STATISTICAL ANALYSIS PLAN

Heavy weight training or hometraining as a treatment for Achilles midsubstance tendinopathy when needed supplemented with injection of glucocorticosteroid with low volume or high volume.

Trial Registration

Clinicaltrials.gov Trial registration identifier: NCT04210999

Ethical Committee of the Capital Region: H-19040270,

Protocol Version and Date

This document has been written based on information contained in the study protocol version 3, October 2019 approved by the Ethical Committee.

Statistical Analysis Plan Version and Date

Version 1

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1 SIGNATURES

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1 INTRODUCTION

Achilles tendinopathy is a frequent and often long-term injury especially seen in sports active. The cumulative incidence in former elite athletes is 50% compared to 5.9% in inactive athletes (kujala, 2005). In particular, athletes involved in running and jumping are at risk (Kvist 1991). In the case of runners, the incidence is 9% (Lysholm 1987).

As primary treatment, eccentric exercises are recommended, where load rteduction is described in 60% to 90% of patients (Silbernagel 2001, Maffuli 2008, Ohberg 2004). Other studies have shown the effect of stretching exercises (Porter 2002), and in a randomized study, no difference in outcomes could be detected when treated with eccentric exercises compared to stretching exercises (Nørregård 2007). In a recent study at our institute, slow heavy strength training 3 times a week has been shown to have the same treatment effect as daily eccentric training (Beyer 2015). In these randomized efficacy studies in exercise-motivated patients, an improvement is seen in 60-90%. However, in a pragmatic effectivenes study, we found that only 26% performed satisfactorily with training alone (Wetke 2015), and in a Canadian study, only 10% had satisfactory effects of eccentric home training (Ram 2013). This is consistent with the clinical experience, where we find that a significant proportion of exercisers do not improve significantly by training alone.

Corticosteroid injection (CS) is often used in the clinic, but since there is rarely evidence of inflammation in the Achilles tendons, the rationale behind the treatment is controversial (Khan 2002). However, a randomized clinical controlled trial (RCT) has shown good efficacy of CS injections given ultrasound-guided to patients with chronic achilles tendinopathy (Fredberg 2004). A significant short-term effect on symptoms and thickness of the tendons was observed, but with relapses after 6 months, possibly due to an aggressive rehabilitation course. In the study by Wetke (2015), it was found that patients who did not improve from exercise therapy alone, had a good effect by supplementing the training with injection of CS (40 mg Depomedrol). This resulted in 76% being cured or clearly better. Whether this effect was due to the fact that the 2 ml injected caused a slight rupture of the peritendinous tissue, from which vascular ingrowth into the tendon is frequently seen in Achilles tendinopathy (Johannsen 2010, Sterkenburg 2011) or an anti-inflammatory effect of CS is not known. Boesen (2016) documented that training supplemented by "High Volume Injection" (HVI), in which 50 ml (saline, local anesthesia, CS (20 mg Depomedrol))

US guided into the peritendinous and thus loosens the entire tenosynovium, had better effect than training supplemented with placebo injection and training supplemented with "platelet rich plasma" (PRP) injection. In another study, the same group has shown better effect of HVI with CS than HVI without KS (Boesen in press).

According to clinical guidelines in the Danish Sports Medicine Society (DIMS) and the Danish Rheumatology Society (DRS), the existing standard treatment of AT is primarily load reduction supplemented by training with stimulating exercises. If necessary, this can be supplemented by injection of CS, usually mixed with local anesthetics.

In cases where the above treatment measures are ineffective, surgery may be considered. Surgery of midsection AT has been tried for many years. Traditionally with longitudinal incisions of the tendon in the thickened part, but in recent years mainly as a minor intervention with a removal of the peritendium around the tendon (tenolysis) – especially on the front of the tendon, where vascular ingrowth with nerve fibers is assumed to be a large part of the cause of the pain from the tendon. Ruergård A et al (2019) have indicated a success rate of 89% with painlessness and return to sports at the same level as before the Achilles problems. In addition to this study, there are only small retrospective series of the effect of tenolysis, and in all the studies it is unclear to what extent and how effectively conservative treatment has been tried.

