CLINICAL TRIAL TITLE

The ASPIRE trial: AchilleS tendinoPathy treated with cortIcosteRoid injEctions

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EU trial number	***2025-524057-13-00***
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DOCUMENT HISTORY

Document	Date of version	Summary of Changes
Original protocol	24-12-2025	Not applicable
Version number 2	06-03-2026	The protocol has been updated following the CTIS Request for Information (RFI). Main changes include clarification of the recruitment and prescreening procedures (including GDPR compliance), confirmation that written informed consent is obtained prior to study procedures, specification of certain exclusion criteria, addition of hyperglycemia monitoring in participants with Diabetes Mellitus, clarification of the identical injection schedule for both treatment groups, and updates to safety monitoring and injection procedures. Minor editorial updates were made to improve consistency with other CTIS documents. No changes were made to the study design, primary objectives, or primary endpoints.

CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

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1. ABBREVIATIONS

AE	Adverse Event
AxMP	Auxiliary Medicinal Product
BMI	Body Mass Index
CRF	Case Report Form
CTR	Clinical Trials Regulation
CTIS	Clinical Trials Information System
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels Questionnaire
EU	European Union
GCP	Good Clinical Practice

GDPR	General Data Protection Regulation
GEE	Generalized Estimating Equations
GMP	Good Manufacturing Practice
GROC	Global Rating of Change
ICER	Incremental Cost-Effectiveness Ratio
IMP	Investigational Medicinal Product
iMCQ	iMTA Medical Consumption Questionnaire
iPCQ	iMTA Productivity Cost Questionnaire
QALY	Quality-Adjusted Life Year
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TENDINS-A	TENDINopathy Symptoms and Disability–Achilles
US	Ultrasound
UTC	Ultrasound Tissue Characterisation
VAS	Visual Analogue Scale
VISA-A	Victorian Institute of Sport Assessment–Achilles
Wbp	Wet bescherming persoonsgegevens
WMO	Wet medisch-wetenschappelijk onderzoek met mensen

2. SYNOPSIS

EU trial number and Full trial title

EU trial number: 2025-524057-13-00.
Title: The ASPIRE trial: **A**chille**S** tendino**P**athy treated with cort**I**coste**R**oid inj**E**ctions.

Rationale

Achilles tendinopathy is a common and often long-lasting tendon injury that causes pain, loss of function, and reduced sports participation. Standard care includes education, load management advice, and progressive calf-strengthening exercises. However, about half of patients remain symptomatic after this treatment. Corticosteroid injections are frequently used in daily practice, but the scientific evidence is conflicting: some studies show short-term benefits, while others raise concerns about lack of long-term effect and possible tendon ruptures. This leaves doctors and patients uncertain whether corticosteroid injections are a safe and useful second-line treatment. A large, high-quality clinical trial is needed to provide clarity.

The hypothesis is that adding 1–3 ultrasound-guided corticosteroid injections to standard care (education, load management advice and exercise therapy) is safe and provides greater improvement in pain and function (assessed with the VISA-A score) within 1 year than standard care with placebo injections in patients with chronic midportion Achilles tendinopathy.

Objective

Main objective: To evaluate whether 1–3 ultrasound-guided corticosteroid injections, in addition to standard care, improve symptoms and is safe for patients with chronic midportion Achilles tendinopathy compared with placebo injections plus standard care.

Secondary objectives: To assess minor side effects of corticosteroids, global rate of change, physical function, quality of life, return to sports and activity, imaging changes in the tendon, and cost-effectiveness. Blood samples will also be collected to explore biological mechanisms of treatment effects and long-term clinical outcomes will also be assessed.

Main trial endpoints

1. Change in disability and symptoms during 1-year follow-up, measured with the validated VISA-A questionnaire (0–100 scale).
2. Incidence of full-thickness Achilles tendon ruptures during 1-year follow-up (confirmed by medical records or clinical tests and imaging).

Secondary trial endpoints

- Minor adverse effects of corticosteroids (e.g. skin abnormalities, fat percentage, mood changes)
- Tendon-related symptoms and disability measured with the validated and disease-specific TENDINS-A questionnaire
- Pain during and after activity (VAS).
- Global perceived improvement (11-point GROC).
- Functional tests (e.g., single-leg heel-rise test).
- Health-related quality of life (EQ-5D-5L).
- Return to sport/activity level (5-point scale).
- Healthcare use and productivity loss (for cost-effectiveness).
- Imaging outcomes: tendon structure, thickness, and blood vessel growth (UTC and US).
- Proteomic analyses from blood samples to study molecular changes.

Trial design

This is a multicentre, randomized, double-blind, placebo-controlled phase III trial in 276 patients. Participants are randomly allocated to receive either corticosteroid injections or placebo injections, both combined with standard care (education, load management advice and exercise therapy). The study includes 1 year of close follow-up, with extended questionnaires up to 10 years.

Trial population

Main inclusion: Adults (18-65 years) with clinically-diagnosed midportion Achilles tendinopathy confirmed by ultrasound, symptoms lasting ≥6 months, and persistent complaints after standard care (education, load management, and ≥3 months of exercise therapy).

Main exclusion: Previous corticosteroid injections or surgery on the tendon, insertional tendinopathy, systemic inflammatory disease, current pregnancy or breast feeding, or other medical conditions that make injections unsafe.

Interventions

Intervention group: 1–3 ultrasound-guided peritendinous injections of Depo-Medrol (methylprednisolone acetate 40 mg) with Lidocaine.

Placebo group: 1–3 ultrasound-guided injections of Lidocaine only.

Injection schedule: All participants receive one injection at baseline. Up to two additional injections may be given within the first 8 weeks, at intervals of at least 4 weeks, if symptoms persist and predefined criteria are met.

Both groups: All participants receive standard care (education, load management advice, and a structured progressive calf-muscle strengthening exercise program supported by an online app/website).

Monitoring: Physical examinations, ultrasound imaging, questionnaires, functional tests, and blood samples at baseline, 3 months, and 1 year. Online questionnaires at 4 and 8 weeks, 6 and 9 months, and at 2, 5 and 10 years.

Ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risks

The study is designed to minimize risks: injections are performed under ultrasound guidance by experienced physicians. Possible side effects include local pain, skin changes (atrophy, discoloration), or in rare cases infection or tendon rupture. These risks are uncommon and will be closely monitored by an independent Data Safety Monitoring Board.

Potential benefits include reduced pain, improved function, and earlier return to physical activity. Even participants in the placebo group benefit from standardized care, structured follow-up, and early identification of complications. The expected value of this trial is high, as it directly addresses a major uncertainty in clinical practice and will inform future clinical guidelines.

Protocol Samenvatting (Dutch)

EU trial nummer en volledige titel

EU trial nummer: 2025-524057-13-00.
Titel: The ASPIRE trial: **A**chille**S** tendino**P**athy treated with cort**I**coste**R**oid inj**E**ctions

Rationale

Achillespeesklachten (achilles tendinopathie) komen veel voor, duren vaak lang en zorgen voor pijn, beperkingen en minder sport- of beweegdeelname. De standaardbehandeling bestaat uit uitleg, advies over belasting en een oefenprogramma om de kuitspieren te versterken. Toch houdt ongeveer de helft van de patiënten klachten.
In de dagelijkse praktijk worden vaak corticosteroïd injecties gebruikt. Daarover bestaat echter veel onzekerheid: sommige studies laten een (kortdurend) positief effect zien, andere tonen geen voordeel en er is zorg over mogelijke bijwerkingen, zoals een peesscheur.
Daarom onderzoeken we in deze studie of 1–3 injecties met corticosteroïden, gecombineerd met oefentherapie, veilig zijn en betere resultaten geven dan placebo-injecties met dezelfde oefentherapie.

Doel van het onderzoek

Hoofddoelstelling: Het beoordelen of 1–3 echogeleide corticosteroïd injecties, als aanvulling op de gebruikelijke zorg (uitleg, belasting advies en oefentherapie), veilig zijn en pijn en functie verbeteren (gemeten met de VISA-A score) binnen 1 jaar bij patiënten met chronische achillespeesklachten van het middengedeelte, vergeleken met placebo-injecties plus standaardzorg.

Secundaire doelstellingen: Het onderzoeken van milde bijwerkingen van corticosteroïden, de algemene indruk van herstel, fysieke functie, kwaliteit van leven, terugkeer naar sport en activiteit, veranderingen in de pees op beeldvorming en kosteneffectiviteit. Daarnaast worden bloedmonsters

verzameld om biologische mechanismen van het behandeleffect te onderzoeken en worden lange termijn uitkomsten geëvalueerd.

Belangrijkste onderzoeksvariabelen / eindpunten

- Verandering in klachten en beperkingen gedurende 1 jaar, gemeten met de VISA-A vragenlijst (0–100 schaal)
- Aantal volledige achillespeesrupturen gedurende 1 jaar (vastgesteld met medische rapportage of onderzoek en beeldvorming)

Secundaire onderzoeksvariabelen / eindpunten

- Geringe bijwerkingen van corticosteroïden (bijv. huidafwijkingen, vetpercentage, stemmingsveranderingen)
- Vragenlijst TENDINS-A (peesgerelateerde klachten)
- Pijn tijdens en na activiteit (VAS-score)
- Algemene verbetering zoals door de patiënt ervaren (11-punts GROC)
- Functionele test (o.a. op één been op de tenen staan)
- Kwaliteit van leven (EQ-5D-5L)
- Terugkeer naar sport/activiteiten
- Zorggebruik en ziekteverzuim (kosten-effectiviteit)
- Echo-uitkomsten: peesdikte, structuur en doorbloeding (UTC en US)
- Moleculaire veranderingen in bloed (proteomics)

Onderzoeksopzet

Multicenter, gerandomiseerd, dubbelblind en placebo-gecontroleerd fase III-onderzoek.
In totaal doen 276 patiënten mee.
Behandelperiode: maximaal 12 weken (1–3 injecties), met oefentherapie.
Follow-up: 1 jaar intensief, met extra vragenlijsten tot 10 jaar.

Onderzoekspopulatie

Voornaamste inclusiecriteria:

- Volwassenen ≥18 jaar
- Langdurige klachten (≥6 maanden) van het middendeel van de achillespees
- Diagnose bevestigd met echografie
- Geen of onvoldoende herstel na minimaal 3 maanden standaardzorg (educatie, belastingadvies, oefentherapie)

Voornaamste exclusiecriteria:

- Eerdere corticosteroïd injecties of operatie aan de achillespees
- Achillespeesklachten bij de aanhechting (insertie tendinopathie)
- Zwangerschap of borstvoeding
- Systemische ontstekingsziekten of medische redenen waardoor injecties onveilig zijn

Interventies

Interventiegroep: 1–3 echogeleide injecties met corticosteroïden (Depo-Medrol 40 mg) plus Lidocaïne.

