Which treatment is most effective for adults with Achilles tendinopathy? A protocol for a living systematic review including network meta-analysis

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Abstract

Introduction Achilles tendinopathy is a condition that affects both active and sedentary individuals. It is characterized by localized pain in relation to tendon-loading activities. As chronic Achilles tendinopathy results in substantial disease burden, it is vital to treat it effectively. There are many different conservative and surgical treatments available, but the comparative effectiveness of these treatments has never been evaluated.

Methods and analysis The primary outcome measure of this living systematic review with network meta-analysis is the Victorian Institute of Sports Assessment-Achilles (VISA-A) score. The secondary outcome measures are return-to-sport (yes/no) at 6–12 weeks, 13–52 weeks and >52 weeks. Completed published and unpublished randomized controlled trials with full-text reports are eligible for inclusion. We will search Embase, MEDLINE Ovid, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and CINAHL, SPORTDiscus and AMED OpenGrey, WorldCat, Google Scholar, the WHO trial registry and Clinicaltrials.gov register for potentially eligible trials. Two researchers will appraise trial eligibility and perform data extraction. The risk of bias will be assessed using the Cochrane Risk of Bias Tool V2. Bayesian network meta-analyses will be constructed for VISA-A score and return-to-sport. Consistency between direct and indirect comparisons will be assessed. We will explore between study variability, and perform a threshold analysis for the credibility of the network meta-analyses' conclusions.

Ethics and dissemination No ethical approval is required. The study commenced on 1st November 2018, and its expected completion date is 15 August 2019. Upon completion, we will seek publication in an international peer-reviewed journal and publish translational articles to disseminate the work to clinicians.

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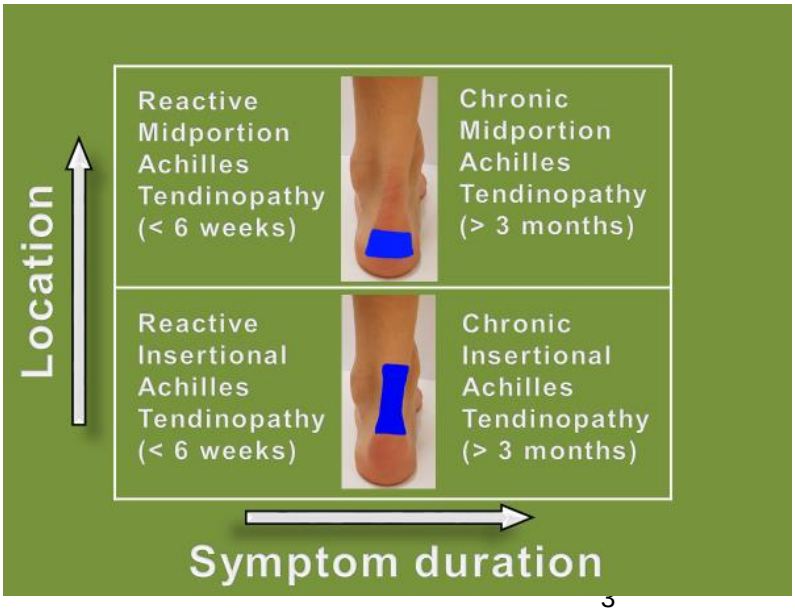
Introduction

Achilles tendinopathy is common in active and sedentary individuals.[1,2] The incidence in general medical practice is 2-3 per 1,000 patients.[3] It is most frequent in specific populations; more than half of runners will suffer Achilles tendinopathy and hampers return to health-promoting activities.[4,5] The incidence of Achilles tendinopathy is expected to increase due to intensive campaigns to promote physical activity as an intervention for sedentary individuals. Recent qualitative studies report a decreased quality of life with impact on the identity, social well-being, living with the condition, frustration, and lifestyle adaptations.[6,7] The reported reduced work ability due to lower-limb tendinopathy is 36% and the associated decreased work productivity is up to 58%.[8] The impact increases even more when Achilles tendinopathy becomes chronic. This is reflected in the long symptom duration. Approximately 60% of patients with chronic Achilles tendinopathy have persistent symptoms 5 years after initiating conservative treatment.[9]

