RESEARCH PROTOCOL

The 10-year follow-up of the ESCAPE trial:
Do patients with a degenerative meniscal tear develop more knee osteoarthritis after knee surgery compared to exercise therapy?

PROTOCOL TITLE The 10-year follow-up of the ESCAPE trial: Do patients with a degenerative meniscal tear develop more knee osteoarthritis after knee surgery or after exercise therapy?

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Subsidising party	***-Stichting Wetenschap OLVG***
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Laboratory sites	***Not applicable***
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TABLE OF CONTENTS

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: Osteoarthritis in the knee is a disease with a large burden. Previous study shows that meniscal surgery seems to be one of the etiological factors to accelerate the development of osteoarthritis in the operated knee, but this still lacks proof. The ESCAPE trial (meniscal surgery versus exercise therapy) was one of the biggest multicenter randomized controlled trials in this area of expertise, in which 321 patients have participated. The participants of the ESCAPE trial (age 45 – 70 years at baseline) were all diagnosed with a symptomatic, non-obstructive meniscal tear. After 5 years a similar progression of osteoarthritis was found for both treatment allocations. In this 10-year follow-up study, we are interested in the long-term progression of osteoarthritis in the knee. We hypothesise that patients who underwent surgery show a more severe progression of osteoarthritis in the affected knee, 10 years after surgery, compared to patients who underwent exercise therapy.

Objective: To compare the degree of osteoarthritis in the knee after 10 years, in patients with non-obstructive meniscal tear, between meniscal surgery and exercise therapy treatment.

Study design: Observational follow-up study of a randomized controlled trial.

Study population: Participants of the ESCAPE trial who gave consent to be approached for a follow-up study.

Intervention (if applicable): Not applicable in the 10-year follow up of the ESCAPE trial.

Main study parameters/endpoints: Osteoarthritis in the knee, measured with the MOAKS score on MRI images at 10 year follow-up. OARSI score and KL-classification based on the 10 year follow-up X-ray images.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants will be asked to visit the hospital once for an MRI and a radiograph of the affected knee, 10 years after treatment. Additionally, participants will be asked to fill out four questionnaires about their knee function and quality of life. These will take around 30 minutes to fill out. Patients will not benefit from participation. The risk of participating in the study is low; the radiation exposure for an X-ray of the knee is 0.01 mSv. In comparison, the standard annual radiation exposure in the Netherlands is approximately 2.9mSv.

1. INTRODUCTION AND RATIONALE

Knee osteoarthritis (OA) is a condition with a significant burden on both the patient and society[23]. Randomized clinical trials have shown that arthroscopic partial meniscectomy is not beneficial in terms of physical functionality compared to exercise therapy in the first two years [3-11]. Mid-term RCT's with follow-up of 3-5 years comparing surgical versus conservative treatment have consistently found no clinical difference in knee function[12-16].

There are indications that meniscal surgery is one of the etiological factors for the accelerated development of OA in the operated knee[2,3]. However, this has not been convincingly demonstrated in a long term RCT. Ten years ago our ESCAPE trial[1] was initiated where patients with a non-obstructive meniscal tear where randomized between surgery and exercise therapy. The progression of osteoarthritis and physical function was measured over a timeframe of five years. This study found that self-reported knee function after exercise therapy was non-inferior to arthroscopic partial surgery[17]. Furthermore, both treatments resulted in a similar mean progression of OA (1.1 points on the OARSI) from baseline to five year.

We would like to further investigate the progression of OA at a minimum of 10 years follow-up. The ESCAPE population is particularly suitable, because the relevant baseline data (PROMs, MRI and X-ray) are already present and treatment allocation was randomized. Furthermore, a large amount of participants were included (N=321) and completed the 5 year trial (N=278). These patients all reach the 10-year mark after randomization between July 2023 and November 2025.

The findings of the 5-year trial were based on a comparison of X-ray imaging. However, an MRI scan provides higher specificity and accuracy than an X-ray in determining the degree of knee OA[16]. Therefore, to accurately assess the formation of OA and compare the progression of knee OA between exercise therapy and meniscal surgery in patients with a meniscal tear, we aim to repeat the MRIs performed at baseline in the ESCAPE trial population after 10 years. In addition to evaluating knee OA, we also intend to investigate potential differences in knee function and quality of life. These measures will be assessed using Patient Reported Outcome Measures (PROMs).

