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Neuromuscular and structural tendon adaptations after 6 weeks of either concentric or eccentric exercise in individuals with non-insertional Achilles tendinopathy: protocol for a randomised controlled trial

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ABSTRACT

Introduction There is limited evidence on the neural strategies employed by the central nervous system to control muscle force in the presence of non-insertional Achilles tendinopathy (NIAT). Additionally, the neuromuscular mechanisms by which exercise may help to resolve tendon pain remain unclear.

Objective This study aims to first establish changes in the gastrocnemius-soleus motor unit firing properties after applying a training protocol of 6 weeks based on either controlled eccentric or concentric contractions in individuals with NIAT. Second, we want to determine changes in the level of pain and function and mechanical and structural properties of the Achilles tendon after applying the same training protocol. Additionally, we want to compare these variables at baseline between individuals with NIAT and asymptomatic controls.

Methods and analysis A total of 26 individuals with chronic (>3 months) NIAT and 13 healthy controls will participate in the study. Individuals with NIAT will be randomised to perform eccentric or concentric training for 6 weeks. Motor unit firing properties of the medial gastrocnemius, lateral gastrocnemius and soleus muscles will be assessed using high-density surface electromyography, as well as Achilles tendon length, cross-sectional area, thickness and stiffness using B-mode ultrasonography and shear wave elastography. Moreover, participants will complete a battery of questionnaires to document their level of pain and function.

Ethics and dissemination Ethical approval (ERN-20-0604A) for the study was obtained from the Science, Technology, Engineering and Mathematics Ethical Review Committee of the University of Birmingham. The results of the study will be published in peer-review journals.

Trial registration number ISRCTN46462385.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The use of high-density surface electromyography to obtain gastrocnemius-soleus motor unit firing properties in response to a training protocol.
⇒ The use of B-mode ultrasound and Shear wave elastography to assess the morphological and mechanical properties of the Achilles tendon in response to a training protocol.
⇒ The training protocol will be based on pure eccentric or concentric contractions controlled using an isokinetic dynamometer.
⇒ Participants' age range is a limitation of our study, as it might affect the reproducibility of our findings in older populations.

INTRODUCTION

Achilles tendinopathy (AT) is a painful overuse injury of the Achilles tendon and it is common among athletes, especially those involved in running and jumping sports.[1–3] AT is clinically diagnosed when the patient presents with a combination of localised pain, swelling of the Achilles tendon and loss of function.[4] The essence of tendinopathy is a failed healing response, with degeneration and proliferation of tenocytes, disruption of collagen fibres and subsequent increase in non-collagenous matrix.[5] These structural changes in the tendon result in increased cross-sectional area, reduced tendon stiffness and altered viscoelastic properties in both symptomatic and asymptomatic tendons.[6]

The aetiology of AT remains debated and is likely caused by intrinsic and extrinsic factors.[7] One of the most accepted theories is that pain perception during early support loading may trigger inhibition of neuromuscular activity of the calf muscles detected as a reduction in electromyographic (EMG) amplitude.[8 9] Thus, the decrease in the ability to generate force in patients with AT could also reflect the decline in neuromuscular activity observed.[10 11] Moreover, it has been observed that this motor inhibition also

affects synergist and antagonist muscles.[12] Additionally, individuals with tendinopathy tend to use movement patterns that place an excessive or abnormal load on their tendons,[6] and it is believed that these motor adaptations may generate greater torsional stress in the tendon.[12 13] Finally, studies have shown that AT reduces tendon's stiffness,[14] which impairs the mechanisms responsible for transmitting force to the bone. Therefore, it is very likely that these alterations in tendon properties may produce changes in the neural drive received by the calf muscles.

Until now, most studies examining the neuromuscular impairments induced by AT have focused on investigating changes in interference EMG amplitude which is an indirect estimate of neural activity with many factors of influence.[15–17] Clearer information about the neural strategies employed by the central nervous system to control muscle force in the presence of AT can be obtained through motor unit recordings, since motor unit firing properties represent the direct neural output from the spinal cord to muscles.[18] Nevertheless, there are no studies that have measured motor unit firing properties in individuals with non-insertional Achilles tendinopathy (NIAT).

Although eccentric exercise has been widely used for the treatment of NIAT, the mechanisms by which eccentric exercises may help to resolve tendon pain remain unclear.[7] Regarding eccentric exercise alone, two prospective studies have reported a significant reduction in pain intensity and change on the Victorian Institute of Sports Assessment-Achilles questionnaire (VISA-A) in recreational athletes following a 12-week exercise programme.[19 20] In contrast, another study in non-athletic individuals found no significant improvement after a similar 12-week exercise programme.[21] Concerning eccentric exercises with an adjunctive treatment (eg, pulsed ultrasound, ice, sensory motor training), a 4-week intervention study resulted in decreased pain and higher plantarflexion peak torque in individuals with NIAT compared with controls.[22] However, studies that include eccentric exercises with an adjunctive treatment showed limited evidence of improvement over eccentric exercises alone.[23]

There are few studies where the effectiveness of eccentric versus concentric exercises has been compared. Mafi *et al* showed that patient satisfaction and return to previous activity were significantly superior after participating in a 12-week rehabilitation protocol based on eccentric exercise compared with concentric exercise. Although pain intensity decreased significantly in both groups, the amount of pain reduction was significantly greater for those that performed eccentric exercise.[24] Likewise, Yu *et al*[25] demonstrated that 8 weeks of eccentric exercise was more effective at reducing pain than concentric in individuals with chronic NIAT. Additionally, they found that eccentric exercise was more effective than concentric exercise at increasing muscle strength and endurance, and improving function.[25] In these investigations, participants performed the rehabilitation protocols with insufficient control over the load, speed, pain tolerance or the range of motion in which the exercises were performed. Moreover, it is essential to consider that when participants perform an eccentric plantar flexion exercise without adequate equipment, it is difficult to achieve pure eccentric contractions, which could have influenced the results obtained in these studies.