The clinical diagnosis of Achilles tendinopathy is established in presence of localized Achilles tendon pain in relation to tendon-loading activities.[10] Different types of Achilles tendinopathy are considered, based on location and duration of the disease.[10,11] Achilles tendinopathy localized in the midportion – 2-7 cm proximal from its insertion on the calcaneus – is a different condition compared to Achilles tendinopathy localized at the distal bony insertion. Additionally, new-onset reactive Achilles tendinopathy is considered to have a different underlying pathology compared to chronic or recurrent Achilles tendinopathy. These different entities influence prognosis and treatment options and, therefore, they are categorized into 4 groups (Figure 1).[12,13] Ultrasound is the most suitable method to detect changes in Achilles tendinopathy, as it is widely accessible, user-friendly and has low costs.[14] On ultrasound, tendinopathy can be characterised by tendon thickening, decreased tendon structure and/or increased Doppler flow. While additional diagnostics can be used to verify the diagnosis of Achilles tendinopathy, the associations between diagnostic abnormalities and patient-reported pain is weak.[15-18] Therefore, the presence of clinical signs remains the cornerstone for establishing the diagnosis.[19]

Figure 1. Achilles Tendinopathy categorized into 4 different entities



Treatment of tendinopathies is challenging for both healthcare providers and patients. Treatments can be broadly classified into the following categories: exercise-based therapies, passive modalities, medications, injection-based therapies and surgery. The large number of treatment options is represented in the number of available systematic reviews. In 2018, at least 9 separate systematic reviews on the effects of treatments for Achilles tendinopathy were published.[20-28] We also identified a number of ongoing systematic reviews into the effectiveness of (groups of) treatments for Achilles tendinopathy. While all these reviews focus on different treatment options, the comparative effectiveness of all available treatments has never been examined. Being faced with so many potentially effective treatments, it is challenging to take an informed shared-decision in clinical practice about how to treat the condition.

Conventional systematic reviews provide head to head comparisons, e.g. exercise therapy versus an injection therapy, and injection therapy versus a passive modality. In this approach multiple treatments cannot be compared simultaneously, leaving the clinician and patients with incomplete, interpretations about the comparative effectiveness of all available treatments.[29] Network meta-analysis (NMA) provides the opportunity to combine evidence from head to head comparisons with indirect treatment comparisons in a single analysis, while maintaining the randomized nature of the evidence. As long as the network of treatment comparisons is connected, NMA allows all treatments to be compared, even if they have not been investigated head to head in a randomized controlled trial.[30-32] Treatments can be ranked from “most likely to be effective” to “least likely to be effective” for a given outcome. This provides useful information for the shared-decision making process in clinical practice. NMA assumes that the included studies do not differ in important factors that interact with treatment effect.

Systematic reviews are soon out of date, particularly in an ever-evolving field like Achilles tendinopathy.[33] Living systematic reviews are regularly updated and have the potential to provide a comprehensive and up-to-date overview of the comparative effectiveness of all available treatments for Achilles tendinopathy.[34,35]

The aim of this living systematic review with network meta-analysis is to evaluate the comparative effectiveness of all available treatments for adults with any subtype of Achilles tendinopathy, providing a comprehensive and consistently updated overview of evidence-based treatments.

Review questions

1. Which treatments are most likely to be effective for adults with Achilles tendinopathy on the VISA-A score, and return to sport activities?
2. Which treatment classes are most likely to be effective for adults with Achilles tendinopathy on the VISA-A score, and return to sport activities?
3. Which treatment is most likely to lead to (highest levels of) patient satisfaction?
4. Which treatment class is most likely to lead to patient satisfaction?

Outcome measures

Primary outcome measure:

- Victorian Institute of Sports Assessment-Achilles (VISA-A) score. This is an 8-item patient-reported outcome measure, specifically designed and validated for patients with Achilles

tendinopathy.[36] The score ranges from 0 – 100, with 0 points indicating worst symptoms imaginable, and 100 points indicating no symptoms.