Worldwide this is the first study to evaluate the important long-term end-points of a randomized controlled trial comparing meniscal surgery with exercise therapy.

2. OBJECTIVES

Primary Objective:

To examine the progression of knee osteoarthritis in older patients with non-obstructive meniscal injuries who were randomized to either surgical or conservative treatment 10 years ago.

Secondary Objective(s):

Furthermore, we will examine patient reported outcomes (knee function and quality of life) for the study population 10 years after treatment.

Hypothesis:

We hypothesize that the progression of osteoarthritis is less among patients who underwent conservative treatment (exercise therapy) compared to those who underwent surgical treatment (arthroscopic partial meniscectomy) 10 years after treatment.

3. STUDY DESIGN

The current study is a long-term follow-up of the ESCAPE trial, in which 321 patients (age ≥45 years) with a meniscal tear were randomized between surgical and conservative treatment. MRI images were made at baseline to confirm a non-obstructive meniscal tear. Table 1 shows the timeline of the measurements during the 5-year trial. At baseline and during a five-year period (at 3, 6, 12, 24 and 60 months) knee function and quality of life of these patients was measured using PROMs. Additionally, X-ray scans were conducted at baseline, 2 year and the 5 year point to determine the progression of osteoarthritis. The data collected in this multicenter non-inferiority randomized controlled trial (RCT) will be utilized for the present study. Ten years after the treatments, we aim to once again invite these patients to undergo an MRI and X-ray to evaluate the degree of OA and measure knee function and quality of life using PROMs.

✓ **Baseline**	• MRI • X-ray (OARSI score) • PROMs
✓ **3,6 and 12 months**	• PROMs
✓ **2 and 5 year**	• X-ray (OARSI score) • PROMs
➔ **10 year**	• MRI (MOAKS) • X-ray (OARSI score) • PROMs

Table 1- Timepoints measurements

All patients were included between July 2013 and November 2015 and therefore will reach the 10-year mark after their treatment between July 2023 and November 2025. The study design is visualized in table 2.

Study Design	**2023**	**2024**				**2025**				**2026**	
	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Data collection											
Data analyses											
Reporting results											

Table 2 - Study timeline

4. STUDY POPULATION

4.1 Population

All participants for this study were already enrolled in the ESCAPE trial (n=321), between July 2013 and November 2015. This follow-up study will initially include patients from OLVG (n=168). Based on the high response rate of 87% for the 5-year follow-up, a high level of willingness to participate is expected. All randomized patients (except the ones who did not wish to be contacted for future research (N=2) will be contacted. If patients do not wish to participate and are willing to share their reason why, this will be recorded in the screening log.

4.2 Inclusion criteria

The inclusion criteria for the initial ESCAPE study[1] consisted of the following criteria:

1) Aged between 45 and 70 years
2) Non-obstructive meniscal tears identified on MRI.

We anticipate that some patients from the initial study, whether in the surgery or exercise therapy group, may have subsequently undergone a Total Knee Arthroplasty (TKA) or Unicondylar Knee Arthroplasty (UKA) procedure. Placement of such a prosthesis is only considered in cases of severe progression of OA. Consequently, the frequency of UKA and TKA placements holds significant importance as an outcome measure for this study. Patients who received either a UKA or TKA will therefore also be requested to provide written informed consent. These patients will be included in the study but are not eligible for MRI or X-ray imaging and the progression of OA cannot be determined. PROMs are not inquired from these patients. Their data is used to determine the amount of UKA and TKA in each treatment group.

4.3 Exclusion criteria

The following exclusion criteria for patient selection were established during the initial ESCAPE trial[1]:

1) Knee locking or trauma leading to acute surgery.
2) One of the following associated injuries on the index knee:
   a. A symptomatic partial ACL rupture or any total ACL rupture determined by clinical examination (positive Lachman test and/or positive Pivot Shift) and shown on MRI;
   b. A complete PCL injury;
   c. Cartilage change down to bone; grade 4 of the Kellgren Lawrence Grading Scale for Osteoarthritis visualized on X-ray;
   d. An injury to the lateral/posterolateral ligament complex with significantly increased laxity.
3) A history of knee surgery other than diagnostic arthroscopy on the index knee.
4) Tumors on MRI suspected for a malignancy.
5) Obese patients with BMI > 35.
6) ASA 4-5 (appendix D) patients which can interfere with revalidation.