The purpose of our study is to compare an app based daily home training with physiotherapist supervised slow heavy strength training combined with load reduction by abstaining from running and jumping activities. This will be interesting because app based training is less costly than physiotherapeutic guided training. In addition, we will compare 50 ml of HVI with CS with 2 ml of CS injection as a supplement to training, in those patients who do not achieve satisfactory results with training alone. Finally, patients with continued problems will be offered surgery with Achilles tenolysis in an open prospective study.

The study is based on the following hypotheses:

1) Treatment with an app based daily home workout is as effective as slow heavy strength training (non-inferiority study).
2) 50 ml HVI with CS is better than 2 ml CS injection in addition to continued training, in those patients who do not achieve satisfactory results with training alone (superiority study).

3) Surgery with surgical tenolysis results in a clinically relevant reduction of pain symptoms in patients without sufficient effect of structured and monitored conservative treatment (the above conservative regimen).

2 MATERIAL AND METHODS

Patients with suspected Achilles tendinopathy are usually referred to the Department of Sports Medicine, BBH or specialist practice in rheumatology.

Inclusion Criteria:

1. Ultrasound diagnosed mid-substance Achilles tendinopathy.
2. For unilateral symptoms, symptomatic Achilles tendon should be more than 20% thicker than on the asymptomatic side or more than 7 mm thick
3. For bilateral symptoms, the Achilles tendon should have a diameter above 7 mm.
4. Duration of pain should be a minimum of 3 months
5. Participants are at least 18 years old and a maximum of 65 years old.
6. Participant may provide relevant and adequate informed consent.
7. The patient must have a smartphone that can work with the training app: Injurymap.

Exclusion criteria:

1. Previous lower limb surgery. Arthroscopy of the knee excepted.
2. No known medical conditions, including insulin-dependent diabetes mellitus or rheumatic diseases.
3. Infection of the foot or lower leg.
4. Mental state that does not allow participation.
5. Judged not to be able to follow the exercise intervention.
6. Lack of presence in the region during the project period.
7. Daily use of painkillers.
8. Cannot read or understand Danish*.
9. Corticosteroid injection to treat Achilles tendinopathy within the last 6 months.
10. Previous allergic reaction to treatment with corticosteroid (Depomedrol®) or local anesthetics.

11. Pregnancy/breastfeeding or planning of pregnancy during the intervention period.

*Due to the cost of an interpreter and home training app in Danish, the subjects need to be able to read and understand Danish.

3 STUDY METHODS

Sub-study 1:

Single blinded (assessor and statistics) Randomized Controlled Trial.

Randomization method

Randomization must be preceded by informed consent and power of attorney. The randomization of patients is performed by an independent office employee not involved in patient care (Charlotte Bilde) using a computer generated randomization schedule (MINIMPY, Maghaei 2010) using permuted block sizes (four to six). The employee is blinded to the block sizes. The allocation of each patient is stored in a computer drive with exclusive access only for the responsible office employee (Charlotte). Patients will be divided equally into 2 groups. Symptom duration will be stratified < 1 year> and VISA-A score (0-100) at entry <50>

The secretary is then in charge of filling out randomization sheets and preparing the CRF (clinical research files).

Blinding

The study will be evaluated blinded. Patients cannot be blinded to the training performed. The effect of the training is evaluated monthly by the patient himself at home without interference with any investigators on an app (Redcap). At every doctors appointment US assessment of the Achilles tendon will be performed.

The 2 primary treatment arms are:

GROUP 1 (HSR): Treatment with **Heavy Slow Resistance training** (HSR) thoroughly guided by physiotherapists. The training will take place in a gym and lasts for 3 months. Simultaneous load reduction from harmful activities (running, jumping) is advocated.