Based on the above, the aims of this study are to (1) establish changes in the gastrocnemius-soleus motor unit firing properties after applying a training protocol of 6 weeks based on either controlled eccentric or concentric contractions in individuals with NIAT; (2) determine changes in the level of pain and function and mechanical and structural properties of the Achilles tendon after applying the same training protocol; (3) compare these properties at baseline between individuals with NIAT and asymptomatic controls.

METHODS

Participants

Twenty-six individuals with NIAT and 13 asymptomatic controls will be recruited from the University of Birmingham staff/student population and the local community via leaflets, e-mail and social media.

Men or women aged 18–55 years old will be recruited. This age range was selected based on previous findings showing lower stiffness and Young's modulus of the Achilles tendon in older than younger population.[26] Inclusion criteria are NIAT determined by an experienced physiotherapist based on defined clinical findings (VISA-A[27] and NRS (Numerical Rating Scale)[28] scores), physical examination and ultrasound assessment, as well as having pain for at least 3 months.[29] VISA-A scores less than 90 will be considered as a reference to identify individuals with NIAT.[30] Regarding the NRS scores, previous studies have shown high variability in individuals with NIAT,[29 31] thus we will consider individuals with an NRS score≥2. Physical examination will include palpation of the Achilles tendon along its whole length in a proximal to distal direction, and gentle squeezing the tendon between the thumb and the index finger to identify tenderness over the tendon.[20] Ultrasound evaluation of the tendon's mid-portion will include identifying local thickening of the tendon and/or irregular tendon structure with hypoechoic areas and/or irregular fibre orientation.[31]

The exclusion criteria for both groups will include the following: (1) systemic or inflammatory conditions including rheumatic, neuromuscular disorders and malignancy, (2) current or history of chronic respiratory, neurological or cardiovascular diseases and (3) history of lower limb surgery. Specific exclusion criteria for the participants with NIAT are participation in any other treatment or rehabilitation programme for AT, corticosteroid injections in the previous 12 months and insertional AT. Additionally, if any participants present non-insertional and insertional AT concurrently in the same limb, they will be excluded. Specific exclusion criteria for the control group are pain/injury in the lower

limbs within the previous 6 months, history of AT or lower limb surgery.

Study design

This two-arm, parallel-group, randomised controlled trial will be conducted from October 2021 to December 2022 at a laboratory within the Centre of Precision Rehabilitation for Spinal Pain (CPR Spine), University of Birmingham, UK. The Science, Technology, Engineering and Mathematics Ethical Review Committee, University of Birmingham, UK, approved the study (ERN-20-0604A). All participants will provide written informed consent prior to participation. The study will be conducted according to the Declaration of Helsinki. This protocol has been designed following the SPIRIT 2013 statement[32] (see online supplemental file 1). The Trial Registration Data can be found as online supplemental file 2. Time schedule of enrolment, interventions, assessments and visits can be found as online supplemental file 3. The consent forms provided to healthy controls and patients can be also found as supplementary files (online supplemental files 4 and 5). Reporting will follow the Consolidated Standards of Reporting Trials (CONSORT) statement and the CONSORT flow diagram will be used to describe the flow of participants throughout the trial (see online supplemental file 6).

Participants with NIAT will visit the laboratory over six consecutive weeks for the experimental sessions (at weeks 1, 3 and 6) and training sessions (2–3 sessions per week) (figure 1). We will randomly allocate these participants into two groups: eccentric (ECC) or concentric (CON) training. Healthy participants will visit the laboratory once to allow baseline comparison with ECC and CON groups. Additionally, we will randomise the assessed leg in the healthy control group, and the most symptomatic leg in the ECC and CON groups will be evaluated. Finally, foot preference in specific daily activities (foot dominance) will be determined using a behavioural foot-preference inventory.[33] Each experimental session will last 2.5 hours, and each training session will last 40 min.

Sample size

According to power calculations (G*Power software),[34] a total of 26 individuals with NIAT (ECC group=13, and CON group=13) and 13 healthy controls will be required for this study. This sample size considers a power=0.80, alpha=0.01, 25% loss of participants and an effect size (d) of 1.7 calculated from the study of Yu *et al*,[25] where the authors compared reductions in pain after an 8-week concentric and eccentric training protocol in individuals with NIAT.

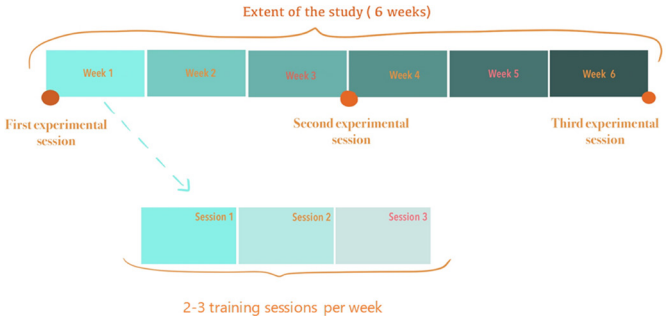

Figure 1 Overview of the study design.

Experimental sessions

These sessions will involve the completion of questionnaires, ultrasound imaging of the gastrocnemius-soleus muscles and the Achilles tendon, surface electromyography and torque recordings. All the procedures during the experimental sessions will be done by Ignacio Contreras-Hernandez (IC-H) and Joeri van Helden (JVH). IC-H is a PhD student at the University of Birmingham, Master in Physiology, Physiotherapist and member of the CPR Spine group. Joeri is a PhD student at the University of Birmingham, Master in Neuroscience, Psychologist and member of the CPR Spine group.