7) General disease that effects physical function or systemic medication/abuse of steroids (e.g., rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, gout, pseudogout)
8) Any other medical condition or treatment interfering with the completion or assessment of the trial, e.g. contraindications to MRI or surgery.
9) Drugs or alcohol abuse.
10) Patients unable to speak or read Dutch.

For the 10-year follow-up study the following exclusion criteria will be checked again:

11) Unable or unfeasible for MRI, e.g. due to claustrophobia, metal components or pacemaker

4.4 Sample size calculation

In the initial the primary outcome was the IKDC questionnaire and this was used for the sample size calculation. For the current follow-up however, the primary outcome on which the sample size is based is the progression of OA. Unfortunately, there is no existing data to support the required assumptions for a well-founded power calculation; both the standard deviation in the outcome and the threshold for a clinically relevant difference are unknown. Therefore, we rely on a convenience sample, based on general assumptions and the available budget. We aim to include the maximum amount of participants but are limited by both the patient group (OLVG patients = 168) and available budget. We target a minimum of 114 persons who complete the study, which is a realistic target considering the study population size and response rate in the previous study. Because we want to take in account drop-outs and erratic data, we aim to include 130 patients. With a minimum of 57 patients in each group, we have 80% power (at an alpha of 0.05) to detect a difference in the progression of OA of approximately half a standard deviation (medium Cohen's effect size). This method is generic and can be used for both the primary as secondary outcome parameters. So, for example, if the standard deviation is around 2 points, we will find a statistically significant difference when one group scores an average of 4 and the other group scores an average of 5. We will not solely focus on p-values but also report the variability within the groups and the magnitude of the difference between the groups. Regardless of the established power and statistical significance, this study will provide important insight in the progression of OA at 10 year after surgery or exercise therapy in patients with a degenerative meniscal tear.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study outcome

The main study outcome will be the progression of osteoarthritis scored according to the MOAKS score. The MOAKS score is a new semi-quantitative scoring tool to quantify OA status based on MRI images. MOAKS score is based on articular cartilage and bone marrow lesion (BMLs) in 14 articular sub regions scored from 0 to 3. A higher score means are more sever progression of OA. The MOAKS score has shown to have a good inter-rater and intra-rater reliability[25] and will be calculated for both the baseline as for the 10 year follow up MRI images. All images will be analyzed by the same rater in a random and blinded manner. This way, it is possible to analyze the progression of osteoarthritis after 10 years, based on MRI-imaging.

When the participant has since received a TKP or UKP the main study parameters cannot be calculated. These procedures only occur in case of a severe status of OA and therefore the maximum score for these parameters will be allocated to these patients.

5.1.2 Secondary study parameters/endpoints

Osteoarthritis:

- The degree of knee osteoarthritis is also assessed through X-ray images, using the Kellgren and Lawrence (KL) grading scale which evaluates knee osteoarthritis at 5 different levels, ranging from 0 (no osteoarthritis) to 4 (severe knee osteoarthritis). Furthermore, the progression of OA is also measured using the Osteoarthritis Research Society International (OARSI) Atlas sum score, ranging from 0 to 18 based on 6 items[17]. A higher score indicates a more severe level of OA. The OARSI score evaluates both the extent of joint space narrowing and the degree of osteophyte formation, differentiating between different compartments of the knee. The severity of these changes on each item is scored on a categorical scale (0: normal, 1: mild changes in joint space or osteophytes, 2: moderate changes in joint space or osteophytes, and 3: severe changes in joint space or osteophytes). The scores are derived from MRI images obtained at the baseline assessment and will be obtained again at the 10-year mark.