GROUP 2 (App): Treatment with 3 months **of home training guided via an app (Injurymap)**. The only aid is a rubber band. Simultaneous load reduction from harmful activities (running, jumping) is advocated.

Description of the load reduction during the controlled training

The first 3 months the patients is advocated to abstain from all jumping and running activities (impact training). They are free to do non-impact training such as cycling, swimming, rowing and strength training. After 3 months of controlled rehabilitation, patients should slowly return to their previous sports activity and level, without provoking further pain or morning stiffness.

Description of Heavy Slow Resistance Exercise

The strength training will consist of a gradual progressive training program with training 3 times a week starting after instruction by the physiotherapist. The training is supervised by a physiotherapist for the first 3 months by supervised training 4 times or more if needed. As the tissue becomes stronger and the pain becomes less, the tissue is challenged at higher loads. Instruction in the exercises will be handled by two project physiotherapists. The exercises are also handed out in text and images. For bilateral symptoms, both sides must be trained, but only one side is included in the evaluation of effect parameters. For unilateral symptoms, only the symptomatic side is trained

Description of app guided home workouts

The app contains the same exercises that were included in the study of Wetke (2015). The exercises do not require special equipment and can be performed at home at convenient times. The exercises only use the patient's own body weight or an exercise rubber band as a load. The exercises include movement exercises, balance exercises, strength exercises and stretching exercises. The strength exercises start without dorsal flexion in the ankle and are slowly progressed with increasing dorsal flexion if this does not trigger pain of 50 or more on a VAS 100 pain score. The app contains an algorithm that responds to the patient's feedback on each exercise (difficulty of the exercise, pain provocation of the exercise) and based on this, the app assesses which exercises to offer next time. It is thus an interactive app that results in an individual training program, as the exercises are

offered in different order and with different progression depending on the patient's feedback. See www.injurymap.com/da/doctors/diagnoses under "Achilles tendonitis".

Trial Design

Substudy 1 is an evaluator blinded randomized controlled trial with follow-up after 3, 6, 9 and 12 months. Patients not satisfied with the outcome in substudy 1 after at least 1 month of training, have the possibility to drop-out of this substudy and be included in substudy 2. Drop-outs are recorded as "non-survivors" and a "Survival" curve is recorded for each exercise group. A total of 90 patients are included, 45 patients in each of the 2 training groups. All patients will be included in the intention to treat analysis, but we will also perform a per-protocol analysis only including patients performing at least 75% of the training programs.

Anyone who ceases due to unsatisfactory effect in sub-study 1 can be included in the second part of the study after at least 1 months of training and no later than after 12 months.

Sub-study 2

Single blinded (assessor and statistics) Randomized Controlled Trial.

Randomization method

Randomization must be preceded by informed consent and power of attorney. The randomization of patients is performed by an independent office employee not involved in patient care (Charlotte Bilde) using a computer generated randomization schedule (MINIMPY, Maghaei 2010) using permuted block sizes (two to four). The employee is blinded to the block sizes. The allocation of each patient is stored in a computer drive with exclusive access only for the responsible office employee (Charlotte). Patients will be divided equally into 4 groups. No further stratification will be carried out in part 2 of the study.

The secretary is then in charge of filling out randomization sheets and preparing the CRF (clinical research files).

Blinding

The study will be evaluated blinded. The doctors who give the injections cannot be blinded due to the large difference in the injection volume. Patients cannot be blinded to the training performed and can probably feel whether a small or large volume is being injected. The effect of the training is evaluated monthly by the patient himself at home without interference with any investigators on an app (Redcap). At every doctors appointment US assessment of the Achilles tendon will be performed.