Anthropometric data (age, gender, weight, height, leg dominance and body mass index) will be obtained, and the participants will then be asked to complete a battery of questionnaires. This includes the International Physical Activity Questionnaire short form (IPAQ-SF),[35] VISA-A,[27] Foot and Ankle Ability Measure (FAAM),[36] Pain Catastrophising Scale (PCS)[37] and Tampa Scale for Kinesiophobia (TSK).[38] Additionally, participants will be asked to report their current level of pain using the NRS score. After that, participants will lie prone on the chair of a Biodex System 3 dynamometer (Biodex Medical Systems), and ultrasonography (LOGIQ S8 GE Healthcare, Milwaukee, USA) will be used to measure the length, thickness and cross-sectional area of the Achilles tendon, fascicle length, thickness and pennation angle of the medial gastrocnemius (MG), and thickness of the lateral gastrocnemius (LG) and soleus (SO) muscles during rest. Then, we will prepare the skin and place the electrodes on the MG, LG and SO muscles, and using high-density surface electromyography (HD-sEMG); we will ensure minimal electrical activity of these muscles during rest conditions for the measurements of the Achilles tendon stiffness (passive elastography).

Following the ultrasound assessment the maximal voluntary contraction (MVC) will be recorded during three isometric plantarflexion contractions of 5 s each.[15] Between each MVC, the volunteers will have 2 min of rest[15] and all MVCs will be performed at 0° of plantarflexion. The highest MVC value will be used as the reference maximal torque. We will use this MVC value as a reference for the isometric and dynamic plantarflexion contractions during the experimental and training sessions, to avoid multiple MVC measurements that may be produce pain and discomfort in individuals with NIAT. Afterwards, we will measure the stiffness of the tendon during two isometric plantarflexion contractions at 10% MVC (1 s ramp-up, 12 s hold, 1 s ramp-down and 30 s rest) (active elastography). Subsequently, using HD-sEMG, we will record motor unit activity of the MG, LG and SO muscles during two isometric plantarflexion contractions

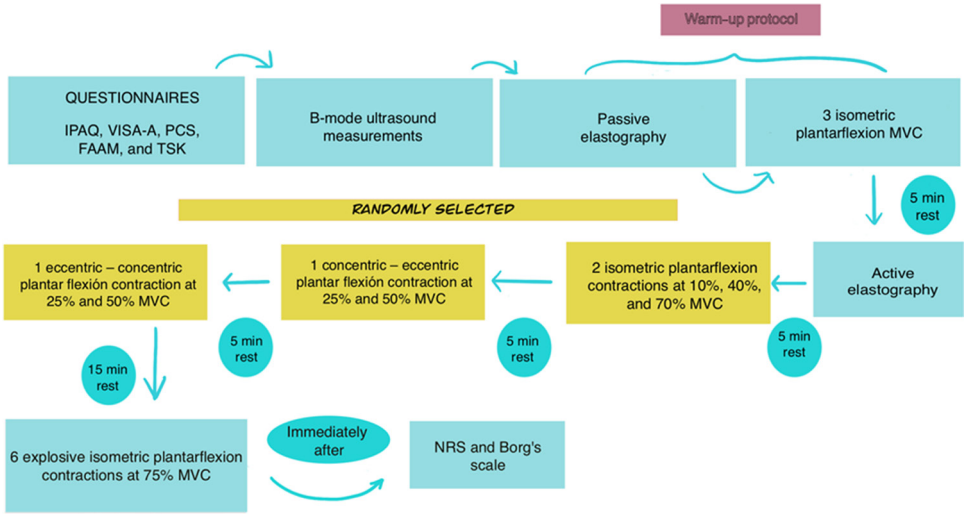

Figure 2 Experimental session design. FAAM, Foot and Ankle Ability Measure; IPAQ-SF, International Physical Activity Questionnaire short form; MVC, maximal voluntary contraction; NRS, Numerical Rating Scale; PCS, Pain Catastrophising Scale; TSK, Tampa Scale for Kinesiophobia; VISA-A, Victorian Institute of Sports Assessment-Achilles questionnaire

at 10%, 40% and 70% MVC (10% MVC/s ramp-up, 10 s hold, 10% MVC/s ramp-down and 30 s rest), one concentric–eccentric plantarflexion contraction at 25% and 50% MVC and one eccentric–concentric plantarflexion contraction at 25% and 50% MVC (the order of the different types of contractions will be randomly selected). Volunteers will have 5 min of rest at the end of each type of contraction (isometric, concentric–eccentric and eccentric–concentric). After 15 min of rest, HD-sEMG will be recorded from the MG, LG and SO muscles during six explosive (fast force development) isometric plantarflexion contractions at 75% MVC (1 s ramp-up, 3 s hold, 1 s ramp-down and 10 s rest).[39] Finally, both the rate of perceived exertion and the level of pain will be monitored regularly throughout the session, using the Borg ratings of perceived exertion scale[40] and the NRS (figure 2).

During all contractions, visual feedback of the target torque output will be provided via computer monitor positioned 1 m from the participant. Prior to the contractions, participants will be instructed to match the force output as closely as possible to the target force for the full duration of the contraction. For the dynamic contractions, the range of motion will be set at the total of 30° (neutral position 0°–30° of plantarflexion) and the angular speed will be set at 3°/s.

Training sessions

The training sessions will be done by Michalis Arvanitidis (MA). MA is a PhD student at the University of Birmingham, Master in Advanced Manipulative Physiotherapy, and Specialist Musculoskeletal Physiotherapist (Member of the Musculoskeletal Association of Chartered Physiotherapist) and member of the CPR Spine group.

All the training sessions will be done in prone position on the Biodex System 3 dynamometer.