Placebogroep: 1–3 echogeleide injecties met alleen Lidocaïne.

Injectieschema: altijd één injectie bij de start; eventueel twee extra injecties in de eerste 8 weken bij aanhoudende klachten (op basis van standaard criteria).

Beide groepen: krijgen standaardzorg met uitleg, belastingadvies en een gestructureerd oefenprogramma via een app/website.

Monitoring: Lichamelijk onderzoek, echografie, vragenlijsten, functionele testen en bloedafname bij baseline, 3 maanden en 1 jaar. Online vragenlijsten op 4 en 8 weken, 6 en 9 maanden en na 2, 5 en 10 jaar.

Ethische overwegingen gerelateerd aan het onderzoek zoals het verwachte voordeel voor de individuele deelnemer of de groep patiënten vertegenwoordigd door de onderzoeksdeelnemers alsmede de belasting en risico's van het onderzoek

De maatschappelijke waarde van deze studie is groot. Door 276 patiënten zorgvuldig te volgen, geeft dit onderzoek eindelijk duidelijkheid over de rol van corticosteroïd-injecties bij hardnekkige achillespeesklachten. De resultaten zullen direct richting geven aan behandelrichtlijnen en betere zorg in de toekomst mogelijk maken.
Het onderzoek is zo ingericht dat de risico's voor deelnemers tot een minimum worden beperkt. De injecties worden altijd onder echogeleide verricht en door ervaren artsen uitgevoerd, waardoor de kans op complicaties klein is. Mogelijke bijwerkingen zijn lokale pijn of huidveranderingen (atrofie of verkleuring). In zeldzame gevallen kan er een infectie of zelfs een scheur in de achillespees optreden. Deze risico's worden nauwlettend bewaakt door een onafhankelijke Data Safety Monitoring Board en door duidelijke adviezen middels oefentherapie en terugkeer naar sport en de regelmatige controles tijdens het onderzoek.
Tegenover deze beperkte risico's staan belangrijke mogelijke voordelen. Voor de deelnemer kan deelname leiden tot minder pijn, beter functioneren en een snellere terugkeer naar sport en werk. Ook deelnemers in de placebogroep profiteren van gestructureerde oefentherapie, zorgvuldige begeleiding en het vroegtijdig opsporen van complicaties.

3. INTRODUCTION AND RATIONALE

3.1 Therapeutic condition and current treatment status

Tendinopathy is a frequent and often long-lasting tendon disorder, causing pain, impaired function and reduced sports participation. Prevalence is 11.8 per 1,000 person-year.[1] In the Netherlands, Achilles tendinopathy occurs in 2–3 per 1,000 adults (≈40,000 new cases annually).[1,2] It has a major impact on quality of life and work productivity.[3,4] Standard care according to the current Dutch multidisciplinary guideline consists of education, load management and progressive calf-strengthening exercises[5], with ~50% recovery at 3 months.[6] However, 20–30% remain symptomatic at 10 years.[4] The current guideline[5] discourages the use of corticosteroid injections as 2nd line treatment for Achilles tendinopathy because of uncertain long-term efficacy and potential harms (tendon rupture), but a recent (2022) randomized trial challenged this recommendation.[7] This causes substantial variation in current clinical practice, with the majority of health professionals (64%) still using corticosteroid injections for this indication. The conflicting data leave health professionals and patients in doubt whether or not to administer corticosteroid injections for Achilles tendinopathy. A well-designed randomized controlled trial of sufficient size will provide strong evidence for the efficacy and safety of corticosteroid injections combined with standard care (including strengthening exercises) for Achilles tendinopathy. This will directly influence the current guideline and ultimately

further improve patient care by clear treatment recommendations and performing implementation strategies.

3.2 Clinical trial rationale

Evidence on corticosteroid injections is conflicting. Reviews show short-term benefit in other tendinopathies[8], but inconsistent results in Achilles tendinopathy.[7,9] A recent RCT (n=100) reported that 1–3 peritendinous corticosteroid injections combined with exercise were safe (no ruptures) and more effective than placebo in both short- and long-term follow-up.[7] Limitations included high risk of bias and modest sample size.[10,11] Therefore, uncertainty remains regarding efficacy, safety and cost-effectiveness. This trial addresses this knowledge gap and will provide high-quality evidence to inform guidelines and clinical practice.

The study is classified as a low-intervention clinical trial under EU CTR, since the investigational product (methylprednisolone acetate) is used within its marketing authorisation, administration is supported by recent scientific evidence, and additional diagnostic procedures do not impose more than minimal risk or burden compared with routine clinical care.

3.3 Mechanism of action, Drug class

Methylprednisolone acetate (Depo-Medrol) is a corticosteroid with strong local anti-inflammatory effects, reducing cytokines and inflammatory mediators, thereby lowering pain and improving function. Its depot formulation ensures slow release with limited systemic exposure.

Lidocaine, added to both active and placebo injections, provides local anaesthesia and short-term pain relief. In clinical practice it is often combined with corticosteroids, both to create a more homogeneous distribution of the corticosteroid in the injection mixture and to reduce post-injection pain.

3.4 Rationale for Dose Regimen/Dose Justification

The regimen of 1–3 peritendinous injections of Depo-Medrol 40 mg with Lidocaine is based on prior RCTs and common clinical use.[7,9] The recent RCT of Johannsen et al.[7] showed superiority of providing multiple peritendinous injections, when combined to exercise therapy and load management. All participants receive one baseline injection; up to two further injections may be administered within 8 weeks if symptoms persist, with ≥4 weeks between injections. This schedule balances efficacy with safety, limiting cumulative steroid exposure and reducing risk of tendon rupture. Ultrasound guidance and experienced injectors with training prior to the start of the trials further minimize risk.

4. STRUCTURED RISK ANALYSIS

4.1 Potential issues of concern

4.1.1 Level of knowledge about mechanism of action

Depo-Medrol (methylprednisolone acetate) is a synthetic glucocorticoid. Its mechanism is well established: it binds to intracellular glucocorticoid receptors, modifying gene transcription and leading to reduced production of pro-inflammatory mediators and suppression of local immune responses.

Lidocaine is a well-known local anesthetic with a clearly described mechanism of action. It blocks voltage-gated sodium channels in nerve membranes, resulting in a reversible inhibition of nerve impulse conduction and rapid, short-acting local anesthesia.

4.1.2 Previous exposure of human beings

Methylprednisolone and other corticosteroids have been used in millions of patients worldwide for decades, including in musculoskeletal conditions. Peritendinous injection is part of standard care in many practices, though guidelines recommend caution due to uncertain long-term efficacy and potential safety risks. In a recent Danish study (Johannsen et al. 2022)[7] peritendinous methylprednisolone injections improved symptoms of Achilles tendinopathy both in the short term and long term and did not cause adverse events.
Lidocaine has been widely used for decades in various medical fields, including anesthesia, musculoskeletal injections, and minor surgical procedures. Millions of patients worldwide have safely received Lidocaine at comparable or higher doses than those planned in this study. A previous RCT in patients with Achilles tendinopathy, a peritendinous injection with Lidocaine did not result in adverse events.[16]

4.1.3 Induction of the mechanism in animals and/or *ex-vivo*

The anti-inflammatory and immunosuppressive actions of corticosteroids are well documented in both animal models and in vitro human cell studies. The anesthetic mechanism of sodium channel blockade has been demonstrated extensively in animal studies and in vitro human cell and tissue experiments. Preclinical work has also shown potential negative effects of corticosteroids with anesthetics on tendon tissue, such as reduced fibroblast viability, decreased collagen synthesis, and structural disorganisation.[14,15] However, these findings are largely from controlled laboratory settings, often at higher concentrations and with direct intratendinous exposure, which may not accurately reflect peritendinous use in clinical practice. The clinical relevance and magnitude of these adverse tissue effects remain uncertain, especially at the low doses and routes used in this study.

4.1.4 Selectivity of the mechanism

The drug acts locally at the injection site, but some systemic absorption may occur. The anti-inflammatory action is not selective for tendon tissue and may also affect surrounding soft tissues. The anesthetic effect is also not tissue-specific but acts on nerves within the injected region, providing local sensory blockade. The effect is transient and often wears off within 1–2 hours.

4.1.5 Analysis of potential effect

Desired effects are reduction of pain and local inflammation, facilitating rehabilitation. Known potential but rare adverse effects include local skin atrophy, hypopigmentation, infection, and full tendon rupture, particularly with intratendinous injection and repeated doses.[10] The desired anesthetic effect is short-term pain relief during and shortly after injection, which aids patient comfort and blinding in the trial. Lidocaine is not expected to have therapeutic effects on tendon healing or long-term outcomes.

4.1.6 Pharmacokinetic considerations

Depo-Medrol is a depot formulation with slow release. After peritendinous injection, the local concentration is highest at the injection site with minimal systemic exposure. Elimination occurs primarily via hepatic metabolism. When injected peritendinously, Lidocaine acts locally and is gradually absorbed into the systemic circulation. At the low dose used in this study, systemic exposure is minimal, and plasma levels remain far below toxic thresholds. Lidocaine is rapidly metabolised by the liver and excreted in the urine.

4.1.7 Predictability of effect

Short-term pain reduction is predictable based on prior literature (Depo-Medrol for weeks to months and Lidocaine for hours)[6,7]. Longer-term outcomes are variable, with conflicting evidence.[5] Adverse events are rare and mostly mild, but tendon rupture is a known, though uncommon, complication.[7]

4.1.8 Interaction with other products

At the low doses used in this study, clinically significant drug–drug interactions are unlikely. Patients on anticoagulants or with significant comorbidities are excluded to prevent complications as a result of the intervention. Participants with known allergy for Lidocaine or Depo-Medrol will be excluded.

4.1.9 Managing of effects

Procedures are standardized, using ultrasound guidance to minimize risk of intratendinous injection. Injections are performed by experienced physicians. Any adverse event will be managed according to standard clinical practice, including prompt treatment of infection or referral in case of tendon rupture. In addition, a Data and Safety Monitoring Board (DSMB) has been installed to oversee participant safety throughout the trial and to allow early intervention if unexpected safety signals occur.

4.1.10 Study population

Capacitated adults with chronic midportion Achilles tendinopathy. No minors, incapacitated adults, or high-risk groups are included. Participants have failed first-line conservative care. We will not include individuals with an age > 65 years, as this group might be more prone to a full-thickness tendon rupture after corticosteroid exposure (advice from Trial Advisory Board).

4.2 Overall synthesis of the direct risks for the research subjects

Depo-Medrol–Lidocaine combines a widely used corticosteroid (methylprednisolone acetate) with a well-known local anesthetic (Lidocaine). Both agents have an extensive history of clinical use and generally well-described safety profiles. The corticosteroid offers anti-inflammatory effects, while Lidocaine provides short-lasting analgesia to improve patient comfort during and after the injection.