The 4 secondary treatment arms

Patients continue in the allocated training (Heavy Slow Resistance exercise or App guided training) and treatment is supplemented with either corticosteroid injection (CS) or High Volume Injection (HVI). This results in 4 groups:

GROUP 3 (HSR+HVI): Continued Heavy Slow Resistance exercise supplemented by injection of 50 ml of HVI with CS (9.5 ml Lidocaine + 20 mg Depomedrol 40 mg/ml, followed by 40 ml isotonic saline). Only one injection is given (Boesen 2017)

GROUP 4 (HSR+CS): Continued Heavy Slow Resistance exercise supplemented by injection of 1 ml Lidocaine + 1 ml (40 mg/ml) corticosteroid (Depomedrol®) , total 2 ml (standard care). Injection is given every 6 weeks if needed. Max 3 injections.

GROUP 5 (app+HVI): Continued app-based training supplemented by injection of 50 ml HVI with CS (9.5 ml Lidocaine + 20 mg Depomedrol 40 mg/ml, followed by 40 ml isotonic saline). Only one injection is given (Boesen 2017)

GROUP 6 (app+CS): Continued app based training supplemented by injection with 1 ml. Lidocaine + 1 ml (40 mg/ml) corticosteroid (Depomedrol®), total 2 ml (standard care). Injection is given every 6 weeks if needed. Max 3 injections.

Description of the load reduction and controlled exercise therapy

Continuous as described under sub-study 1.

Description of injection of 2 ml with corticosteroid

The injection consists of the mixture of the corticosteroid: Depo-medrol ® 1 ml (40mg/ml) and 1 ml Lidocaine 1%. The mixture will be injected underneath the thickest part of the tendon. Regardless of whether the symptoms are bilateral or unilateral, only one side is selected for treatment. The first corticosteroid injection is given to everyone included in this group. The second corticosteroid injection after 1 month is given only if the tendon is over 7 mm thick or more than 20% thicker than the healthy one. The third injection is given 2 months after inclusion if, in addition to continued thickening, there is also morning pain above VAS 20 (100 mm VAS score) or VAS under function above 20 (100 mm VAS score). Thus, a maximum of 3 corticosteroid injections are given. This is the usual standard treatment.

Description of injection of 50 ml HVI and corticosteroid.

The injection consists of the mixture of the corticosteroid: depo-medrol ® 0.5 ml (40mg/ml) and 9.5 ml lidocaine 1%. The mixture will be injected underneath the thickest part of the tendon. The needle remains in place and 2 x 20 ml of isotonic saline is injected afterwards. Regardless of whether the symptoms are bilateral or unilateral, only one side is selected for treatment. The injection is made only once.

Trial Design

Substudy 2 is also an evaluator blinded randomized controlled trial with follow up after 1,2,3,6,9,12 months.

Anyone who ceases due to unsatisfactory effect in sub-study 2 can be included in the third part of the study after at least 3 months of exercise therapy and no later than after 12 months.

Sub-study 3:

Open prospective study

Patients who do not achieve sufficient efficacy from conservative treatment in sub-studies 1 and 2 will be offered surgery with tenolysis, which is the standard treatment for patients with Achilles tendonpathy who do not respond adequately to conservative treatment. The operation is performed at the Sports Surgery Section, Orthopaedic Surgery Department, Bispebjerg Hospital.

Description of the operation

The patient is operated on in lower leg block or universal anesthesia.
Preoperative antibiotics with either Dicillin 2 g iv or Zinacef 11/2 g iv.
The thickening of the tendon is determined by palpation. Incision (about 3 cm long) is made corresponding to the anterior/medial edge of the tendon along the thickened part of the tendon. The peritendium is cleaved and the tendon is released from the peritendium throughout the circumference corresponding to the swelling and approximately 3 cm distally and proximally to the swelling. Afterwards the skin is closed with nylon sutures.

Trial Design

Open prospective quality assurance study with follow-up 3, 6 and 12 months after surgery

4 OUTCOME MEASURES

Primary outcome measures:

The primary endpoints in sub-study 1: VISA-A at 3 and 6 months. Collected by independent evaluator via "Redcap".