The participants in the ECC group will be asked to perform a warm-up consisting of three eccentric plantarflexion contractions at 25% MVC; this will be followed by the eccentric training protocol. This protocol consists of 4×15 eccentric plantarflexion contractions at 50% MVC, range of motion of 30° (neutral position 0°–30° of plantarflexion), time under tension of 10 s, angular speed of 3°/s and 3 min of rest between each series. Visual feedback of the exerted torque will be provided. Participants in the CON group will perform a warm-up consisting of three concentric plantarflexion contractions at 25% MVC, and then, the concentric training protocol. This protocol consists of 4×15 concentric plantarflexion contractions at 50% MVC, range of motion of 30° (neutral position 0°–30° of plantarflexion), time under tension of 10 s, angular speed of 3°/s, and 3 min of rest between each series.

Preceding the contractions, participants will be instructed to match the torque output as closely as possible to the target torque for the full duration of the contraction.

Follow-up

Participants with NIAT will be asked to report their level of pain and function at 3 and 6 months after completing the training protocol.

Outcome measures

Primary outcomes measure

The primary outcomes for this study will be GM, GL and SO muscles motor unit firing properties assessed using HD-sEMG and decomposition techniques. These properties include motor unit discharge rate, recruitment and de-recruitment thresholds and discharge rate variability.

Secondary outcomes measure

Secondary outcomes will include level of pain and function assessed using the NRS and VISA-A questionnaire, Achilles tendon length, thickness, cross-sectional area and stiffness using B-mode ultrasonography and shear wave elastography (SWE). Additionally, secondary

outcomes will include GM, GL and SO muscles thickness, and GM muscle fascicle length and pennation angle evaluated using B-mode ultrasonography, as well as the level of physical activity, physical function, pain catastrophising and fear of movement assessed using the IPAQ-SF, FAAM, PCS and TSK questionnaires, respectively.

Questionnaires

In each experimental session, participants will be asked to complete the IPAQ-SF, VISA-A, FAAM, PCS and TSK questionnaires to measure physical activity level, symptoms in individuals with AT, physical function, pain catastrophising and fear of movement, respectively. The IPAQ has become the most widely used physical activity questionnaire,[41] and it has acceptable measurement properties for monitoring population levels of physical activity among 18–65 years old adults in diverse settings.[35] The VISA-A was developed with the aim of evaluating the symptoms of AT and their impact on physical activity. This questionnaire is valid, reliable, easy to use and ideal for comparing patients' progress in clinical settings.[27] The FAAM was developed to meet the need for a self-reported evaluative instrument that comprehensively assesses the physical function of individuals with musculoskeletal disorders of the leg, foot and ankle. The FAAM is a reliable, valid and responsive measure of self-reported physical function.[36] Additionally, we will use the PCS to understand the psychological processes that lead to heightened physical and emotional distress in response to aversive stimulation. This questionnaire is a reliable and valid measure of catastrophising.[37] Finally, we will apply the TSK to measure the fear of movement/(re)injury. This questionnaire has been validated in patients with chronic back pain,[42–44] acute back pain,[45 46] osteoarthritis[47] and fibromyalgia.[43 44]

Measurement set-up

For the measurements of the Achilles tendon, MG, LG and SO muscles, participants will lie prone on the dynamometer, with their knees extended and their tested foot tightly strapped on the footplate. The pelvis will be stabilised with another strap to minimise compensatory movements. The ankle will be positioned in 0° of plantarflexion and the axis of the dynamometer will be aligned with the inferior tip of the lateral malleolus. The setting and position of the set up (ie, chair and isokinetic device) will be saved, so the participants' position will be similar in each experimental session.

Ultrasound measurements

All ultrasound images will be obtained using an ultrasound imaging device equipped with SWE (LOGIQ S8 GE Healthcare, Milwaukee, USA). For the measurements of the length, thickness and cross-sectional area of the Achilles tendon, and the measurements of the fascicle length, thickness and pennation angle of the calf muscles, B-mode will be used with a 16-linear array probe (50 mm, 4–15 MHz). Subsequently, for the measurements of the Achilles tendon's stiffness during rest conditions and isometric plantarflexion contraction, the elastography mode will be used with a 9-linear array probe (44 mm, 2–8 MHz).

An adaptation of the protocol developed by Arya and Kulig[14] will be used to measure the structural properties of the Achilles tendon. Briefly, to obtain tendon length, the ultrasound transducer will be placed longitudinally over the posterior aspect of the heel, and the distal part of the Achilles tendon will be imaged and the corresponding point will be marked on the skin with a marker. Then, the ultrasound probe will be moved proximally to locate the musculotendinous junction of the MG, and this point will be marked on the skin. The distance between these two points will be measured with a tape and this distance will represent the resting length of the Achilles tendon. Marks at 2, 4 and 6 cm above the Achilles tendon insertion will then be made on the skin. Later, these marks will be used to place the probe in the transversal plane and determine the cross-sectional area of the Achilles tendon at 2 4 and 6 cm of its insertion. Additionally, we will use these marks to place the probe in the sagittal plane and determine the thickness of the Achilles tendon at 2, 4 and 6 cm of its insertion.