The main risks are local and rare: skin changes (atrophy or depigmentation), and very rarely superficial infection or tendon rupture. Lidocaine-related adverse effects are uncommon at this low dose and include only brief numbness or, in extremely rare cases, systemic toxicity if accidentally injected intravascularly. The study minimizes these risks by using ultrasound-guided, peritendinous injections, single or limited repeat dosing, strict aseptic techniques, and injections provided by trained physicians.

A Data and Safety Monitoring Board (DSMB) will oversee the trial and can advise the Trial Steering Committee and Sponsor early if unexpected safety concerns arise. The study population consists of capacitated adults who have failed first-line conservative care, and who may benefit from improved pain relief and function. Given the known properties of the drugs, the precautions taken, and the relevance of the research question for clinical practice, the remaining risks are

considered low and acceptable in proportion to the potential benefits for participants and future patients.

5. OBJECTIVES AND ENDPOINTS

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint for the primary objective(s)**
To evaluate whether 1–3 ultrasound-guided corticosteroid injections in addition to standard care improve symptoms and function in patients with chronic midportion Achilles tendinopathy compared with placebo injections plus standard care.	Change in symptoms and disability from baseline to, 4 and 8 weeks, 3, 6, 9 months and 1-year follow-up measured with the VISA-A questionnaire (0–100 scale).[17,18]
To assess safety of corticosteroid injections.	Incidence of full-thickness Achilles tendon ruptures during 1-year follow-up (confirmed through medical records or by clinical examination and/or imaging).[19]
Secondary objective(s), if applicable	**Endpoint(s) for secondary objective(s), if applicable**
To assess minor side effects of peritendinous corticosteroid injections	Changes in indicators of systemic corticosteroid exposure between baseline, 3 months, and 1 year: • Change in body fat percentage (skinfold caliper)[20] • Change in body mass (kg) • Skin color changes at injection site (visually assessed as present/absent) • Changes in indicators of systemic corticosteroid exposure between baseline, 3, 6 and 9 months, and 1 year:Hot flashes, Menstrual irregularities, Sleep disturbances, Mood change, and Increased appetite (using a single question per item)
To evaluate tendon-related symptoms and disability with an alternative disease-specific instrument.	Change in TENDINS-A questionnaire scores at baseline, 3, 6 and 9 months and at 1 year.[21,22]
To assess pain during and after activity.	Mean pain scores on VAS (0–10)[23] at baseline, 3, 6 and 9 months and at 1 year: • During a predefined physical activity in the past week • 24h after a predefined physical activity in the past week
To assess global perceived improvement.	Patient-reported global rating of change (11-point scale) at 3, 6 and 9 months and at 1 year.[24] This GROC will be dichotomized, with

	success defined as “moderately better” to “very much better”.

To evaluate tenderness and physical function.	Performance in functional tests at baseline, 3 months and 1 year:
	• Pain (VAS 0-10) on palpation[16]
	• Pain (VAS 0-10) during 5 single-leg heel rises[16]
	• Pain (VAS 0-10) during 5 hops[16]
	• Single-leg heel-rise endurance (HRET) test assessed with the calf raise app[25]
	  ○ number of repetitions
	  ○ total work
	  ○ vertical displacement
	  ○ peak height
	  ○ pain (VAS 0-10) during the single-leg HRET

To assess health-related quality of life.	EQ-5D-5L questionnaire at baseline, 3, 6 and 9 months and at 1 year.[26]
To determine return to sport/activity.	Return to sport/activity levels at 3, 6 and 9 months and at 1 year (patient-reported).[16]
To determine cost-effectiveness.	Healthcare use and productivity loss (questionnaires) at baseline, 3, 6 and 9 months and at 1 year: • iMCQ[27] • iPCQ[28]
To evaluate tendon structure changes.	Ultrasound outcomes at baseline, 3 months and 1 year: • Tendon thickness[29] • Organized tendon structure (% Echo-types I+II)[30] • Degree of intratendinous and peritendinous Doppler flow (using SAQ method)[31]
Exploratory objective(s), if applicable	**Endpoint(s) for exploratory objective(s), if applicable**
To explore biological mechanisms of treatment effects.	Proteomic analyses from blood samples collected within a subgroup of the participants (only included at study site Erasmus MC) at baseline, 3 months and 1 year.[32]
To evaluate long-term outcomes.	Online follow-up questionnaires at 2, 5 and 10 years (VISA-A, self-reported tendon rupture, TENDINS-A, return to sport/activity, healthcare use).[33]

6. STUDY PLAN AND DESIGN

6.1 Trial Design

A multi-centre participant-blinded, physician-blinded, assessor-blinded and statistician-blinded randomized placebo-controlled clinical phase III trial (RCT) in 276 patients. An RCT is the appropriate design being the gold standard for evaluating an intervention's efficacy. This design directly compares the effects of corticosteroid injections to placebo, controlling for confounding variables. The intervention has been previously studied[7,9]; this trial will assess its efficacy, safety and cost-effectiveness with low risk of bias and in a larger population.

6.2 Number of Patients

276 patients will be included (138 in the intervention group and 138 in the control group).

6.3 Overall study duration and follow-up

Primary and secondary outcomes will be collected during 1 year follow-up. We also planned an exploratory blood biomarker analysis (subgroup of participants included at study site Erasmus MC) and a questionnaire-based long term follow-up at 2, 5 and 10 years. The total duration of this project (from study start until the last visit of the last patient) is expected to take 3-4 years.

6.4 Patient participation

Patients have been actively involved in the design of this clinical trial at several stages, ensuring that the study addresses relevant needs and remains feasible in clinical practice.
First, the Knowledge Agenda Sports Medicine, which was developed in collaboration with patients, explicitly identified the lack of high-quality evidence on corticosteroid injections for Achilles tendinopathy as a major knowledge gap. This provided the initial rationale for the study focus.
Second, a patient survey was conducted among 48 individuals diagnosed with chronic midportion Achilles tendinopathy who attended the participating centers (mean age 46 years, 38% women, median symptom duration 13 months). The survey showed that 89% of patients were willing to participate in such a trial. Their feedback supported the acceptability of the study procedures and confirmed the importance of the research question.
Third, a dedicated patient panel of three individuals with Achilles tendinopathy reviewed the study design. They unanimously confirmed the importance of the trial and endorsed the relevance of the primary outcome measures (VISA-A and tendon rupture). Based on their input, additional secondary outcomes such as ultrasound-based tendon characteristics were included to capture both patient-perceived and clinically observable effects. This patient panel will continue to be part of the research team in the next phases of the trial, using the patient participation matrix.
Finally, patients contributed to the assessment of burden. Both patients and health professionals considered the proposed study procedures (clinical visits, ultrasound imaging, functional tests, and blood sampling) as acceptable and proportionate to the expected benefits.
In summary, patients were involved in (i) identifying the research objectives, (ii) assessing the burden and feasibility of study procedures, and (iii) refining the choice of outcome measures. Their contributions have ensured that the study design is aligned with the perspectives and priorities of patients with Achilles tendinopathy.

7. STUDY POPULATION

7.1 Population

The RCT targets patients with clinically diagnosed and ultrasonographically confirmed Achilles tendinopathy, who have not responded to standard care. This ensures that the study population is representative of the clinical scenario where 2nd line treatments are needed.
The study will be performed in 3 academic institutions (Erasmus MC, Amsterdam UMC and UMC Utrecht), 3 large regional hospitals (Haaglanden Medical Centre, Isala Zwolle, Gelderse Vallei Ede), and 1 private clinic (Bergman Clinics Naarden). We have a strong track record for recruiting patients

with Achilles tendinopathy in randomised trials (inclusion of 1-3 patients/week in a single centre with injection treatments and placebo-controlled design)[16,33] With a multicentre study design, we expect to increase this rate to a mean of 4 participants/week. In the past 5 years, 395 patients with Achilles tendinopathy attended the clinic in Erasmus MC of whom 85% would have been eligible for this study. In our patient survey, 89% of the patients would consider participating. Our survey showed that health professionals find the study useful, suggesting strong feasibility for recruitment. Based on these numbers, we are confident that the project is feasible.
We will include a diverse group of adults with Achilles tendinopathy. The PhD student and research nurse will travel to the participating centres, so that participants will be able to visit a medical centre close by their home with limited travel time and easier access to the study site.
To enhance accessibility for culturally diverse populations, recruitment materials will be available in multiple languages (Dutch, English, Turkish, and Arabic), aligning with the linguistic backgrounds of Achilles tendinopathy patients in Dutch urban areas. In the analysis of the primary and secondary outcomes, we will adjust for age, sex, BMI, symptom duration, socioeconomic position based on clinical reasoning and previous research.[16,33,36]

7.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Clinical diagnosis of midportion Achilles tendinopathy (localized Achilles tendon pain above the calcaneal border, which increases on tendon loading and upon Achilles tendon palpation)
- Ultrasonographic findings that are consistent with midportion Achilles tendinopathy (spindle shaped Achilles tendon thickening and/or presence of intratendinous hypoechoic areas and/or intra-tendinous or peritendinous Doppler flow)
- Symptom duration ≥ 6 months
- Persisting symptoms after education, load management advice and a 3-month exercise programme[5]
- Age 18-65 years

7.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Clinical suspicion of insertional Achilles tendinopathy (pain at the calcaneal insertion site)
- Clinical suspicion of Achilles tendon rupture (abnormal Thompson test and/or palpable gap)
- Clinical suspicion of plantar flexor tenosynovitis (posteromedial pain during resisted toe plantar flexion)
- Clinical suspicion of sural nerve pathology (sensory disturbance in the sural nerve distribution)
- Clinical suspicion of peroneal tendon subluxation (visible luxation with localized pain) or peroneal tendinopathy (posterolateral ankle pain on palpation and during resisted eversion).
- Clinical suspicion of posterior ankle impingement syndrome (pain at the posterior ankle joint and provocation during rapid passive dorsiflexion)
- Suspected systemic/inflammatory disorders as the cause of symptoms (e.g. spondylarthropathy, gout, rheumatoid arthritis)
- Any condition that prevents participation in an active exercise program
- History of Achilles tendon rupture of the index tendon
- Previous local corticosteroid injection on the index Achilles tendon
- Previous surgical intervention on the index Achilles tendon
- Refusal to undergo one of the study treatments
- Medical conditions that compromise the safety of injection

  - Local skin infection at injection site (cellulitis, abscess, infected wound). Suspected systemic infection with fever
  - Vitamin K Antagonist use with INR above therapeutic range (>3.0) measured within 3 days prior to injection or unknown INR. Use of Direct Oral Anticoagulant (DOAC), antiplatelet therapy, and Vitamin K Antagonist with INR within therapeutic range measured within 3 days prior to injection are allowed.