Secondary outcome measures:

- Return-to-sport (yes/no)
- Patient satisfaction

Keywords

Tendon, tendinitis, tendinosis, Haglund deformity, exercise therapy, injection, surgery

Inclusion criteria

Type of studies

Published or unpublished randomized controlled trials (RCTs), including randomisation through minimisation, or clustering, for which a full report or full protocol of a completed trial is available, are eligible for inclusion. RCTs that randomise on the tendon level are only included when study authors can provide data that allow re-analysis on the patient level, or when study authors provide such results. This will be done by including patients with unilateral pain only. Otherwise, these RCTs will be excluded. This is to ensure the NMA provides outcomes relevant at the patient level. Within participant-controlled designs (i.e. cross-over studies, or studies using the contralateral Achilles for the control arm) will be excluded. Studies having 1 or more treatment arms with ≤10 participants will also be excluded.

Type of population

All patients with a clinical diagnosis of Achilles tendinopathy are included. We will include trials when the authors mention that a clinical diagnosis has been made. We will study populations with midportion and insertional Achilles tendinopathy, and populations with individuals having a combination of midportion and insertional tendinopathy (if such trials exist in the latter case). If the location of Achilles tendinopathy is not clear from the report, authors will be contacted. If the type of tendinopathy is still unknown, we will exclude the trial from further analyses. The diagnostic criteria used in the original trials will be followed. Only trials investigating an adult population with Achilles tendinopathy (age ≥18 years) will be included to prevent including patients with extra-articular osteochondrosis (Sever's disease).[37] Trials including athletes and/or inactive patients will be eligible. Trials evaluating the effect of treatment options in full-thickness ruptures of the Achilles tendon will be excluded.

Type of treatments and control treatments

Any treatment, control treatment, placebo, wait-and-see, or no treatment group studied in a RCT is eligible for inclusion. Examples of treatment classes are exercise-based therapies, passive modalities, medications, injection-based therapies and surgery. Trials with co-interventions (for example; exercise therapy + pain medication) will be eligible, provided that these were applied to all participants in the treatment arm.

Type of outcomes

Trials assessing the following outcomes will be included:

- VISA-A
- Return to Sport (Yes/No)
- Patient satisfaction

Methods

Protocol registration

The protocol for this living systematic review with network meta-analysis has been registered on PROSPERO [CRD42018086467]. This protocol is written based on, and along the lines of, a recently published protocol for a living systematic review with network meta-analysis for patients with patellofemoral pain.[38] We followed the PRISMA-P and PRISMA extension for network meta-analysis for reporting systematic review protocols and network meta-analysis.[39-41]

Patient involvement & prioritising outcomes

We performed a pilot round of focus interviews with consecutive patients suffering from chronic midportion Achilles tendinopathy (n=9) who were participating in an ongoing trial (ClinicalTrials.gov Identifier: NCT02996409). We asked which complaints were most disabling and important to patients and gained knowledge and experience about how to question patients regarding their Achilles tendon pain.

The most frequently mentioned symptoms were restriction in sports participation (n=6), pain during daily activities (n=6), stiffness (n=4) and pain due to pressure (e.g. shoes; n=4). After obtaining this information and summarizing the results, we sent a digital questionnaire in collaboration with the Dutch Patient Federation. We asked 97 patients' subtype of Achilles tendinopathy and their main treatment goal (open question). Twenty-three percent of the patients were <40 years of age, 19% was 40-49 years, 34% was 50-59 years, 24% was 60-69 years, and <1% was 70 years or older. Forty-nine percent was male and 79% participated in regular sports activities. Based on a pain map, 56% reported insertional Achilles tendinopathy, 20% midportion Achilles tendinopathy and 24% had a combined insertional and midportion Achilles tendinopathy. Forty-four percent of patients discussed their treatment aims with their treating physician.

Eighty-five patients (88%) reported their treatment goal(s). The most frequently reported treatment goals were 1) participating in sports without mentioning pain status (36%); 2) pain free participation in sports (27%); 3) pain free participation in activities of daily living (22%); 4) pain without specification (20%) and 5) regaining normal function in activities of daily living without mentioning pain status (9%).