Knee function (Assessed using the following questionnaires):

- IKDC (International Knee Documentation Committee): Assesses knee-specific symptoms, function, and activities.
- KOOS-PS (Knee Injury and Osteoarthritis Outcome Score - Physical Function Shortform): Assesses symptoms and limitations associated with knee complaints.
- EQ-5D-5L: Evaluates general health status.
- VAS (Visual Analog Scale) for pain: Measures pain levels at rest and during activities.

Other study parameters:

- Height
- Weight
- Smoking status
- Any knee procedures undergone since the previous follow up, such as (delayed) meniscal surgery, partial or total knee replacement.

5.2 Randomisation, blinding and treatment allocation

The patients were randomly assigned to either surgical or conservative treatment during the initial study. Blinding was not possible. The current study is an observational 10-year follow up, without additional randomization or treatment.

5.3 Study procedures

A significant amount of valuable data has already been collected during the 5-year ESCAPE trial. The following procedures will be repeated at the 10-year follow-up.

5.3.1 MRI

MRI for the 10-year follow up will be conducted and analysed at OLVG hospital. The MRI images are used to determine the progression of OA between baseline and 10-year using the MOAKS score. MRI imaging is considered the most precise non-surgical method to evaluate knee OA[22].

5.3.2 X-ray

All patients without a knee prosthesis will also undergo one X-ray at the 10-year follow up. This allows us to evaluate the progression of OA in terms of OARSI score and KL-classification over time, because we also have X-rays at 2 and 5 years follow up.

5.3.3 PROMs

Furthermore, PROMs (Patient-Reported Outcome Measures) were obtained at baseline and multiple times during the 5 years trial to assess knee function, knee pain, physical health and quality of life.

We will ask the patients to repeat these questionnaires (PROMs) via Castor EDC. For the 5-year follow-up, we have previously sent questionnaires via Castor EDC. We intend to use the same questionnaires for the 10-year follow-up, allowing us to utilize the existing Castor EDC database. The following self-reported questionnaires are included in the 10-year follow-up:

- *IKDC:* International Knee Documentation Committee (IKDC) developed the 'Subjective Knee Form' (2006). It was developed for knee-specific measurement of symptoms, function, and sports activities in patients with a variety of knee conditions, including ligament and meniscal injuries, articular cartilage lesions, and patellofemoral pain. The IKDC is a self-administered questionnaire with a total of 19 questions. Response options include dichotomous, 11-point numeric rating scales and 5-point Likert scales. All items,

except item 10a, are converted to a score with a maximum of 100 indicating no restrictions in daily and sports activities and the absence of symptoms. The IKDC 'Subjective Knee Form' has been validated for meniscal injuries[19] by and was translated and validated in Dutch [20].

- *EQ-5D5L - Quality of Life:* The generic effects on quality of life will be assessed with the Euroqol EQ-5D5L[21]. This widely used quality-of-life instrument includes five dimensions of health related quality of life, namely mobility, self-care, daily activities, pain/discomfort, and depression/anxiety. These five dimensions will be combined into a health state.
- *KOOS-PS:* A questionnaire to evaluate the symptoms and limitation experienced by patients with knee injury. It employs a Likert scale ranging from 0 to 4 (lower scores indicate fewer issues). Total score can be converted within a 0-100 scale. The questionnaire takes approximately 2 minutes to complete.
- *VAS Pain*: Pain scores using a visual analog scale to measure the pain score between 0-100 during rest and activity. The questionnaire takes approximately 1 minutes to complete.

After collecting all the data, it can be extracted from Castor EDC and transferred to an SPSS file were it can be combined with the existing data from the 5-year trial.

5.4 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.

5.5 Replacement of individual subjects after withdrawal

This sample size is based on the required number of MRIs, so does not include patients whose MRI is not made or available for analysis. For this study we will not include patients outside the initial ESCAPE population and withdrawals will therefore not be replaced. If the target sample size of 57 in each group is not reached within OLVG patient group, patients from other centra will be contacted. Treatment allocation will be considered when adding patients from other centra to achieve an equal group size and distribution between groups.

5.6 Follow-up of subjects withdrawn from treatment

Not applicable; this study does not include treatment.

6. SAFETY REPORTING

6.1 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.