- Current pregnancy or breastfeeding
- Potential medication-induced tendon pathology (fluoroquinolone use within 3 months before symptom onset, or statin initiation within 12 months before symptom onset)
- Inability to provide informed consent
- Participation in another concomitant interventional program for Achilles tendinopathy
- Known hypersensitivity or allergy to Depo-Medrol or Lidocaine
- Participants with Diabetes Mellitus may participate in the study, but participants with unstable or poorly controlled Diabetes Mellitus may be excluded at the discretion of the investigator for safety reasons.

7.4 Vulnerable populations and clinical trials in emergency situations

Not applicable.

8. STUDY TREATMENTS

8.1 Investigational Medicinal Product(s) (IMP(s))

8.1.1 Name and description of the IMP

Depo-Medrol® (methylprednisolone acetate, 40 mg suspension for injection), supplied by Pfizer.
Formulation: sterile aqueous suspension, white, must be shaken before use.
In the ASPIRE trial, Depo-Medrol (40 mg) is combined with Lidocaine hydrochloride (10 mg) to form the investigational mixture. The investigational product thus consists of Depo-Medrol 40 mg + Lidocaine 10 mg, administered as a 1 ml peritendinous injection under ultrasound guidance.

8.1.2 Status of development of the IMP

Methylprednisolone acetate is a well-established corticosteroid with strong anti-inflammatory properties. It has been extensively used for musculoskeletal injections (arthritis, bursitis, tendinopathies). Clinical experience shows short-term pain reduction, but evidence in Achilles tendinopathy is inconsistent. Safety concerns focus mainly on risk of tendon rupture, especially after repeated or intratendinous injections.[10] Recent RCT data[7] suggest that up to three peritendinous injections combined with exercise therapy are safe and effective, though replication is needed.[11]
Lidocaine hydrochloride is a licensed local anaesthetic, widely used for infiltration and nerve block. It provides rapid but transient anaesthesia (1–2 h) and no long-term therapeutic tendon effect. In this trial, its role is to make up a homogeneous injection mixture, decrease post-injection pain and ensure blinding.[6,16]
Both products are EU-licensed, GMP-manufactured, and have long-established pharmacological and toxicological profiles.

8.1.3 Description and justification of dosage and route of administration

Dosage: Each injection contains 1 ml Depo-Medrol (40 mg) + Lidocaine (10 mg).
Schedule: All participants receive one injection at baseline. Up to two additional injections may be administered within 8 weeks if symptoms persist. The 2nd and 3rd injections will only be considered when 1 of the following specific criteria for lack of improvement are met during at least 1 week of the rehabilitation:

1) mean ≥5 mm on the 0-10 mm Visual Analog Scale (VAS; higher scores indicate worse pain) during activities of daily living (ADL); or
2) less than 3 on the numerical GROC scale (range from -5 to 5 points); or
3) patient-reported lack of improvement and a desire to repeat the injection

All participants follow the same injection schedule consisting of one injection at baseline with the option of up to two additional injections within the first 8 weeks if predefined symptom criteria are met. These criteria are identical for both treatment groups and are independent of treatment allocation.
Route: Peritendinous, anterior to Achilles tendon, ultrasound-guided, sterile conditions.
Rationale: Dose is consistent with clinical practice and the recently published RCT.[7] Combination with Lidocaine ensures optimal distribution and reduces post-injection pain. Peritendinous injection with guidance of ultrasound and the use of exercise therapy with load management advice mitigates steroid risk.

8.2 Comparator IMP(s)

Not applicable.

8.3 Placebo

Lidocaine hydrochloride 10 mg/ml injection solution.
Formulation: clear, colourless solution, sterile single-use flacons.
Role: placebo comparator. Provides transient anaesthesia without long-term tendon effect. Dosage and route identical to active arm (1 ml peritendinous injection under ultrasound guidance). Lidocaine has frequently been used in Achilles tendinopathy injection trails for these reasons.[6]

8.4 Auxiliary Medicinal Product(s) (AxMP(s))

Not applicable.

8.5 Additional considerations for trials involving a medical device

Not applicable.

8.6 Additional considerations for trials involving an in-vitro diagnostic or companion diagnostic

Not applicable.

8.7 Preparation and labelling of the study treatment(s)

The hospital pharmacy of Erasmus MC is responsible for ordering, receiving, quality checking, storing and preparing the study medication (Depo-Medrol and Lidocaine) under GMP conditions.
A Good Clinical Practice (GCP)-approved electronic data management system (Castor EDC, Amsterdam, the Netherlands) will be used to generate a computer-based block randomisation scheme. Patients will be stratified by study centre and activity level, using variable block sizes of 2, 4, or 6, to ensure balanced allocation and concealment of treatment assignment.
A trained person at the participating site, not involved in the research consortium, will perform randomisation in Castor EDC. This unblinded person will access the randomisation code and select and blind the assigned injection accordingly. For participants in the intervention arm, 1 ml Depo-Medrol (40 mg) and Lidocaine (10 mg) will be selected. For participants in the placebo arm, 1 ml

Lidocaine (10 mg) will be selected. The unblinded person will conceal the syringe with an opaque cover to ensure blinding. After the injection has been administered, the unblinded person will have no further contact with the participant to fully preserve blinding integrity.
The unblinded person will ensure that the syringes are selected and blinded according to standard operating procedures (SOPs) so that the appearance and volume of the injections are identical across groups. The physician performing the injection, the coordinating investigator, participants and the statistician remain blinded throughout the trial. One member of the advisory board will also perform a blinded interpretation of the results.
All study medication will be labelled in accordance with EU CTR Annex VI, including trial identification code, product code (active or placebo, blinded), batch number, expiry date, and storage conditions. Labelling and accountability will be managed by the pharmacy.

9. OTHER TREATMENTS AND RESTRICTIONS

9.1 Concomitant therapy

All participants, regardless of treatment allocation, will receive standard care consisting of:

- patient education about Achilles tendinopathy and prognosis,
- load management advice to adapt activity levels to symptoms and to refrain from explosive sports (running, jumping, sprinting) within the first 3 months after the last injection, and
- a structured progressive calf-muscle strengthening exercise programme, supported by an online website with movies of the exercises.

This standard therapy is considered essential and must be continued by all participants throughout the study.

9.1.1 Permitted medication(s)

- Simple analgesics (e.g. paracetamol/acetaminophen up to 4 g/day) as rescue medication.
- Any medication unrelated to Achilles tendinopathy as deemed necessary by the treating physician.

9.1.2 Prohibited medication(s)

- Systemic corticosteroids (except in emergencies or when deemed necessary by the treating physician).
- Any local injection into or around the Achilles tendon other than study IMP/placebo.
- Participation in another interventional drug/device trial.
- Fluoroquinolone antibiotics (due to tendon rupture risk).
- NSAID or opioid use for tendon pain.

9.2 Lifestyle restrictions

9.2.1 Contraception measures

- Pregnancy and breastfeeding are exclusion criteria.
- No additional contraception required, as systemic exposure is negligible.

9.2.2 Other requirements

- Avoid high-impact/explosive activities (e.g. running, sprinting, jumping, heavy plyometrics) during the first 3 months post-injection.
- Adherence to the exercise programme and load management advice is strongly advised.

10. TRACEABLILITY, STORAGE, ACCOUNTABLILITY AND COMPLIANCE

10.1 Traceability and storage of the study treatment(s)?

The study is classified as a low-intervention clinical trial, as both investigational products (methylprednisolone acetate and Lidocaine) are authorised medicines used within their marketing authorisation, and administration is supported by scientific evidence.

Ordering and receipt: The Erasmus MC hospital pharmacy will order, receive, and locally store Depo-Medrol and Lidocaine.
Storage: IMPs will be stored under controlled conditions (room temperature, protected from light) in the pharmacy, in accordance with the manufacturer's SmPC. Storage conditions will be monitored and documented.
Dispensing and traceability: The hospital pharmacy will provide the study medication to the GCP-certified research nurse. All batches, expiry dates, and quantities will be logged in pharmacy accountability records.
Preparation and use: At the study site, a trained person will perform randomisation in Castor EDC and select the assigned injection. The unblinded person will conceal the syringe with an opaque cover to ensure blinding and hands it over in blinded form to the injecting physician.
Return and destruction: Unused IMP and placebo vials will be documented, and destroyed at the study site according to local procedures.
Justification: Given the low-intervention classification, routinely maintained pharmacy documentation (ordering, receipt, dispensing, destruction) is considered sufficient to ensure traceability, in combination with patient medical records documenting injection dates and doses.

10.2 Accountability of the study treatment(s) and compliance

Accountability:

- The Erasmus MC pharmacy maintains full accountability records for ordering, receipt, dispensing, preparation, and destruction of IMP and placebo.
- The randomisation code is securely stored using the electronic data management system (Castor EDC, Amsterdam, the Netherlands). The unblinded person selects and covers the injection according to SOPs, ensuring treatment concealment.
- Labelling and documentation follow EU CTR Annex VI requirements.
- If a study participant is ultimately not included in the study, this will be reported to the trial pharmacy so that a note can be made in the drug accountability records.
- In Castor, the randomisation result will automatically be emailed to the trial pharmacy to ensure correct medication dispensing for subsequent doses and to prevent wastage. Medication will be delivered in a sealed bag. After each randomisation, the study team will also send a separate email to the trial pharmacy containing the patient's PID number, name, and date of birth, as only the subject number is visible in Castor.

Blinding maintenance:

- The unblinded person will access the randomisation result, select the allocated injection accordingly, and blind the syringe using an opaque covering sheath to conceal its contents.
- The unblinded person has no role in patient care or outcome assessment.
- The treating physician, coordinating investigator, research nurse, statistician and participants remain blinded until database lock. Emergency unblinding will only occur if necessary for patient safety (See DSMB charter). One member of the advisory board will also perform a blinded interpretation of the results.

Compliance monitoring:

- Compliance with the injection protocol is ensured by on-site documentation of each administered injection.
- Compliance with the exercise programme and load management advice is monitored through patient-reported exercise diaries. We will structurally assess compliance with the exercise programme and load management advice during the standard follow-up visits
- Missed injections, deviations, and adverse events will be recorded in the eCRF.

11. STUDY ASSESSMENTS AND PROCEDURES

11.1 Screening procedure

The screening of potential participants will take place in two steps. Potential participants may contact the study team directly or may be informed about the study by their treating physician, after which contact with the study team can be established.
In the first step, interested patients will complete a short online questionnaire or provide information by email or telephone, allowing an initial assessment of the main inclusion and exclusion criteria, such as symptom duration, location of symptoms, previous treatments, and previous corticosteroid injections. This prescreening is intended solely to assess whether a hospital visit for screening is likely to be useful. The collected information will not be stored in a research database and will not be used for study purposes before written informed consent is obtained. Patients will receive oral and written information about the study during this phase. In the second step, patients will be invited for a hospital visit. During this visit, a researcher and a medical specialist will perform a comprehensive evaluation. Patients will have the opportunity to ask questions about the study, after which written informed consent will be obtained. After informed consent has been obtained, eligibility will be assessed and baseline assessments will be performed. Participants who meet the eligibility criteria will subsequently be randomised and receive the injection procedure, followed by oral information about load management and the exercise program.