The primary endpoints in sub-study 2: VISA-A (total and pain subscales) 6 months after the 1st injection date in substudy 2. Collected by independent evaluator via "Redcap".

The primary endpoints in sub-study 3: VISA-A score at 6 and 12 months from the day of surgery.

All patients are thoroughly instructed in visa-A score, on all visits, as it can be difficult to understand. However, it is important that they fill out the score at home directly in the assessment-

app: “Redcap” without interference of any involved investigators. Intention to treat is used so that patients who do not show up for primary outcome will have scores transferred from the last attendance.

Secondary outcome measures

Sub-study 1:

Lickert scale at 3, 6, 9 and 12 months: 11 point box scale from -5 to +5, where 0 is the status at **entry,** +5 is cured, and -5 is much worse.

VISA-A scores 1,2, 9 and 12 months, including VISA-A pain subscore during

Function at all timepoints (1,2,3,6,9,12 months)

Assessment of the exercise therapy at 3 months: 11 point box scale from 0-10, where 0 is very uninspiring / boring training, and 10 is very inspiring and motivating training.

Thickness of the Achilles tendon measured by ultrasound scan, cross-sectionel image on the thickest of the tendon at 3, 6, 9 and 12 months. The thickness of the "healthy" tendon is also measured for comparison.

Ultrasound Scanning Doppler Activity assessed with Color Doppler at 3, 6, 9 and 12 months.

After 6, 9 and 12 months, it is also assessed how many percentage of previous activity level (from before the injury) they have recovered. The patient himself states this as a percentage.

Survival rate to the treatment is assessed by assessing all patients that are not satisfied with the treatment or can not comply to the training protocol.

Sub-study 2:

VISA-A score 1, 2, 3, 9 and 12 months

Thickness of the Achilles tendon measured by ultrasound scan, cross-sectionel image on the thickest part of the tendon at 3,6,9,12 months. The thickness of the "healthy" tendon is also measured for comparison.

Ultrasound Scanning Doppler Activity assessed with Color Doppler at 3, 6, 9 and 12 months.

After 6, 9 and 12 months, it is also assessed how many percentage of previous activity level (from before the injury) they have recovered. The patient himself states this as a percentage.

Any complications are noted on an ongoing basis.

Sub-study 3:

VISA-A score 3 months post operatively.

Thickness of the Achilles tendon measured by ultrasound scan, cross-sectionel image on the thickest part of the tendon at 3, 6 and 12 months.

Ultrasound Scanning Doppler Activity assessed with Color Doppler at 3, 6 and 12 months.

After 6 and 12 months, it is also assessed how many % of previous activity level (from before the injury) they have recovered. The patient himself states this as a percentage.

Any complications are noted on an ongoing basis.

5 SAMPLE SIZE AND POWER

Sub-study 1

The risk of finding a difference between groups, even if there really is none, is set at 5% (risk of type I error), while the risk of overlooking a difference between the groups that is actually present is set at 20% (type II error). All outcome parameters will be analyzed using Mixed Effect Analysis

with treatment regime (group) and time as main factor (GraphPad Prism version 9.3 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com). All analysis are performed as an intention-to-treat analysis. If a patient drops out due to no improvement or too much pain to continue exercise therapy, the missing data will still be included using the mixed effect analysis.

Q-Q plots will be visually examined prior to analysis to ensure that the assumption of normal distribution is not violated. Significance level is set to 0.05. We will also compare the "survival rate" in each training group, and compare the end result after training by performing per protocol analysis. Patients not complying at least 75% with the training protocol are not included in the per-protocol statistics.

The minimum relevant difference in VISA-A is set at 15. However, as a non-inferiority study, the difference is set to 15/2 = 7.5. Based on other studies on pain intensity, we expect a mean baseline of 50 and an average improvement of 17. The standard deviation (SD) on the VISA-A measurements in these studies is 13. Power of 80% gives a sample size of 38 participants in each group. We plan to include 45 in each group in case of data loss and no-shows, for a total of 90 patients.