For muscle ultrasound images, the mid-line of the leg will be marked in the direction of the Achilles tendon. Additionally, a mark will be made on the leg 10 cm above the musculotendinous junction of the MG muscle and 4 cm medial to the mid-line. In this position, we will place the middle point of the HD-sEMG electrode grid and mark the contour of the grid on the skin. We will use these marks to place the probe in the sagittal plane and obtain the images of the MG muscle. Similarly, the leg will be marked 10 cm above the musculotendinous junction of the MG muscle and 4 cm lateral to the mid-line. Then, we will repeat the procedure mentioned above, but now for the LG muscle. Next, the leg will be marked 5 cm below the musculotendinous junction of the MG and 4 cm lateral to the mid-line. Again, we will repeat the procedure mentioned above, but now for the SO muscle (figure 3). The middle column of the HD-sEMG electrode grid will be used as a reference (see HD-sEMG and torque section below) to place the probe in the same position during all the experimental sessions and the images will be acquired with the probe oriented in the sagittal plane, and perpendicular to the skin, according to the recommendations of Bolsterlee *et al*.[48] To ensure that we are measuring the exact location of interest, we will use the procedure described above in each experimental session, and we also will mark the middle point of the ultrasound probe. Then, during the acquisition of the ultrasound images, we will align the mark in the ultrasound probe with the marks on the skin at 2, 4 and 6 cm from the Achilles tendon insertion and with the mark of the middle point of the HD-sEMG electrode grid of each muscle. This procedure will allow us to identify the location of interest during the analysis of the ultrasound images since we know that the middle point of the image represents the location of interest. The software Image J

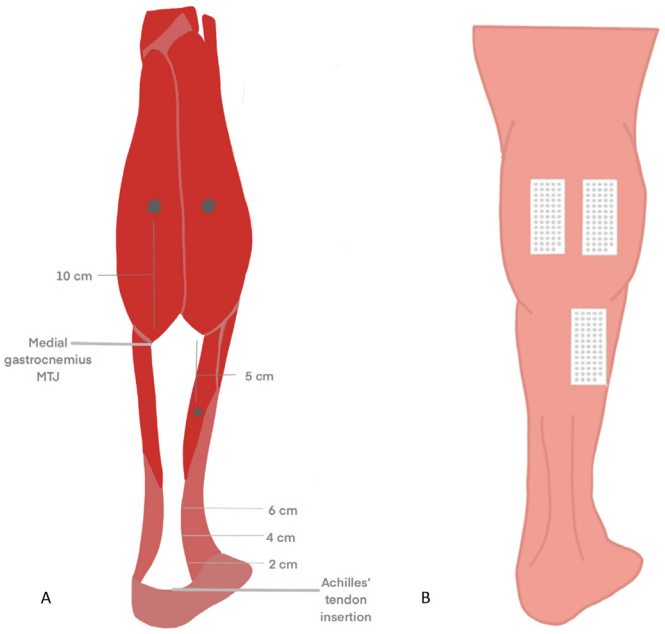

Figure 3 (A) Anatomical landmarks used for ultrasonography and (B) position of the electrodes in the MG, LG and SO muscles. LG, lateral gastrocnemius; MG, medial gastrocnemius, SO, soleus.

(https://imagej.nih.gov/ij/) will be used to analyse these images and determine the fascicle length, thickness and pennation angle.

For tendon stiffness measurements, the probe will be placed in the sagittal plane, with the middle part of the probe located at 4 cm above the Achilles tendon insertion. A probe holder will be used to avoid applying pressure over the tendon and movements that may interfere with the measurements. Then, we will perform a trial SWE to check for possible voids. If voids are detected at this stage, we will remove the probe holder and place the ultrasound probe again. The passive elastography images will be acquired for 12 s (twice), and the active elastography images will be acquired during two isometric plantarflexion contractions at 10% MVC (1 s ramp-up, 12 s hold, 1 s ramp down, 1 min rest). We will check the elastography images following each measurement to determine possible voids that may affect our results. If voids in the middle part of the tendon (at 4 cm of the insertion) are detected in this stage, we will repeat the procedure. A shear elastography colour map (height x width, 2.5 cm x 1 cm) will be chosen using elastography ultrasound tools to allow complete visualisation of the Achilles tendon width, and a region of interest (ROI) of 3 mm diameter[49] will be selected in the middle of each image to determine the shear wave velocity (m/s) and Young's modulus (kPa). Finally, we will average the mean shear wave velocity and Young's modulus over the ROIs of consecutive images.[50]

HD-sEMG and torque recording

Prior to electrode placement, the skin will be shaved (if necessary), gently abraded (Nuprep, Skin Prep Gel, Weaver and Company, Aurora, Colorado) to reduce skin impedance and cleaned with water. Three two-dimensional (2D) adhesive grids (SPES Medica, Salermo, Italy) of 13×5 equally spaced electrodes (each of 1 mm diameter, with an inter-electrode distance of 8 mm) will be used to record the HD-EMG signals. Conductive paste (AC-CREAM, SPES Medica, Genova, Italy) will be placed into the cavities of the grid, and the HD-sEMG electrodes will be placed in the exact position described for the ultrasound measurements of the triceps surae (one electrode grid for each muscle).

All signals will be converted from analog-to-digital by a 16-bit converter (Quattrocento- OTBiolettronica, Torino, Italy). The sampling frequency will be 2048 Hz and the amplifier gain will be set to 150. HD-sEMG signals will be digitally filtered with a bandwidth set up to 10 Hz for high pass cut frequency and to 500 Hz for low pass cut frequency.[51] HD-sEMG will be acquired in monopolar mode with reference electrodes (WhiteSensor WS, Ambu A/S, Ballerup, Denmark) positioned in the head of the fibula and with a strip in the thigh of the evaluated leg. All the electrode grids and reference electrodes will be connected to the same bioelectrical amplifier (Quattrocento-OT-Bioelettronica, Torino, Italy).