11.2 Randomisation, blinding and treatment allocation

Once eligibility is confirmed and baseline assessments have been performed, participants are randomised. A Good Clinical Practice (GCP)-approved electronic data management system (Castor EDC, Amsterdam, the Netherlands) will be used to generate a computer-based block randomisation scheme. Allocation occurs in a 1:1 ratio between the intervention arm (Methylprednisolone acetate plus Lidocaine) and the placebo arm (Lidocaine only). Patients will be randomised stratified by study centre and by activity level (ankle activity score ≥ 4)[33], using variable block sizes of 2, 4, or 6, to ensure balanced allocation and concealment of treatment assignment.

A trained person at the participating site, not involved in the research consortium, will perform randomisation in Castor EDC. This unblinded person will access the randomisation code and select the assigned injection accordingly. The unblinded person will conceal the syringe with an opaque cover to ensure blinding. After the injection has been administered, the unblinded person will have no further contact with the participant to fully preserve blinding integrity. Each participant receives one injection at baseline, with the option for up to two additional injections within 8 weeks if symptoms persist, based on predefined clinical criteria.

The treating physician, coordinating investigator, research nurse, statistician and participants remain blinded until database lock. One member of the advisory board will also perform a blinded interpretation of the results.

The randomisation code is securely stored using the electronic data management system (Castor EDC, Amsterdam, the Netherlands). Emergency unblinding may only occur if deemed essential for participant safety and is documented both in the eCRF and in a deviation log. The independent Data Safety Monitoring Board (DSMB) has access to unblinded safety data (tendon rupture incidence), to allow ongoing safety surveillance. The DSMB may recommend early unblinding for individual participants if necessary, or modification or termination of the study if unacceptable risks are identified. Study syringes are labelled in compliance with EU CTR Annex VI, including trial identification, blinded product code, batch number, expiry date, and storage conditions.

11.3 Study procedures and assessments

Study participation lasts for 1 year, with extended questionnaire-based follow-up at 2, 5 and 10 years. At the baseline visit, participants provide consent, undergo eligibility confirmation, and complete questionnaires. A physical examination with functional testing and ultrasound examination of the tendon are performed. We will collect venous blood samples (6 ml) from participants who are included at the study site Erasmus MC. The number of injections applied will be registered for all participants. All procedures will be performed by a researcher and/or research nurse according to predefined standard operating procedures (SOPs). All transfers of data (physical tests and imaging) will comply with the Data and Material Transfer Agreement (DMTA) between participating centres.

Physical tests

Physical tests are conducted to evaluate pain, and functional capacity of the Achilles tendon during loading. These tests are performed at baseline and 2 follow-up visits (3 months and 1 year) by a trained researcher, following standardized procedures and validated protocols. [6,25] Participants will be instructed to perform the tests barefoot, using their most symptomatic leg. Patients with bilateral complaints at baseline, will perform the tests for both legs. Maximum pain during or shortly after the tests will be scored using an 11-point Visual Analogue Scale (VAS; 0 = no pain, 10 = worst imaginable pain). Participants are advised to rest for 1–2 minutes between trials, if necessary.

1. Achilles Tendon Palpation [6]

From a prone position, standardized palpation is applied to the midportion of the Achilles tendon by the examiner. The examiner will be trained to provide similar pressure in all participants before the start of the study, using a dynamometer. Participants are asked to rate the pain intensity experienced during palpation using a visual analogue scale (VAS; 0–10). This assessment provides a standardized measure of local tendon tenderness and reflects pain sensitivity at the affected tendon site.

2. Single-Leg Heel Rise Test [6]

From an upright standing position, participants perform 5 consecutive heel rises on one leg, aiming for consistent rhythm and height. Pain intensity during and immediately after this test is recorded on the VAS (0-10). The test provides a standardized load challenge to the Achilles tendon and reflects tendon function under isotonic loading conditions.

3. Single-Leg Heel-Rise Endurance Test (HRET) [25]

Participants stand on one leg on a ten degrees inlcine board, with the contralateral leg flexed to avoid assistance. They perform consecutive single-leg heel rises through the full range of motion, keeping the knee extended and using fingertip support on a wall for balance. The test continues until the participant is no longer able to lift the heel or stops due to fatigue or pain. Additional stopping criteria are applied when: the participant is unable to maintain the pace of the digital metronome; the knee angle or trunk position can no longer be maintained; or more than fingertip support against the wall is required. If any of these stopping criteria are observed, a verbal cue is provided. The test is terminated if the participant does not correct the movement after a second verbal cue. The number of repetitions, peak height, vertical displacement and total work (number × height) are recorded using the Calf Raise App. This test quantifies endurance and calf muscle strength and has been validated as a reliable measure of plantar flexor performance. Pain intensity during and immediately after this test is recorded on the VAS (0-10). Tests will be discontinued if pain exceeds 5/10 or in case of muscle fatigue that prevents further continuation.

4. 5-Hop Pain Test [6]

Participants perform 5 consecutive single-legged hops, and pain during and immediately after the final hop is scored using a VAS (0-10). This test is sensitive to symptom provocation and serves as a functional pain outcome related to plyometric tendon loading.

Ultrasound imaging

Ultrasound examinations will be performed to evaluate Achilles tendon morphology, structure, and vascularity. All scans will be performed by a trained researcher according to SOPs. Participants will be examined in a prone position with the feet extending over the examination table. Both tendons will be scanned from the musculotendinous junction to the calcaneal insertion. All image data will be anonymized and stored for centralized analysis. All ultrasound data will be entered into the eCRF and archived according to Good Clinical Practice (GCP) standards.

1. B-mode Ultrasound Geometry

Longitudinal and transverse B-mode images will be obtained using a high-frequency (multi-frequency 5–16 MHz) linear-array transducer.
Maximum anterior–posterior (AP) Achilles tendon diameter will be identified in the sagittal view for the midportion (2–6 cm proximal to the calcaneal insertion) region and measured at the point of greatest thickness in transversal view.[29]

2. Power Doppler Ultrasound (PDUS)

Neovascularization will be assessed using standardized PDUS settings (pulse repetition frequency 1.0 kHz, gain 50 %, colour box ≈ 4.6 cm^2). The probe will be held perpendicular to the tendon with minimal pressure to avoid flow suppression.
Doppler flow will be quantified using the Surface Area Quantification (SAQ) method, which measures the colour fraction (% of pixels showing flow) within a defined ROI using ImageJ-based analysis.[31]

3. Ultrasound Tissue Characterization (UTC)

UTC imaging will be performed using a motorized tracking device (UTC Imaging, Stein, The Netherlands) with a 5–16 MHz transducer. The probe will move automatically over a 12 cm trajectory covering the Achilles tendon.
Participants remain prone with the ankle in maximum tolerable dorsiflexion. The transducer is positioned perpendicular to the tendon surface. Raw image data will be reconstructed into a 3-D dataset using the UTC software.
For the analysis, 4 echo types (I–IV) are automatically classified, reflecting collagen alignment and tendon matrix integrity. Outcome measures include: Percentage echo type I + II (structurally intact tendon) and percentage echo type III + IV (disorganized tendon structure).[29]

Blood samples
Venous blood samples will be collected from patients who will be included at Erasmus MC to explore potential systemic biomarkers related to tendon healing. Blood sampling will be performed, following standardized venipuncture procedures. The research team will perform the venipuncture using standard aseptic technique after verifying participant identity and trial code. A single blood tube of 6 mL will be drawn from the antecubital vein using a serum-separating tube. Within two hours after collection, the sample will be centrifuged at 2000 rpm for 10 minutes at room temperature. The serum fraction will be pipetted into 4 pre-labelled cryovials (500 µL each) using sterile disposable pipettes. All vials will be coded with the participant's unique study ID, date, and time of collection, without any directly identifying personal data.
Immediately after processing, samples will be frozen and stored at –80°C at the local site. All samples will finally be logged in the biobank tracking system and stored according to Erasmus MC Biobank SOPs and ISO 20387 standards.

Samples will be retained for future exploratory biomarker analyses, which may include proteomic, metabolic, and inflammatory marker profiling relevant to Achilles tendon pathology.[32] No genetic analyses will be performed.

Injection procedure
Study injections will be administered by trained physicians experienced in ultrasound-guided musculoskeletal injections. They will be trained before the study using an instructional video. The injection will consist of 1 ml methylprednisolone acetate 40 mg combined with lidocaine 10 mg or 1 ml lidocaine 10 mg (placebo), selected by unblinded personnel according to the randomisation code.

Prior to injection, allergies to corticosteroids or local anaesthetics will be checked and the injection site will be inspected for signs of infection or other contraindications. The injection site will be inspected prior to injection. The injection will not be performed in case of:

- Local skin infection at the injection site (e.g. cellulitis, abscess or infected wound)
- Clinical suspicion of systemic infection
- Vitamin K antagonist therapy with an INR >3.0 or unknown INR

For participants using vitamin K antagonists, a recent INR ≤3.0 measured within 3 days prior to injection must be available.

Use of direct oral anticoagulants (DOACs) or antiplatelet medication is not considered a contraindication for peritendinous injection.

The participant will be positioned prone with the ankle in a relaxed position. Hand hygiene will be performed and the skin will be disinfected with chlorhexidine or 70% alcohol. A clean technique will be used. Under ultrasound guidance, a peritendinous injection will be administered at the midportion of the Achilles tendon at the point of maximum tendon thickening. The needle will be positioned between the Achilles tendon and Kager's fat pad, avoiding intratendinous placement. The full volume (1 ml) will be injected slowly under real-time ultrasound visualisation.

After injection, light pressure will be applied and a dressing will be placed. Participants will be observed briefly for immediate adverse reactions such as dizziness, allergic reactions or acute pain. Participants will receive standardised post-injection instructions and the injection procedure will be documented in the study records, including date, injection number and any complications. These procedures will also be followed in case of the optional 2nd and 3rd injection.

Participant instructions
After baseline testing, randomisation is carried out, and the allocated injection is administered. The education, load management advices and standardised progressive exercise programme will be instructed to the participants. These will be supported by a written form and an online application (Website).

Schedule
Optional second and third injections may be given between week 4 and week 8 if predefined symptom criteria are met (assessed using a short digital questionnaire at week 4 and 8). A telephone call will be scheduled to discuss the results of this short questionnaire and to make the final decision on performing the repeat injection. At the 3 months follow-up visit, questionnaires, ultrasound, physical examination, functional tests, and blood sampling (Erasmus MC) are repeated. Online questionnaires are completed at 6 and 9 months. At the 1-year visit, participants undergo the full assessment protocol including questionnaires, physical examination with functional testing, ultrasound examination of the tendon, and blood sampling. Long-term follow-up consists of online questionnaires at 2, 5 and 10 years. An overview of the measurements during the ASPIRE trial is provided below.