6.2 AEs, SAEs and SUSARs

6.2.1 Adverse events (AEs)

All participants in this study had a non-obstructive meniscal tear 10 years ago and received either exercise therapy or knee surgery. They were followed for adverse events two years after the initial treatment[1]. This 10-year follow up study has a cross-sectional design and includes only one single visit to the hospital. Prior to this visit, patients will be queried about any medical procedures performed on either the affected and unaffected knee joint. These data will be utilized for data analyses, but will not be reported as a serious adverse event (SAE) because these events did not occur during the study. Following the visit, participants will not be followed up.

7. STATISTICAL ANALYSIS

The statistical analysis will largely follow the method used in the 5-year trial. As was done in this analyses, the groups are analyzed using the intention-to-treat principle[18]. The random treatment allocation is used to divide the patient in two equal groups. Because several patient who were allocated in the exercise therapy group eventually had delated surgery, we will also perform an analyses based on an as-treated allocation. For the analysis, IBM SPSS Statistics 27 will be used and all statistical significance will be assessed at the 0.05 level. In all analysis the exercise therapy will be considered the reference treatment.

7.1 Primary study parameter(s)

The primary outcome is the severity of OA based on the MOAKS score at 10-year follow up based on MRI imaging. To compare the progression of MOAKS scores between groups we will use ANOVA repeated measurement analyses. With time period (Baseline and 10-year point) as within subjects factor and treatment allocation as between subjects factor (surgery vs exercise therapy) to test for superiority. We expect no missing data and are comparing two time periods therefore ANOVA repeated measures is a suitable analytic method.

7.2 Secondary study parameter(s)

The continuous values resulting from the PROM questionnaires between the two treatment allocations will analyzed using a linear mixed model to determine whether a difference between the groups is significantly different.

Furthermore, the OARSI and KL-score will be calculated by analysing the X-ray imaging. This allows comparisons with intermittent time points at 2 year, 5 year follow up. The OARSI and KL score will be analyzed using linear mixed model.

7.3 Other study parameters

A table with is used to report the relevant group characteristics, averages and 95% confidence interval at 10-year point which includes:

- Group characteristics (Age, gender, height, weight, smoking status, affected side(s).
- Procedures on knee, such as:
  - (Delayed) menisectomy
  - Exercise therapy (Outside of initial study)

- Amount of TKA and UKA
- Other

7.4 Missing data

All patients who participated in the ESCAPE trial had an MRI at baseline (this was an inclusion criterion). All patients involved in the 10-year follow-up of this study will also undergo an MRI, so we do not expect any missing values for the MOAKS score. From all the participants X-ray on baseline is available. However, from some participants the images and/or PROMs from the 2 or 5 year point were not collected and therefore are considered missing data. The analytic method that we use, linear mixed model, is able to handle some missing data. The appointment for 10 year MRI and X-ray will only be planned after completion of the PROMs to limit the missing data.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki - 59th WMA General Assembly, Seoul, Korea, October 2008 – and in accordance with the Medical Research Involving Human Subjects Act (WMO).

8.2 Recruitment and consent

Eligible participants are not currently under treatment but have previously consented to be contacted about future research. They were given the option to indicate whether they could be approached for future research. Previous contact with this ESCAPE study population was mostly via email. The initial contact for this 10 year follow up is also sent via email which is sent by the investigator also on behalf of the principal investigator and treating physician. The research aim will be briefly summarized in the email. The email also contains a link to the website Castor EDC. Clicking this link will provide the person with the complete patient information letter. In this letter, it is explained how the participant can ask questions either before participation or during the study. Furthermore, it is explained how a participant can revoke their consent during the study. Contact information of the investigator is provided in both the e-mail and the information letter. If the person is interested in participation, they can confirm this with an electronic informed consent (eConsent) using a Castor EDC survey presented at the next page.

Since July 2022, the option for eConsent has been accepted for WMO studies under certain conditions. We believe this study is particularly suitable for using eConsent for the following reasons:

Firstly, the patients were already informed and included in the initial study, so they are familiar with the study procedures (MRI, X-ray, and PROMs) and the Castor EDC system. This application is proven to safely collect and store data in compliance with Good Clinical Guidelines (GCP). The eConsent, screening procedure and questionnaires will all be integrated into Castor EDC. Castor EDC keeps an audit trail so any data entry is recorded with time stamp and editor. Only the investigators involved in the study and who are listed on the delegation log have access to the Castor EDC study page.