The torque exerted by the volunteers will be assessed with the isokinetic dynamometer, which will be synchronised with the HD-sEMG signals. Synchronisation will be obtained by recording torque signals generated by the isokinetic dynamometer through the auxiliary input of the EMG amplifier.[51]

Signal analysis

The torque signal will be low pass filtered at 15 Hz and then used to quantify torque steadiness (coefficient of variation of torque, SD torque/mean torque * 100) from the stable part of the contractions.[52]

The HD-sEMG signals will be decomposed into motor unit spike trains with an algorithm based on blind source separation, which provides automatic identification of motor unit activity,[52] and the accuracy of the decomposition will be tested with the silhouette measure, which will be set to ≥0.90.[53] The signals will be decomposed during the entire duration of the contractions, and the discharge times of the motor units will be transformed in binary spike trains.[54] The mean discharge rate and the discharge rate variability (CoV of the interspike interval (CoV_{isi})) will be determined during the stable plateau of torque signal. Additionally, motor unit recruitment and derecruitment thresholds will be defined as the ankle plantarflexion torques (%MVC) at the times when the motor units began and stopped discharging action potentials, respectively.[52] Discharge rates at recruitment and derecruitment will be determined using the first and last six discharges of the motor units.[52] Erroneous discharges will be visually inspected and edited using a custom algorithm.[52 55] Motor unit activity will be monitored longitudinally with a recent method proposed by Martinez-Valdes *et al*,[56] which allows tracking the same motor units across different experimental sessions.

Adverse event management

Participants will be informed that they may experience some pain during or after the experimental and training sessions. Monitoring of participants' pain will be done in each experimental and training sessions using the NRS. Appropriate rest time will be provided throughout the experimental and training sessions, and extra rest periods will be given to the participants at any time if required. If a participant experiences moderate pain (>6 NRS) during the contractions, they will be given additional time to rest. If the pain intensity is maintained or worsens, we will terminate and reschedule the session. The session will be rescheduled in the upcoming 3 days. If pain intensity is maintained or worsened during these days and rescheduling the session is not possible, the participant will be removed from the study. This will be considered as an adverse effect, and it will be reported to the Science, Technology, Engineering and Mathematics Ethical Review Committee of the University of Birmingham.

Randomisation and blinding

Individuals with NIAT will be randomised by an independent researcher (Dr Eduardo Martinez-Valdes (EM-V)) in a 1:1 allocation ratio to either ECC or CON groups (parallel-groups) using computer-generated simple scheme randomisation (https://sigdaan.com/randomization/app/randomization-app). Allocation concealment will be ensured, as EM-V will secure the randomisation code using password-protected files. EM-V will give access to MA to the randomisation code once each participant has completed the first experimental session.

In order to achieve double-blinding, IC-H and JVH will perform the experimental sessions and MA will perform the training sessions. IC-H will use the blindr (https://github.com/U8NWXD/blindr) software to encode the results from different participants and will be blinded to the training protocol applied to the participants. MA will be blind to the participant's results, but not to the training protocol applied. EM-V will unmask the results after the data analysis is performed. Due to the nature of the interventions, participants' blinding is not possible.

Statistical analysis

IBM SPSS Statistics for Windows, V. 25.0 (Armonk, New York, USA) computer software will be used for statistical analysis of the data. Intention-to-treat and per protocol analysis will be performed. Descriptive statistics will be used to interpret the data which will be presented as mean±SD The Shapiro-Wilk Test will be used to assess data normality. The level of significance for all statistical procedures will be set at α=0.05% and 95% CI will be reported. Independent t-test will be used to determine the differences between individuals with NIAT and healthy controls at baseline. If the data are normally distributed, repeated measures analysis of variance (ANOVA) will be used. Factors of group (ECC and CON) and time (at weeks 1, 3 and 6) will be used to analyse each variable. Bonferroni post hoc analysis will be used if ANOVA is significant. The partial eta-squared (η_p^2) for ANOVA will be used to examine the effect size of changes after the training intervention. An η_p^2 less than 0.06 will be classified as 'small', 0.07–0.14 as 'moderate' and greater than 0.14 as 'large'.[57] If data are not normally distributed, appropriate non-parametric tests will be used.

DISCUSSION

To the best of our knowledge, this is the first study aiming to establish changes in motor unit firing properties of the gastrocnemius-soleus muscles after applying a training protocol based on either controlled eccentric or concentric contractions in individuals with NIAT. Additionally, this study will be the first to determine motor unit firing properties of the gastrocnemius-soleus muscles in individuals with NIAT compared with asymptomatic controls.

Regarding the variables related to the EMG activity and motor unit firing properties (ie, discharge rate, recruitment and discharge rate variability) of the gastrocnemius-soleus muscles; previous studies have estimated the activation of the triceps surae muscles in people with AT during walking,[58] running,[59] isometric plantarflexion tasks[60] and dynamic plantarflexion tasks.[61 62] Currently, there is no agreement in the literature in terms of plantarflexion torque measured during maximal contractions in individuals with NIAT; some authors did not find any difference between groups,[14 63] while others found statistically significant differences.[60 64] Interestingly, an investigation has observed a significant increase in LG activation during isometric plantarflexion tasks in people with AT following a 12-week training programme.[60] Despite all of these efforts, currently there are no studies that have evaluated motor unit firing properties of calf muscles in individuals with NIAT.

A strength of this study is that we will perform a detailed assessment of the mechanical and structural properties of the Achilles tendon and the calf muscles. One study showed that tendinopathy alters both the mechanical and material properties of the human Achilles tendon.[14] Morphological comparisons of tendinopathic and healthy tendons demonstrated a larger cross-sectional area for the degenerated Achilles tendon. Typically, a larger tendon is considered mechanically stronger due to its ability to dissipate stresses across the tendon and yield lower strain energy. Nonetheless, in the study of Arya and Kulig,[14] they demonstrated that despite having a larger cross-sectional area, the degenerated tendon had lower stiffness and Young's modulus compared with healthy tendons. Additionally, our study includes the use of SWE. This procedure has been used to measure tissue elasticity in tendons and might add to a better understanding of the effects of different types of exercises in tendons.[65] Furthermore, SWE is able to measure the Young modulus (slope of the stress–strain curve in the linear region[66] of Achilles tendon with high reliability).[67] Previous studies

suggest that SWE might be a useful tool for diagnosing and monitoring AT.[68] For instance, one study demonstrated that symptomatic Achilles tendons had lower Young modulus compared with healthy tendons and that stiffness increases in correlation with VISA-A scores after 6 months of treatment.[69]

Another strength of our study is using an isokinetic dynamometer to perform the training sessions. This device will allow us to control the intensity (50% MVC), range of motion (0°–30° of plantarflexion) and angular speed (3°/s) of the contractions, enabling us to have close control over the time under tension (10 s) of the Achilles tendon. Although the use of isokinetic dynamometers is common to measure peak torque in musculoskeletal research, its use during a training protocol is limited. To the best of our knowledge, there are no studies using isokinetic dynamometers to train individuals with NIAT. This represents an essential aspect of our RCT because previous studies investigating the effects of exercise in individuals with NIAT usually apply training protocols with insufficient control over the load, speed, pain tolerance or the range of motion, and this could have influenced their results.