Procedure / Assessment	Baseline	4w	8w	3 mo	6 mo	9 mo	1 yr	2 yr	5 yr	10 yr
Informed consent	X									
Eligibility (in/exclusion)	X									
Demographics, health status, activity level	X									
Presence of pregnancy	X	X	X	X						
VISA-A questionnaire (primary)	X	X	X	X	X	X	X	X	X	X
Full-thickness rupture assessment (primary)	X	X	X	X	X	X	X	X	X	X
Minor side effects corticosteroids (body mass, fat%, mood)	X			X	X	X	X			
Presence of visually assessed skin changes	X			X			X			
TENDINS-A questionnaire	X			X	X	X	X	X	X	X
Global rating of change		X	X	X	X	X	X	X	X	X
Pain on examination (VAS on palpation andduring/after activity)	X			X	X	X	X	X	X	X

Procedure / Assessment	Baseline	4w	8w	3 mo	6 mo	9 mo	1 yr	2 yr	5 yr	10 yr
EQ-5D-5L	X			X	X	X	X			
Return to physical activity scale				X	X	X	X	X	X	X
iMCQ / iPCQ	X			X	X	X	X			
Physical tests	X			X			X			
Ultrasound tendon structure / UTC	X			X			X			
Neovascularisation (Power Doppler)	X			X			X			
Blood sampling (6 mL, only Erasmus MC site)	X			X			X			
Injection (intervention/placebo)	X	X[1]	X[1]							
Single question on success blinding after injection	X	X[1]	X[1]							
Assessment criteria repeated injection		X	X							

X[1] – optional, when criteria for repeated injection are met.

Blood sample collection totals approximately 18 ml per participant included at Erasmus MC across the trial during 1 year. These samples will be stored for exploratory proteomics analyses. Ultrasound assessments are limited to the Achilles tendon. Should incidental findings of potential clinical relevance be identified, such as unrelated structural abnormalities, participants will be informed and referred for appropriate follow-up. No genetic analyses are performed in this trial.

11.3.1 Efficacy assessments

The primary efficacy endpoint is the change in VISA-A score from baseline to 1 year.[17,18,34,35]
Secondary efficacy outcomes include:

- TENDINS-A questionnaire[21,22]
- Pain during and after activity (VAS)[23]
- Global perceived improvement[24]
- Physical tests and tenderness evaluation (pain on Achilles tendon palpation, single-leg heel-rise, hopping test, single leg heel rise endurance test)[16,25]
- Return to sport and activity level[16]
- Health-related quality of life (EQ-5D-5L)[26]
- Healthcare consumption (iMCQ)[27] and work productivity loss (iPCQ)[28]
- Ultrasound imaging (tendon structure, thickness, degree of power Doppler flow)[29-31]

These assessments are performed at baseline, 3 months, and 1 year, with interim data collected through online questionnaires at 4 and 8 weeks and at 6 and 9 months. Extended outcomes at 2, 5 and 10 years are obtained via digital follow-up questionnaires. We will also obtain measures for minor adverse events and cost-effectiveness.

Participants will be asked at baseline whether they experience symptoms in one or both Achilles tendons. In participants with bilateral symptoms, the most symptomatic side, as reported by the participant and confirmed during clinical assessment, will be selected as the index tendon and will receive the study intervention.
At baseline, and at the 3-month and 12-month follow-up visits, bilateral assessment will be performed in participants who report bilateral symptoms at baseline. This assessment includes palpation pain (VAS score), physical tests, and ultrasound/UTC evaluation of both tendons.

Only the index tendon will receive the study intervention and will be used for the primary outcome analyses.

11.3.2 Safety assessments

The primary safety endpoint is a full-thickness Achilles tendon rupture.[19] Safety monitoring includes systematic recording of all adverse events (AEs) and serious adverse events (SAEs) from baseline to the 12-month visit. Particular attention is paid to tendon rupture, skin atrophy or depigmentation, local infection, and systemic corticosteroid-related effects. For participants with Diabetes Mellitus, hyperglycaemia will be specifically monitored as potential AE during follow-up. Physical and imaging examinations of the tendon are performed at baseline, 3 months, and 1 year. Ultrasound imaging can be repeated on request at other timepoints on request to detect potential tendon ruptures in case of clinical suspicion.

Participants experiencing adverse reactions are followed until resolution or stabilisation. Any suspected tendon rupture is confirmed through clinical testing and ultrasound on an extra appointment. Confirmation of an Achilles tendon rupture in another hospital is also considered as confirmed event. Treatment of adverse events will be done through regular care routes. All safety data are overseen by an independent Data Safety Monitoring Board (DSMB), which reviews Achilles tendon rupture incidence, and has the authority to recommend protocol modification or trial termination if necessary.

12. STUDY DISCONTINUATION AND COMPLETION

12.1 Definition End of Trial

The end of the clinical trial is defined as the date of the last visit of the last participant at 1 year follow-up. Although extended questionnaires will be collected at 2, 5 and 10 years, these long-term data collections are considered post-trial observational follow-up and not part of the interventional clinical trial.

Discontinuation criteria for the IMP include:

- confirmed Achilles tendon rupture during the study,
- development of a medical condition that makes further injections unsafe (e.g. systemic infection, allergy to IMP components), or
- pregnancy during the first 8 weeks of the trial when criteria for a repeated injection are met.

All participants receive standard care (education, load management, and exercise). This will not be discontinued unless the participant withdraws consent, develops a condition that makes exercise unsafe, or requests discontinuation.

Subjects can withdraw at any time without consequences for their future care. Investigators may also decide to withdraw a subject for urgent medical reasons, including serious adverse events.

12.2 Criteria for temporary halt and early termination of the clinical trial

The trial may be temporarily halted or terminated early if:

- advice to do so is given by the Data Safety Monitoring Board (DSMB),
- regulatory authorities request suspension or termination, or

- logistical or ethical issues prevent continuation.

In case of early termination, the sponsor will inform the competent authorities and ethics committees according to regulatory requirements. Participants will be informed promptly and arrangements made for appropriate medical follow-up.

12.3 Discontinuation/withdrawal of individual subjects

Subjects may be withdrawn from the trial if they:

- withdraw consent,
- experience disease progression (e.g. tendon rupture),
- do not respond to treatment and request withdrawal,
- develop medical conditions making continuation unsafe,
- are non-compliant with trial procedures.

Data collected up to the point of withdrawal of the participant will, unless the participant requests deletion, be retained and used for analysis. If a withdrawal request is made, the participant may ask for deletion of their identifiable data. However, where use or retention of those data is necessary for the integrity of the study or required by law or regulation, data may be retained (possibly in an anonymised form) and used. Participants will be informed of this at the time of consent. Subjects will not be replaced after withdrawal; the trial sample size accounts for anticipated drop-outs.

Participants who withdraw will, where possible, be asked to complete final safety assessments (e.g. questionnaires, physical exam and ultrasound assessments) and will be encouraged to continue questionnaire follow-up even if they discontinue repetition of injection therapy or exercise therapy.

12.4 Arrangements for subjects after their participation in the clinical trial ended

After completing their 1-year follow-up visit, participants return to usual care. No additional trial-specific interventions are provided. Usual care includes standard clinical follow-up by the health professional who referred the patient or by the general practitioner if needed. Participants with complications (e.g. rupture, persistent pain, or new diagnoses) will be referred to appropriate clinical services. These arrangements do not differ from normal management of Achilles tendinopathy in clinical practice, but the structured monitoring during the trial ensures earlier detection and referral compared with routine care.

13. SAFETY REPORTING

13.1 Definitions

13.1.1 Adverse events (AEs)

Any untoward medical occurrence in a subject administered a medicinal product, not necessarily with a causal relationship.

13.1.2 Serious adverse events (SAEs)

Any event that results in death, is life-threatening, requires or prolongs hospitalisation, causes persistent/significant disability/incapacity, or results in a congenital anomaly/birth defect.

13.1.3 Suspected unexpected serious adverse reactions (SUSARs)

An event qualifies as a SUSAR if:

- it is serious;
- it is reasonably related to the investigational product; and
- it is unexpected compared to the reference safety information (RSI).

13.2 Recording of AEs/SAEs/SUSARS

All AEs will be actively elicited at each visit by the investigator and recorded in the source documents. AEs critical to safety evaluations (e.g. tendon rupture, severe injection site reactions, severe systemic steroid effects) will be documented in the eCRF and reported to the sponsor.

Minor, expected and transient injection-site reactions (e.g. mild pain, transient swelling <48h) will be recorded in source documents but not reported to the sponsor, unless they progress to a more severe AE.

13.3 Reporting of AEs and SAEs

13.3.1 Reporting of SAEs by the investigator to the sponsor

Investigators must report all serious adverse events (SAEs) to the sponsor within 24 hours of becoming aware of the event during the active study period up to 12 months follow-up. This includes tendon rupture, severe local complications (e.g. severe skin atrophy or deep infection), severe systemic corticosteroid reactions, and any event requiring hospitalisation. Participants will be instructed to actively report such events between scheduled follow-up assessments to ensure timely safety monitoring. For long-term follow-up assessments at 2, 5, and 10 years, safety data will be collected prospectively through scheduled follow-up questionnaires. However, SAE assessment during this long-term follow-up will occur after completion of data collection for the respective follow-up time point. As a result, reporting within 24 hours is not feasible for these long-term assessments. SAEs identified during long-term follow-up will therefore be evaluated and reported after data review. Given the extended time interval since administration of the investigational medicinal product, the causal relationship between the study medication and reported events may be less clear. These events will nevertheless be documented, assessed by the sponsor, and reported in accordance with applicable regulatory requirements for long-term safety follow-up.

13.3.2 List of SAEs which do not require immediate reporting and procedure for reporting

Planned hospitalisation for elective reasons unrelated to the study does not require immediate reporting. These events will be documented in the eCRF and reviewed during monitoring.

13.4 Follow-up of adverse events

All AEs are followed until resolution or stabilisation. Follow-up may include additional tests or referrals. SAEs are reported until the defined end of study (1-year visit of last patient).

Participants with Diabetes Mellitus will be instructed to monitor their blood glucose levels more intensively for at least 3 days after each injection. Increased glucose levels may occur after corticosteroid administration. Participants will be advised to perform additional glucose measurements preferably in the late afternoon or before the evening meal, as corticosteroid-related hyperglycaemia may be most apparent at these times. Participants will be instructed to contact their treating physician or the study team in case of symptoms of hyperglycaemia or

repeated blood glucose values above 15 mmol/L. Any adjustment of diabetes medication will be managed by the participant's treating physician according to standard clinical practice.