Furthermore, a recent study has found that eConsent results in a better understanding of the clinical trial information and is rated as a more acceptable and usable consenting process compared to paper-based consenting[24].

Finally, the patients will be able to ask questions using the contact information of the research team provided in the information letter. It will be emphasized that participation is voluntary, and

they can withdraw at any time during the study. Declining to participate in the research will not influence any potential treatment.

By clicking the personalized URL in the e-mail, patients will enter an introduction screen of a survey in Castor EDC where the information letter is provided. In this survey, they confirm that they understand the information and are willing to join in the study. Patients can give consent to participate and whether or not they want to be contacted for future research using checkboxes which are locked after completion (yes/no). They also select the date on which they signed the consent. Only if all boxes are selected the consent procedure can be completed. The participant will receive a copy of the informed consent form from the researcher by email. A reminder e-mail will be send twice and the patient will be called when there is no reaction on the initial study invitation.

After signing the eConsent, the participant will be asked to complete a short screening survey about their medical procedures. This survey is used to screen the patients and check for criteria (e.g. TKA, metal components) that excludes them for MRI and X-ray imaging. If the patient is not eligible for the imaging, the participant has reached the endpoint of the study and will be informed about this. The answers to the screening survey will be saved and used in the data analysis. If the patient is eligible, a set of questionnaires will be asked to fill out in Castor EDC. When both the screening and questionnaires are completed, a date for the imaging (X-ray and MRI) will be scheduled by the researcher.

If, at any point, the participant wishes to stop participating in the study, they can contact the investigator by phone or email using the provided contact information. The participant is not required to provide a reason and will no longer receive reminders or questionnaires. The withdrawal of their consent, with corresponding date, will be recorded in Castor EDC using a consent revocation form filled in by the investigator. Data collected up to this date can be used unless a participant specifically indicates otherwise. Preferably, we conduct the entire process of information and consent digitally (via Castor EDC). However, if individuals express a lack of digital proficiency or prefer to be informed via post, that option is available.

8.3 Benefits and risks assessment, group relatedness

The participants have previously been randomized in the initial study and are only getting an evaluation of their condition at 10-years follow up. There are, in our view, no risks for the study subjects associated with participation in this study. If desired, the results can be provided back to the patient. Therefore, dispensation for a separate study subject insurance for participation in this research is requested of the Medical Ethical Review Committee.

8.4 Compensation for injury

The sponsor/investigator has a continues liability insurance (Centramed) which is in accordance with article 7, subsection 6 of the WMO (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003).

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

Questionnaire data will be collected using Castor EDC. Imaging will be conducted by the radiology department of OLVG hospital and stored on a local server. All subject data will be anonymized by assigning study numbers to each subject. The same study number will be used as in the 5-year trial. The study numbers are not based on the patient initials or birth-date. The key to these study numbers is only available to the coordinating investigator and research assistant(s) and will be kept in the secured research location on Sharepoint. Outcome data, anonymised, is only accessible for the coordinating investigator, principal investigators, statistical analyzers and authorized research personnel of the Joint Research group at OLVG Amsterdam. Data will be collected and stored for a period of 15 years. An encrypted keyfile with contact information is already made for the initial study.
Data without identifiable patient variables will be processed and stored in SPSS. Security requirements: Data input capabilities are limited to the coordinating investigator. Data processing capabilities are limited to the coordinating investigator, statistical analyzers, the principal investigators and authorized research staff.
The handling of personal data will comply with the Dutch Personal Data Protection Act (de Wet Bescherming Persoonsgegevens, Wbp).

9.2 Monitoring and Quality Assurance

A monitoring plan will be developed and conducted locally by a dedicated monitor in OLVG.

9.3 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.

9.4 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, problems, and amendments.

9.5 Temporary halt and (prematurely) end of study report

The investigator 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 visit which is estimated November 2025. 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.

9.6 Public disclosure and publication policy

Our intention is to publish the results of this study in a relevant scientific journal after the last patient is measured and the data is analysed.

10. REFERENCES

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