Based on these results, we defined our primary and secondary outcome measures. The VISA-A questionnaire quantifies both pain, pain during functioning in activities of daily living and pain during

sports, including participation in sports. All these topics are important to patients and therefore we decided to define the VISA-A questionnaire as our primary outcome measure.

Search strategy

One investigator (ACV) and a medical librarian developed a sensitive search strategy for each of the data sources. We used a modified version of the Cochrane sensitive search strategy for RCTs.[42] The strategy includes indexed and free text terms, where applicable (supplementary file, Appendix I). We did not impose any restrictions (e.g. language) on our search.

One investigator (ACV) will search conventional databases, grey literature databases and trial registers from their date of inception.

Conventional databases

Conventional electronic databases Embase, MEDLINE Ovid, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and CINAHL, SPORTDiscus and AMED (the latter three via Ebsco) will be searched for relevant reports.

Grey literature and ongoing trials

Databases

OpenGrey.eu, WorldCat.org and Google Scholar will be searched for unpublished trials.

Trial registers

We will search the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) and Clinical Trials.gov, for unpublished or ongoing trials.

Hand searching

We will screen reference lists of all the trial reports included in our systematic review.

Study selection

After duplicate removal by one of the investigators, two researchers (ACV, RJV) will screen titles and abstracts independently. They will seek consensus in case of initial disagreement. If consensus cannot be reached, the report will be included for full text evaluation.

The two investigators will independently apply inclusion and exclusion criteria to the full text reports. In case of disagreement, consensus will be sought. If disagreement persists a third author (AW) will take the decision. Reasons for full text exclusion will be documented.

All selected studies will be uploaded to the Covidence platform (Melbourne, Australia), a not-for-profit management system aiming to improve the production and use of systematic reviews for health and wellbeing. This software facilitates for independent data selection, extraction and risk of bias assessment.

Data extraction

Data will be independently extracted by two random pairs of researchers (ACV, AW, CLA, RJV) using standardised extraction forms adopted from the Cochrane Collaboration.[43] Disagreements will be resolved by seeking consensus, and by a fifth reviewer (MW) in case of persistent disagreement. The following data will be extracted:

- Publication and trial details: e.g. authors, year of publication, funding source, aim study, and design
- Population: e.g. number of included patients, population characteristics for age, sex, setting where population was recruited, baseline scores for outcome measures (mean, standard deviations (SDs), standard errors extracted for continuous outcomes, and number and percentage for categorical outcomes)
- Eligibility criteria and diagnostic criteria used for Achilles tendinopathy
- Treatments: e.g. number randomized to group, detailed description of application, dose, intensity, frequency, adherence. We used items from the Template for Intervention Description and Replication (TIDierR) checklist to assure comprehensive data extraction in this section of the extraction form.[44]
- Outcomes: e.g. time points measured and reported upon, outcome definition, person measuring, scales (upper and lower limits), imputation of missing data.
- Data and analysis: comparisons, outcomes, subgroups, time points, results (central estimates and measures of dispersion; e.g. mean for both groups, mean difference, SDs/95% confidence intervals/standard errors), number of missing patients, statistical methods used and appropriateness of these methods.
- Other information: study authors' key conclusions

Risk of bias assessment

We will use the Cochrane Risk of Bias Tool v2 to assess the risk of bias for each outcome per study, and for outcomes across a (direct) comparison. We will assess risk of bias on the basis of "assignment to intervention" (following the "intention-to-treat" principle). The Cochrane Risk of Bias tool has a fixed set of domains to use for the risk of bias appraisal, i.e. 'bias arising from the randomization process', 'bias due to deviations from intended interventions', 'bias due to missing outcome data', 'bias in measurement of the outcome', 'bias in selection of the reported result', and overall risk of bias judgement for each outcome.[45,46]

Sets of reviewer pairs (ACV + one of the following authors: MW, CLA, AW or RJV) will independently assess risk of bias for each outcome within the study, for each follow-up. Each major domain of bias will be appraised for each outcome. The tool's signalling questions and criteria will be followed to inform a domain-based appraisal of the risk of bias.[45,46] The risk of distortion of the outcome estimate will be appraised as at 'low', 'some' or 'high' risk of bias, according to Risk of Bias Tool v2 guideline. Judgements will be made regarding the direction of distortion 'favours experimental', 'favours comparator', 'towards null', 'away from null', or 'unpredictable'. Each outcome within a study will

receive an overall risk of bias judgement based on the individual domains; 'low', 'some' or 'high' risk of bias.[45,46] Consensus will be sought through discussions in case of disagreements between reviewers. A third reviewer (not part of the reviewer pair; i.e. MW, AW, CLA or RJV) will make the decision if disagreement persists.