Regarding the study's limitations, the relatively short training protocol (6 weeks) might influence the changes expected in the mechanical and structural properties of the Achilles tendon; therefore, longer training interventions might be required to assess changes in these parameters in the long term. Moreover, due to the nature of the training protocol applied (eccentric and concentric exercises), blinding of participants is not possible because we need to explain how to do the different types of exercises on the isokinetic dynamometer. We are aware this introduces bias into the RCT, but unfortunately, it is not possible to achieve participants' blinding. Another study limitation is the inclusion of participants with bilateral symptoms, which could potentially affect the results. Since morphological changes to the asymptomatic tendon are common in this condition[70] and 45% of thickened Achilles tendons progress to develop clinical symptoms within 12 months,[71] we decided to also include these patients in the study. Additionally, participants' age range is another limitation of our study, as it might affect the reproducibility of our findings in older populations; however, we have decided to recruit participants in this age range based on previous studies showing age-related differences in Achilles tendon's stiffness and Young's modulus, which could confound the results of the intervention.

The study of motor units is an area in continuous development, which in recent years has allowed a more profound understanding of the neural mechanisms involved in muscle contractions. However, much of the research in this area has focused on the normal neurophysiology of muscle rather than its relationship with alterations of the musculoskeletal system.

This research will therefore provide new insights regarding the neuromechanical effects of ECC and CON exercises in the management of individuals with NIAT. A more precise understanding of the mechanisms involved in this pathology is essential to improve the rehabilitation programmes commonly used in the management of this condition.

Patient and public involvement

The research question in this study forms part of a larger discussion about exercise and pain relief within our patient and public involvement meetings. Patients will not be involved in the analysis and data collection but will contribute to data interpretation and production of a lay summary of findings.

ETHICS AND DISSEMINATION

Ethical approval and trial registration

The research protocol has been approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee of the University of Birmingham (ERN-20-0604A).

Researchers will inform all participants of the characteristics of the research and will obtain written consent. Participants will be informed that they are free to withdraw from the study at any time without needing to provide a reason. In any unlikely adverse events, this will be immediately reported by the principal investigator to the ethics committee.

The results of this study will be submitted for publication in a peer review journal and presented at conferences.

Confidentiality

All information collected will be kept strictly confidential. Personal information will be retained but only available to the researchers using password-protected files. In addition, all data for presentations will be anonymised and aggregated, so the participants' identities will not be revealed in any way.

Twitter Deborah Falla @Deb_Falla and Eduardo Martinez-Valdes @mredumartinez

Contributors IC-H and EM-V are responsible for the conception, design and development of the protocol. EM-V is the lead supervisor of IC-H and DF is the cosupervisor. EM-V and DF have provided guidance on methodological decisions and critical revision. All authors have read and subsequently approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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SPIRIT 2013 Checklist: recommended items to address in a clinical trial protocol and related documents*

Section and topic	Items N°	Checklist item	Page N°
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary file 2
Protocol version	3	Date and version identifier	23
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,22
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities.	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention.	4-6
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypothesis	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, Interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see fig 1)	Supplementary file 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7-8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	17
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	17
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	17-18
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how	18
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	N/A
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary files 4 and 5
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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From: Chan A, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jeric K, Laupacis A, Moher D. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013; 346:e7586

Trial Registration data

Data category	**Information**
Primary registry and trial identifying number	ISRCTN registry (ISRCTN46462385).
Date of registration in primary registry	13/08/2021
Secondary identifying numbers	N/A
Source(s) of monetary or material support	This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors
Primary sponsor	University of Birmingham
Secondary sponsor(s)	N/A
Contact for public queries	Ignacio Contreras-Hernandez (iac921@student.bham.ac.uk)
Contact for scientific queries	Eduardo Martinez-Valdes (E.A.MartinezValdes@bham.ac.uk)
Public title	Effects of two different exercise protocols in individuals with non-insertional Achilles tendinopathy
Scientific title	Neuromuscular and structural tendon adaptations after 6-weeks of either concentric or eccentric exercise in individuals with non-insertional Achilles tendinopathy: Protocol for a randomised controlled trial.
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Non-insertional Achilles tendinopathy
Intervention(s)	Eccentric plantarflexion contractions Concentric plantarflexion contractions
Key inclusion and exclusion criteria	Men or women aged 18 to 55 years old. Inclusion criteria are non-insertional Achilles tendinopathy determined by an experienced physiotherapist based on defined clinical findings, physical examination, and ultrasound assessment, as well as having pain for at least 3 months. The exclusion criteria for healthy participants and individuals with non-insertional Achilles tendinopathy include: (1) systemic or inflammatory conditions including rheumatic, neuromuscular disorders, and malignancy, (2) current or history of chronic respiratory, neurological, or cardiovascular diseases, (3) history of lower limb surgery. Specific exclusion criteria for the participants with non-insertional Achilles tendinopathy are participation in any other treatment or rehabilitation program for Achilles tendinopathy, corticosteroid injections in the previous 12 months, and insertional Achilles tendinopathy.
Study type	Two-arm, parallel group, randomised controlled trial.
Date of first enrolment	04/10/2021
Target sample size	A total of 26 individuals with non-insertional Achilles tendinopathy and 13 healthy controls
Recruitment status	Recruiting

Primary outcome(s)	The primary outcomes for this study will be gastrocnemius medialis, gastrocnemius lateralis, and soleus muscles motor unit firing properties. These properties include motor unit discharge rate, recruitment and de-recruitment thresholds, and discharge rate variability.
Key secondary outcomes	Secondary outcomes will include level of pain and function, Achilles tendon length, thickness, cross-sectional area, and stiffness.