13.5 Reporting of SUSARs by the sponsor to EudraVigilance

The sponsor will maintain detailed safety records and report SUSARs electronically to EudraVigilance:

- fatal/life-threatening SUSARs within 7 days,
- non-fatal/non-life-threatening SUSARs within 15 days,
- SUSARs initially classified as non-fatal but later determined fatal/life-threatening within 7 days of reclassification.

Initial incomplete reports may be submitted, followed by a complete report.

13.6 Annual safety report

The sponsor will submit an annual Development Safety Update Report (DSUR) for Depo-Medrol and Lidocaine via CTIS to all concerned Member States, in compliance with CTR Article 43.

13.7 Unblinding procedures for safety reporting

Unblinding is only performed if essential for participant safety. In such cases, only the treatment allocation of the affected subject is revealed. Unblinded information is restricted to staff responsible for safety reporting (sponsor pharmacovigilance, DSMB) and is not shared with investigators, monitors, or statisticians involved in trial conduct or analysis. The blinding is maintained for all other staff until database lock.

13.8 Temporary halt for reasons of subject safety

The sponsor will temporarily halt the trial if continuation poses unacceptable risks. Notification, including reasons and corrective actions, will be submitted through CTIS within 15 days. The study will only resume after a positive decision from the competent authorities. All participants will be informed accordingly.

13.9 Urgent safety measures and other relevant safety reporting

If new circumstances arise that may significantly affect the risk–benefit balance, urgent safety measures will be implemented immediately to protect participants. The sponsor will notify Member States via CTIS within 7 days of implementing these measures, in line with CTR Article 54.

13.10 Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

An independent DSMB has been established for this trial. The DSMB is composed of experts in sports medicine, clinical trials, and statistics, with no conflict of interest. The DSMB will review unblinded safety data at predefined intervals of 3 months, focusing on tendon rupture incidence and serious adverse events. It may recommend continuation, protocol modification, temporary suspension, or termination of the trial. A DSMB charter, adapted from the DAMOCLES template, defines membership, responsibilities, frequency of review, stopping rules, and reporting procedures, and will be submitted with the clinical trial application.

14. STATISTICAL ANALYSIS

14.1 Description of statistical methods

14.2 Primary study parameter(s)

The primary analyses will follow the intention-to-treat principle, including all randomized participants. The main efficacy endpoint (course of VISA-A scores) will be analysed using Linear mixed-effects models to model repeated measurements over time, including treatment, time, and interaction terms. Safety (Achilles tendon rupture) will be analysed using logistic regression. Baseline covariates (age, sex, BMI, symptom duration, and socioeconomic position) will be included to improve model precision.

For the primary efficacy endpoint, a clinically relevant effect is defined as an adjusted between-group difference of at least 7 VISA-A points in favor of the experimental arm at two consecutive equally spaced follow-up time points (3, 6, 9, and 12 months) [34,35], together with: (1) statistical evidence of a treatment-by-time interaction in the Linear mixed-effects model (statistically significant at a two-sided α of 0.05, indicating a different course of VISA-A scores over time between groups) and (2) confidence intervals excluding 0 at those time points. This effect will only be considered clinically relevant overall if the experimental arm does not perform worse (adjusted between-group difference of at least 7 VISA-A points) than the placebo arm at 12 months. This combined criterion ensures that statistical superiority reflects a clinically meaningful and sustained improvement in symptoms from the patient perspective.

For the primary safety endpoint, Achilles tendon rupture incidence is estimated to range from 0-4% in patients with Achilles tendinopathy. Population-based data indicate that corticosteroid injection may increase rupture risk, with a reported odds ratio of approximately 2, reflecting a rise from 2% (natural course) to 4% in treated populations.[6,10,12] Based on these data and patient preferences (n=48), a between-group difference in rupture incidence of up to 5% is considered clinically acceptable.

14.3 Secondary study parameter(s)

Secondary continuous outcomes (e.g., tendon thickness, quality of life) will also be assessed using Linear mixed-effects models; categorical outcomes (e.g., return to sport) will be analysed using appropriate regression models. Baseline covariates (age, sex, BMI, symptom duration, and socioeconomic position) will be included to improve model precision. Where relevant, univariate analyses (e.g., t-tests, chi-square tests) will precede multivariable models to explore relationships.

14.4 Other study parameters

All quantitative outcomes will be presented as means and standard deviations (for normally distributed continuous variables), medians and interquartile ranges (for skewed distributions), and frequencies and percentages (for categorical data). The number of injections per participant will be summarised descriptively per treatment group. Graphical displays (e.g., line graphs for VISA-A scores over time, bar charts for rupture incidence) will be used to illustrate trends. Derived parameters, such as change from baseline and minimal important change thresholds, will be calculated where relevant.

An economic evaluation will be conducted alongside the trial to determine the cost-effectiveness of corticosteroid injections added to standard care compared with standard care alone. Analyses will be performed from a societal perspective following the Dutch guideline for economic evaluations in healthcare.

Data on healthcare use (e.g., specialist visits, injections, imaging, physiotherapy), productivity loss, and other relevant costs will be collected using validated questionnaires (iMTA Medical Consumption Questionnaire, iMCQ[27]; and iMTA Productivity Cost Questionnaire, iPCQ[28]) and

medical records. Costs will be calculated using published Dutch unit prices and a bottom-up approach for intervention costs.
Both a cost-utility analysis (CUA) and a cost-effectiveness analysis (CEA) will be performed. In the CUA, outcomes will be expressed as cost per quality-adjusted life year (QALY), derived from EQ-5D-5L utility scores (Dutch tariff). In the CEA, outcomes will be expressed as cost per unit of improvement in disability (VISA-A). Incremental cost-effectiveness ratios (ICERs) will be calculated for both.
Uncertainty around cost-effectiveness estimates will be quantified using non-parametric bootstrapping, presented in cost-effectiveness planes and acceptability curves. Sensitivity analyses (e.g., variation in unit costs, perspectives, and productivity loss estimates) will test the robustness of the results. A budget impact analysis will extrapolate findings to estimate the financial consequences of wider implementation in Dutch healthcare over a 5-year horizon, including analyses from the healthcare, societal, Budgettair Kader Zorg (BKZ), and insurer perspectives.

14.5 Analysis sets

- **Intention-to-treat (ITT, primary analysis):** all randomised participants, analysed in the group to which they were allocated. This set will be used for the primary analyses of efficacy outcomes.
- **Per-protocol (PP, sensitivity analysis):** participants who received at least one injection of the assigned study medication (IMP or placebo), and completed at least 75% of the prescribed exercise sessions during the predefined treatment period (first 3 months).
- **Safety set (SS, sensitivity analysis):** all participants who received at least one injection of study medication (IMP or placebo), regardless of adherence to the exercise programme or other protocol deviations.

Given the injection is administered at baseline and shortly after randomisation, we expect minimal differences between the ITT and SS analysis set. Any discrepancies will be documented.

14.6 Participant demographics and other baseline characteristics

The baseline assessments will be based on general information from history taking and a general questionnaire, specific questionnaires, physical examination and physical testing, imaging and blood samples.
Baseline demographic and clinical characteristics (e.g. age, sex, BMI, duration of symptoms, baseline VISA-A) will be summarised per group using descriptive statistics (means and standard deviations, or medians and interquartile ranges for skewed data; counts and percentages for categorical variables).

14.7 Randomisation and blinding

Participants will be included at the centre of their first outpatient clinic appointment. For each participant the coordinating researcher prepares a syringe with the intervention medication (Depo-Medrol-Lidocaine) and a syringe with placebo (Lidocaine only).
Randomisation will occur in a 1:1 ratio using computer-generated permuted blocks of variable size. Allocation will be stratified by study centre and by baseline activity level, defined as an Ankle Activity Score of ≥4 versus <4. A trained person at each participating site will conduct randomisation in Castor EDC and to select the blinded study injection. After the administration of the injection, this unblinded person will not be involved in further study-related procedures for

that participant to maintain allocation concealment. All participants receive a single injection at baseline, with the possibility of up to two additional injections within a 8-week period if symptoms continue, according to predefined clinical criteria.
The participants, physicians, research nurse, statistician and coordinating researcher will all be blinded to the allocation of the intervention and to the contents of the syringe. The success of blinding of the participants will be assessed by asking participants which injection they think they have received directly after the injection procedure, this will then be registered accordingly.
After the 1 year follow-up of the last patient in the study, the principal investigator and coordinating researcher will be unblinded only after the analysis of the primary outcome and interpretation of the blinded outcome analysis of an expert from the advisory board of the trial.
At 2, 5 and 10-year follow-up, a second blinded researcher will evaluate the outcome measurements.

14.8 Sample size, trail power and level of significance used

We have 2 main outcomes of interest (efficacy and safety). We calculated the sample size for each in collaboration with a biostatistical expert.

Efficacy: Efficacy will be evaluated by modelling the VISA-A scores over follow-up, and comparing between-group differences. The sample size calculation was performed using simulated data (1000 repetitions), based on previous results.[7] Data was modelled with a Generalized Estimation Equations (GEE), with an interaction between time and treatment. To detect a clinically meaningful difference at any time point with a significance level of 0.05 and 80% power, at least 55 participants per treatment arm are required. Accounting for a 10% loss to follow-up, a total of 132 participants need to be enrolled for the efficacy outcome measure.

Safety: Achilles tendon rupture incidence is estimated to be between 0-4% in patients with Achilles tendinopathy.[6,10,12] A population-based observational study shows that a mean of 2 corticosteroid injections can increase the incidence of Achilles tendon ruptures with an odds ratio of 2.[10] Based in these data, the between-group difference in incidence of an Achilles tendon rupture is estimated at 2% (2% in the control group and 4% in the intervention group). Patients accept a 5% risk of tendon rupture associated with the intervention (median, based on our survey). Given the expected rupture rate of 4% and a non-inferiority margin of 5%, along with 90% power, a one-sided significance level of 0.025, and an anticipated 10% loss to follow-up, at least 138 participants per treatment arm are required. Since the safety outcome shows the larger of the two sample sizes, 276 patients will have to be included in this RCT.

We use 80% power for the efficacy analysis, reflecting the commonly accepted balance between statistical certainty and study feasibility, whereas a higher power of 90% is applied for the safety analysis to ensure greater confidence in excluding clinically important risks, given the more serious consequences of potential safety events.

14.9 Planned analysis

14.9.1 Analysis primary endpoint

The primary endpoint (change in VISA-A score over 1 year) will be analysed using a linear mixed-effects model with fixed effects for treatment group, time, baseline VISA-A, and interaction terms for time × treatment. Random intercepts will account for repeated

measures per patient. The treatment effect will be estimated as the between-group difference in mean VISA-A scores at 1 year, with 95% confidence intervals. Multiplicity is limited as there is only one primary endpoint.