Data synthesis and statistical methods

We plan a network meta-analysis (NMA) to assess which treatments for Achilles tendinopathy are most efficacious. Networks of treatment comparisons will be constructed for midportion, insertional and mixed Achilles tendinopathy separately, and for the primary and secondary outcome separately. Three authors (ACV, MW, RV) will appraise the clinical homogeneity before any analysis is commenced, by tabulating study and population characteristics and inspecting them for differences in potential effect modifiers. This is to assess the assumption of exchangeability required for NMA. In addition, treatments will be assigned to a class, e.g. exercise therapy, medical therapy or surgery.

Bayesian network meta-analysis

Networks will be modelled following the Bayesian approach, using Markov chain Monte Carlo simulations in WinBUGS (v1.4, Medical Research Council, United Kingdom, and Imperial College of Science, Technology and Medicine, University of Cambridge, United Kingdom). We will estimate direct, pair-wise comparisons first. For treatments that are connected in a network of comparisons, we will estimate relative treatment effects using network meta-analysis. We will also group treatments into treatment classes, and fit a hierarchical network meta-analysis, to allow both treatment and class effects to be estimated.[47,48] Continuous outcomes will be presented as mean difference (MD), with their 95% credible intervals when outcomes are measured with the same instrument. We will present standardised MDs if different continuous measures are used to evaluate the same construct. We will make attempts to model a time-course function for the continuous outcome VISA-A if sufficient data for this to be possible. We will group outcome follow-ups for return to sport, and for VISA-A if a time function is not feasible, based on the available data, seeking the following approximate timeframes; 6-12 weeks, 13 – 52 weeks and >52 weeks. If there are multiple time points available for an outcome, and these are equally close to the time point to be synthesised across trials, the last follow-up in this timeframe will be used. For >52 weeks, a slightly different approach will be followed, where multiple time points will be synthesized following available follow-up data.

We will use surface under the cumulative ranking curves (SUCRAs) and probability ranks to estimate the likelihood of individual treatments being superior than the other treatments.

Assessing statistical heterogeneity and exploring it with individual participant data

Fixed and random effects models will be fitted and we will compare model fit using the deviance information criterion and posterior mean residual deviance. Lower deviances depict a better model fit. We will assess statistical heterogeneity by inspecting the between trial standard deviation, and comparing fit of the fixed and random effect models. Depending on resources and data availability, individual participant data from a previous randomized controlled trial by our group, will be used

together with trial level data to explore statistical heterogeneity.[49] Otherwise, only study level data will be used. The following factors are considered for exploration when sufficient data are available (>10 studies/events per variable), in the following order: symptom duration, active or sedentary population, sex and publication status (published/unpublished).[50-52]

Exploring inconsistency in the network

We will test the consistency assumption for each network. Results from a model that assumes consistency will be compared with a model that relaxes the consistency assumption, to assess whether there is evidence of inconsistency. To this end, we will examine model fit by comparing the models' residual deviance and deviance information criterion. If evidence of inconsistency is identified, we will use the node-split method to identify where in the network the inconsistency is.[53] We will use a Bonferroni correction for interpreting multiple P-values.