Sub-study 2:

In a previous study, 25% achieved satisfactory effect from training alone. If the same is seen in the current study, approximately 67 will want additional treatment. Of these, we expect that 50 will continue in sub-study 2. Sub-study 2 is a superiority study, and 22 patients are needed to have an 80% chance of finding, with 5% significance level, a difference in VISA-A scores of more than 11 between treatment groups using Mixed Effect Analysis using the intention to treat principle Patients are divided into 4 groups, but this sub study will be powered to detect differences between exercise therapy+HVI and Exercise therapy +CS injection. This means that the combination of group 3 and group 5 are compared to the combination of group 4 and group 6. However, we will also compare group 3 to group 4, and group 5 to group 6.

Q-Q plots will be visually examined to ensure that the assumption of normal distribution is not violated prior to analysis.

Sub-study 3

is a prospective quality assurance study. Paired T-test is used for calculating differences from before operation to 3, 6 and 12 months after operation. Change in VISA-A score is the primary outcome at 6 and 12 months, with an expected preoperative score of 50 and a relevant improvement is set to 15. The standard deviation of the difference is from earlier studies 13. In order to record an improvement of at least 15 points with a risk of type I error of 5% and type II error of 20%, 8 patients would have to be included in this study.

Data processing:

Entry data is registered in Redcap, where all information from each individual subject is collected.

Each patient is assigned an anonymous unidentifiable project number: Ach2019-n.

Project numbers are listed on all CRF and patient diaries.

Folders, CRF and patient diaries are stored blinded only with study numbers in the departments computers. After 12 months follow-up of the last patient, a blinded statistician will make the statistical calculations. After data entry, the patients in sub-study 1 are divided in two groups: group 1A and group 1B by help from independent office employee. The primary investigator will group the patients in the two groups still blinded to the treatment group. After data entry in sub-study 2 the patients are divided in group X, Y, Z, W. and the two groups treated with either HVI or with CS in group 2A and group 2B.

All statistics are performed until agreement of the results. Thereafter the blinding is broken. Analysis of data will take place in consultation with the statistician.

6 Adverse events

The adverse effects committee is chaired by JR. All adverse events, defined as any negative or unwanted reactions to the interventions will be recorded. A patient diary will be given to patients at baseline where patients are asked for any adverse events during the first three months. This will capture additional ill effects not reported at the time of their occurrence.

7 STATISTICAL ANALYSES

7.1 General

In substudy 1 and 2 we will perform a Mixed Effect Analysis. Intention to treat is used so that patients who do not show up for primary outcome will still be included.

In substudy 3 we will perform a paired t-test.

7.2 Statistical Analysis Plan

Statistical analysis will be undertaken using PRISM version 9.3.1. All analyses will be conducted on an intention-to-treat principle using all randomized participants in the groups they were originally randomized to. A blinded statistician will perform the data analysis. In the per-protocol analysis only patients complying at least 75% with the treatment protocol are included in the statistics.

A blinded statistician will perform the data analysis.

Demographic and anthropometric characteristics (gender, age, mass, height, body mass index, sporting activities and pain duration) will be determined at the baseline visit for each treatment group.

Statistical analyses will be conducted on all outcome measures at all timepoints. However, the primary end-point will be the total score of the VISA-A questionnaire at 3 and 6 months in substudy 1; VISA-A total score and pain-subscales at 6 months in substudy 2; and VISA-A total score at 6 and 12 months in substudy 3. Between-group comparisons of treatment effect for all primary and secondary outcomes, will be performed with a mixed effect analysis. To assess for inferiority and superiority, mean between-group differences and two-sided 95% confidence intervals will be calculated.

The ordinal scaled data of patients overall assessment of the treatment effect (Lickert score -5 to +5) will be analyzed with the same mixed effect analysis, if the data is found normally distributed.

The ordinal scaled data on satisfaction with the exercise program is analyzed with the same mixed effect analysis, if the data is found normally distributed.