14.9.2 Analysis secondary endpoint(s)

Secondary outcomes will be analysed using regression models appropriate to their distribution:

- TENDINS-A, VAS pain, EQ-5D-5L, functional tests, imaging outcomes: linear mixed-effects models.
- Global perceived improvement and return to sport/activity: logistic regression.
- Tendon rupture incidence: descriptive statistics and Kaplan–Meier survival analysis.
- Cost-effectiveness outcomes: incremental cost-effectiveness ratios (ICERs) calculated, with uncertainty explored via bootstrapping.

14.9.3 Analysis other study parameters/endpoints

Exploratory analyses proteomic analyses. These will be assessed using mixed models or appropriate multivariate analyses, reported as hypothesis-generating.

14.10Interim analysis

No formal interim efficacy analysis is planned. The Data Safety Monitoring Board (DSMB) will review accumulating unblinded safety data at regular intervals. Stopping rules are based on unacceptable risk (e.g. unexpected high rupture rate in the corticosteroid group).

14.11(Statistical) criteria for termination of the trial

The DSMB may consider recommending trial termination for unacceptable safety signals (disproportionate Achilles tendon ruptures; e.g. ≥ 7 in the intervention group compared to 0 ruptures in the control group), or unforeseen risks outweighing potential benefits. Statistical criteria for futility may include conditional power analyses.

14.12 Procedure for accounting for missing, unused and spurious data

Missing data will be handled by multiple imputation under a missing-at-random assumption. Sensitivity analyses will include complete case analyses and worst-case scenarios. Implausible or spurious values will be queried and corrected via source verification; if unresolved, they will be excluded with justification.

14.13 Procedure for reporting any deviation(s) from the original statistical plan

All deviations from the predefined SAP will be documented, justified, and reported in the clinical study report. Major deviations will also be communicated to the DSMB and ethics committee as appropriate.

15. ETHICAL CONSIDERATIONS

15.1 Declaration of Helsinki

The sponsor will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

15.2 Recruitment and informed consent procedures

All potential participants can contact the study team by email or telephone or register through an online registration form. Potential participants recruited from existing patient populations may also be informed about the study by their treating physician, after which contact with the study team may be established.
In the first stage, a limited number of prescreening questions will be asked via the online registration form or during email or telephone contact. These questions are used solely to assess whether a hospital visit for screening is likely to be useful and whether obvious exclusion criteria are present. The prescreening information will not be stored in a research database and will not be used for study purposes before written informed consent is obtained.
If the prescreening criteria are met, the participant will be informed about the study by the coordinating investigator or research nurse. Participants will receive written study information and will be invited for a screening visit at the outpatient clinic. Participants will have adequate time between receiving the written information and the screening visit.
During the screening visit, eligibility criteria will be verified by the sports physician. Written informed consent will be obtained before any study-specific procedures or baseline measurements are performed.

15.3 Benefits and risks assessment, group relatedness

This study will be conducted in capacitated adults only; no minors or incapacitated participants will be included. Participants will attend up to 3-5 outpatient visits for screening, randomisation, injection, follow-up assessments, and will complete electronic questionnaires at several time points during follow-up (up to 10 years). These study procedures are common in routine clinical care and involve minimal additional burden beyond standard treatment.

The main risks are related to the injection procedure and are considered low. These include minor discomfort or transient pain increase after injection, mild bruising, and rare (<1%) local adverse effects such as skin atrophy, depigmentation, or superficial infection. A full-thickness tendon rupture is a known but uncommon complication of corticosteroid injection. All injections will be performed peritendinously under ultrasound guidance by experienced physicians to minimize this risk. Imaging procedures are non-invasive and carry no risks. Collection of blood samples my cause minor discomfort and bruising.

The expected benefits for participants in the intervention arm include improved short-term symptom relief, functional recovery, and potentially earlier return to work and sports. Even for participants allocated to the control arm, there is benefit from education, standardised exercise therapy, structured follow-up and early identification of complications.

The risk and burden are considered proportionate to the potential value of the research. Achilles tendinopathy often causes long-lasting pain and disability, and there is uncertainty in clinical practice about the role of corticosteroid injections. This trial directly addresses that knowledge gap. Results will have immediate relevance for patients, clinicians, and guidelines and may improve future care by identifying effective and safe treatment options.

15.4 Compensation for injury

The sponsor has an insurance that is in accordance with the legal requirements in the Netherlands (Article 7 WMO, under 1). 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.
The sponsor/investigator has a liability insurance that is in accordance with article 7, under 9, of the WMO.

15.5 Compensation for subjects

Subjects will not receive any financial incentives for participation. Travel expenses related to study visits will be reimbursed according to local hospital policies. All study-related assessments (e.g. imaging, blood samples, questionnaires, physical examinations) are provided free of charge. Participants who sustain an injury directly related to the trial intervention will be covered by the clinical trial insurance in accordance with Dutch law (WMO).

15.6 Compensation for investigators

Investigators and participating centres will receive compensation to cover the costs of trial-related activities. This includes time investment for patient screening, study visits, data entry, and reporting, as well as overhead and administrative support. The financial arrangements are based on fair market value and in line with institutional and national regulations. No performance-based or outcome-dependent payments will be made.

15.7 Other ethical considerations

The trial has been designed to minimise risks and burden for participants. All injections are ultrasound-guided and performed by experienced physicians, which reduces procedural risk. Study procedures (imaging, blood sampling, questionnaires) are standard and proportionate to the research objectives. The use of placebo injections is justified because all participants receive standard care, which is the current best practice for Achilles tendinopathy, ensuring no patient is left without effective treatment.

Subjects may withdraw consent at any time without providing a reason and without any consequences for their standard medical care. Confidentiality and privacy will be safeguarded in accordance with GDPR. Results of the trial will be disseminated to both the scientific community and patient groups, ensuring transparency and societal value.

16. ADMINISTRATIVE ASPECTS, MONITORING AND CONFIDENTIALITY

The study will be conducted in compliance with the protocol, with Clinical Trials Regulation No 536/2014 and with the principles of good clinical practice.

16.1 Approval initial application and substantial modifications

The trial protocol, informed consent form, subject information leaflet, investigational medicinal product dossier, investigators brochure and any other documents required by the Regulation will be submitted for the regulatory approval before the clinical trial is started via CTIS.

The sponsor will also submit and obtain approval for substantial modifications to the original approved documents via CTIS.

A 'substantial modification' is defined in the CTR as any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

16.2 Monitoring

Throughout the trial, 5 monitoring visits will take place. The extent, frequency, and nature of monitoring are proportionate to the trial's low-risk, low-intervention nature and based on risk assessment.

Visit No.	Selected Sites	Planning
Initiation Visit	On-site all sites	Before enrolment of the first participant, but after Ethics Committee approval has been obtained.
Year 1 Monitoring	Remote all sites	Year 1 (after multiple included participants)
Year 2 Monitoring	Remote all sites	Year 2 (after follow-up of included participants)
Year 3 Monitoring	Remote all sites	Year 3 (after a large number of enrolled participants).
Close Out Visit	Remote all sites	After database lock.

16.3 Recording, handling and storage of information

16.3.1 Handling of data and data protection

After providing written informed consent, participants will receive a secure link to complete electronic surveys and sign their consent form via Castor EDC. All study data will be entered directly into Castor EDC, a Good Clinical Practice (GCP)-compliant system that meets Erasmus MC safety criteria. Any digital data collected outside Castor EDC (e.g., imaging files and digital calf raise test data) will be stored on the Erasmus MC secured network drive with restricted access (V drive/MS Teams and MyDRE). Blood samples will be stored at the Erasmus MC Biobank.

All participant data will be coded. The code key (linking participant identifiers to the study code) will be kept separately in a password-protected file on the Erasmus MC network, accessible only to the principal investigator, department head and coordinating researcher. These individuals are responsible for safeguarding the code. Study staff and monitors will

only have access to the coded data; only authorized auditors or regulatory authorities may access source data if required.

Data security is ensured through encrypted data transfer (SSL), daily automated backups, password-protected accounts, and access rights limited to study personnel. The privacy of participants will be maintained at all times in accordance with the Dutch Personal Data Protection Act (Wbp) and GDPR regulations.

All coded study data and the code key will be archived securely for at least 15 years after study completion, after which they will be destroyed according to Erasmus MC data destruction procedures.

16.3.2 Source documents and case report forms (CRF)

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.
All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code.

16.3.3 Clinical trial master file and data archiving

The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to the clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated.

The sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless other EU law requires archiving for a longer period. The medical files of subjects shall be archived in accordance with national law.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request.

16.3.4 Collection and storage of biological samples

Blood samples will be collected to explore proteomic markers of treatment response. Samples will be coded with a unique subject identifier, and the code key safeguarded at each site. Samples will be stored at the certified Erasmus MC Biobank for future research into Achilles tendinopathy and tendon biology, beyond the scope of this trial, subject to participant consent and ethical approval. Only authorised personnel will have access.

16.4 Audits and inspections and direct access to source data/documents

This trial may be subject to internal or external monitoring, auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents including direct access to source data will be given at that time.

16.5 Reporting of serious breaches

The sponsor will notify the Member States concerned about a serious breach of the Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than **seven days** of becoming aware of that breach.

16.6 Notification of the start and the end of the recruitment

The sponsor will notify within 15 days each Member State concerned of the start of a clinical trial in relation to that Member State through CTIS.

The sponsor will notify within 15 days each Member State concerned of the first visit of the first subject in relation to that Member State through CTIS.

The sponsor will notify within 15 days each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU.

16.7 Temporary halt/(early) termination

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in relation to that Member State through CTIS.

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through CTIS.

16.7.1 Temporary halt/early termination for reasons not affecting the benefit-risk balance

The sponsor will notify with 15 days each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through CTIS.

When a temporarily halted clinical trial for reasons not affecting the benefit-risk balance is resumed the sponsor will notify each Member State concerned through CTIS.

The sponsor will notify to the EU portal CTIS of early termination of the clinical trial for reasons not affecting the benefit-risk balance through CTIS. The reasons for such action and, when appropriate, follow-up measures for the subjects will be provided as well.

16.7.2 Temporary halt/early termination for reasons of subject safety

In accordance to article 38 of the CTR, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance will be notified to the Member States concerned through the EU portal CTIS without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification subject to the authorisation procedure laid down in Chapter III of the CTR.

16.8 Summary of the results

Within 1 year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V.

16.9 Public disclosure and publication policy

The trial will be registered in CTIS and results publicly disclosed as required. The sponsor and investigators are committed to transparent reporting of the trial results, irrespective of outcome. Scientific results will be submitted for peer-reviewed publication and presented at relevant conferences. Patient organisations will also be informed of the results in accessible formats.

17. REFERENCES

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