?

13.2 Synthesis

NA

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