The ordinal scaled data of grading the flow within the tendon into 4 categories will be calculated using non parametric statistics: Mann-Whitney U-tests.

Return to sport in percent of earlier sports activity will be compared using unpaired t-test if the data is normally distributed, otherwise non parametric analysis (Mann-Whitney) is performed.

In substudy 1 the survival rate in each exercise group is illustrated on a Kaplan-Meier plot and differences are calculatred using Log rank test (Mantel-Cox test).

A two-sided P value of less than 0.05 will be considered to indicate statistical significance.

7.3 Interim analysis and early stopping rules

Anecdotally, an increased risk of tendon rupture have been reported. To account for this, we have introduced an early stopping rule if the rate of Achilles tendon ruptures exceeds 2 ruptures.

7.4 Timing of analyses

When this statistical analysis plan was signed, recruitment to the main trial was started, but no analysis had been initiated.

SUB-STUDY 1								
	Enrolment	Allocation						
TIMEPOINT	**april 2022 – end 2024**	**april 2022 – end 2024**	***Month 1***	***Month 2***	***Month 3***	***Month 6***	***Month 9 Jan 2023 end 2025***	**Month 12 April 2023 end 2025**
ENROLMENT:								
Eligibility screen	X	X						
Informed consent		X						
Allocation		X						
INTERVENTIONS:								
Intervention group 1			←	—	→			
Intervention group 2			←	—	→			
ASSESSMENTS:								
Diagnosis		X						
VISA-A		X	X	X	X	X	X	X
Morning pain [VAS]		X	X	X	X	X	X	X
Pain after activity [VAS]		X	X	X	X	X	X	X
Return to usual sports participation						X	X	X
Satisfaction with result of treatment			X	X	X	X	X	X
Patient diary for reporting compliance and adverse events			←	—	→			
Ultrasound examinations		X	x	x	X	X	X	X
Demographics		X						

Table 1: SPIRIT figure. Schedule of enrolment, interventions and assessments

SUB-STUDY 2								
	Enrolment	Allocation						
TIMEPOINT	**July 2022 – July 2024**	**July 2022 – July 2024**	***Month 1***	***Month 2***	***Month 3***	***Month 6***	***Month 9 Jan 2023 end 2025***	**Month 12 April 2023 end 2025**
ENROLMENT:								
Eligibility screen	X	X						
Informed consent		X						
Allocation		X						
INTERVENTIONS:								
Exercise group 3+4			◆—	—	—◆			
Exercise group 5+6			◆—	—	—◆			
ASSESSMENTS:								
Diagnosis		X						
VISA-A		X	X	X	X	X	X	X
Morning pain [VAS]		X	X	X	X	X	X	X
Pain after activity [VAS]		X	X	X	X	X	X	X
Return to usual sports participation						X	X	X
Satisfaction with result of treatment			X	X	X	X	X	X
Patient diary for reporting compliance and adverse events			◆—	—	—◆			
Ultrasound examinations		X	x	x	X	X	X	X
Demographics		X						

SUB-STUDY 3					
	Enrolment	Allocation			
TIMEPOINT	**End 2022 – end 2025**	**End 2022 – end 2025**	***Month 3***	***Month 6***	**Month 12 End 2023 – end 2026**
ENROLMENT:					
Eligibility screen	X	X			
Informed consent		X			
Allocation		X			
INTERVENTIONS:					
operation		x			
ASSESSMENTS:					
Diagnosis		X			
VISA-A		X	X	X	X
Morning pain [VAS]		X	X	X	X
Pain after activity [VAS]		X	X	X	X
Return to usual sports participation				X	X
Satisfaction with result of treatment			X	X	X
Patient diary for reporting compliance and adverse events			♦———	———	———♦
Ultrasound examinations		X	X	X	X
Demographics		X			

8 DEVIATIONS FROM THE PROTOCOL

The following details in this SAP represents deviations from protocol version 3

Header in protocol	Change	Reason