From: Chan A, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jeric K, Laupacis A, Moher D. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013; 346:e7586

	STUDY PERIOD																		
	Enrolment	Allocation	Post-allocation (6-weeks period)																Close-out
Timepoint	-t1	0	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16 (follow-up at 3 months)	t17 (follow-up at 6 months)
ENROLMENT:																			
Eligibility screen	x																		
Informed consent	x																		
Allocation		x																	
INTERVENTIONS:																			
Eccentric training				x	x	x	x	x	x		x	x	x	x	x	x			
Concentric training				x	x	x	x	x	x		x	x	x	x	x	x			
ASSESSMENTS:																			
Anthropometric data			x																
NRS			x							x							x	x	x
VISA-A			x							x							x	x	x
IPAQ-SF			x							x							x		
FAAM			x							x							x		
PCS			x							x							x		
TSK			x							x							x		
Motor unit firing properties			x							x							x		
Morphological and mechanical properties			x							x							x		

*** Schedule of enrolment, interventions, and assessments considering two training sessions per week. This template is copyrighted by the SPIRIT Group and is reproduced by BMJ with their permission.**

From: Chan A, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jeric K, Laupacis A, Moher D. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013; 346:e7586

Consent Form

Study Title	Neuromuscular and structural tendon adaptations after 6-weeks of either concentric or eccentric exercise in individuals with non-insertional Achilles tendinopathy		
Participant Name:		**Date:**	
Researcher Name:		**Ethics Number:**	

This information is being collected as part of a research project, which investigates the relationship between the neuromuscular control of the calf muscles and some characteristics of these muscles and the Achilles tendon in individuals with and without Achilles tendinopathy.
The research will be conducted at the School of Sport, Exercise and Rehabilitation Sciences at the University of Birmingham. The information that you supply and that which may be collected as part of the research project will be entered into a filing system or database and will only be accessed by authorised personnel involved in the project. The information will be retained by the University of Birmingham and will only be used for the purpose of research, and statistical and audit purposes. By supplying this information, you are consenting to the University storing your information for the purposes stated above. The information will be processed by the University of Birmingham in accordance with the provisions of the Data Protection Act 2018. No identifiable personal data will be published.

This section to be completed by the participant:
Please initial the boxes at the end of each statement if you agree with it.

1. I confirm that I have read and understood the Participant Information Sheet for the above study. I have had the opportunity to ask questions and these have all been answered satisfactorily ☐
2. I. understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, up to two weeks after my last visit to the lab. ☐
3. I agree to the storage and use of my data for the purposes of this research study. ☐
4. I confirm that I have read and understand the paragraph relating to COVID-19 related risks in the participant information leaflet for this study and will abide by the measures put in place by the University of Birmingham. I have had the opportunity to ask questions if necessary and have had these answered satisfactorily. ☐
5. Based on the above, I agree to take part in this research study. ☐

Signed:

Name in capitals:

Date:

This section to be completed by the researcher
I certify that this participant has read, properly completed and signed the screening and consent forms, witnessed by myself:

Signed: Date:

By supplying this information you are consenting to the University storing your information for the purposes of the stated research study. The information will be processed by the University of Birmingham in accordance with the provisions of the Data Protection Act 2018. No identifiable personal data will be published

Consent Form

Study Title	Neuromuscular and structural tendon adaptations after 6-weeks of either concentric or eccentric exercise in individuals with non-insertional Achilles tendinopathy		
Participant Name:		**Date:**	
Researcher Name:		**Ethics Number:**	

This information is being collected as part of a research project, which investigates the relationship between the neuromuscular control of the calf muscles and some characteristics of these muscles and the Achilles tendon in individuals with Achilles tendinopathy. Additionally, we want to determine which type of exercise protocol has better results in the treatment of this condition.
The research will be conducted at the School of Sport, Exercise and Rehabilitation Sciences at the University of Birmingham. The information that you supply and that which may be collected as part of the research project will be entered into a filing system or database and will only be accessed by authorised personnel involved in the project. The information will be retained by the University of Birmingham and will only be used for the purpose of research, and statistical and audit purposes. By supplying this information, you are consenting to the University storing your information for the purposes stated above. The information will be processed by the University of Birmingham in accordance with the provisions of the Data Protection Act 2018. No identifiable personal data will be published.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section and topic	Items N°	Checklist item	Page N°
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions	2
Introduction			
Background and objectives	2a	Scientific background and explanation rationale	4-6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6, 7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were administered	10,11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11,12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	7,8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	17
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	17
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	17
Implementation	10	Who generated the random allocation sequence, who enrolled the participants, and who assigned participants to interventions	17, 18
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	17, 18
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	18
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A

Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect size is recommended	N/A
Ancillary analysis	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant multiplicity of analyses	18-21
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18-21
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18-21
Other information			
Registration	23	Registration number and name of trial registry	2, 7, 21
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration13 for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials,11 non-inferiority and equivalence trials,12 non-pharmacological treatments,32 herbal interventions,33 and pragmatic trials.34 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

From: Schulz K, Altman D, Moher D. CONSORT 2010 Statement: updated guideline for reporting parallel group randomised trials. BMJ 2010; 340:c 332