Assessing small study bias

We will use comparison-adjusted funnel plots to examine small study bias, if possible. In this examination, we assume that small study bias is consistent across comparisons, and experimental treatments are more likely to be favoured in small studies compared to control treatments/groups. We will evaluate the funnel plot's distribution, where missing small studies are expected favouring the control treatment in the presence of small study bias. We will generate funnel plots for each outcome, but only when ≥10 studies are available.[54] Conventional funnel plots for pairwise comparisons will be constructed when comparison-adjusted funnel plots cannot be constructed.[55]

Threshold analysis for credibility of the NMA conclusions

Risk of bias in the pair-wise estimates has the potential to distort the reliability of the network's estimate, and can affect the credibility of the NMA's conclusion. We will use a threshold analysis to investigate how biased the estimate for each treatment comparisons would have to be before the a recommendation based on the posterior mean treatment effect for VISA-A would change.[56,57] We will perform a threshold analysis where the variance around the bias estimate is assumed to be 0. We will assume bias for both measures to over or underestimate treatment effects by maximally 20%, following empirical estimations of bias in meta-epidemiological studies.[58-60]

Potential limitations of the work

NMA enables comparison of multiple interventions simultaneously and has the potential to provide a coherent recommendation for clinical decision-making. Yet, the ability to compare multiple interventions in an NMA depends on the availability of the comparisons investigated, and studies meeting the assumption of exchangeability. 'Exchangeable' means that patients randomized to an intervention in one study should have had the ability to be randomized to (other) interventions in another study. Coherent recommendations can only be made when the network is connected; it is impossible to compare interventions when they are not connected. The strength of the NMA evidence depends on the risk of bias in study outcomes across the field of Achilles tendinopathy. NMA assumes

that evidence from direct head-to-head studies is consistent with evidence obtained indirectly via the network of comparisons. Therefore, we will check the consistency assumption when direct and indirect evidence are both available.
We acknowledge that there are also limitations to the living nature of the proposed research. Living systematic reviews are labour intensive and require regular updates. The chance of type 1 errors, i.e. incorrectly concluding there is a significant effect in the meta-analysis, increases with the rising number of updates.

Administration, dissemination and updating the living systematic review

This living systematic review will be administered at the Department of Orthopaedics and Sports Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands. We plan to update the network meta-analysis for at least 5 years. The study started at 1 November 2018 and we expect the completion date for the first version is 15 August 2019. We plan to update the search and review process every 12 months, if needed. We will update the analysis when new data are available. In this case, we will present the new findings at the website (www.sportzorg.nl) of the Dutch Sports Medicine Association (VSG). Here, we will also provide a plain-language summary for patients and clinicians dealing with Achilles tendinopathy. We will seek re-publication in an international peer-reviewed journal if there is a change in the conclusions. We will also seek to present the results at national and international conferences. We will submit the full text report for “open access” publication in an international peer-reviewed journal.

Perspectives

Systematic reviews on the treatment of Achilles tendinopathy should inform decisions in clinical practice. Traditional systematic reviews with pair-wise meta-analysis do not adequately inform these decisions when multiple treatments exist. Network meta-analysis is the only design to compare the effectiveness of *all* available treatments for a condition. Although a multitude of systematic reviews on the treatment of Achilles tendinopathy are available, patients and clinicians are still in need of evidence informing clinical decision-making. Network meta-analysis enables ranking treatments according to their probability of being the most effective treatment. In this way, the research directly informs the clinician and patient when making a shared decision about how to treat Achilles tendinopathy. The ‘living’ nature of this study ensures that clinical decisions are based on the most up-to-date Level 1 evidence.

Ethics and dissemination

No ethical approval is required. The study commenced on 1 November 2018, and its expected completion date is 15 August 2019. We will seek publication of the work in an international peer-reviewed journal, as well as translational articles to disseminate the work to clinicians.

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We would like to extent our gratitude to W.M. Bramer, research librarian at Erasmus MC, for his help with developing a sensitive search strategy.

The Dutch Patient Federation assisted in sending, receiving and extracting surveys that were completed online by patients who suffered self-reported Achilles tendinopathy. We are grateful for their help and input in the design of the survey, thereby improving knowledge on important and relevant outcome domains for patients with Achilles tendinopathy.

We designed this study along the lines of another, recently published, protocol for a living systematic review with network meta-analysis[see ref. 38]; we are thankful to dr. Michael Skovdal Rathleff, dr. Sinead Holden, prof. dr. Bill Vicenzino and Carolina Bryne Lura, MSc, for their intellectual contribution, bringing about this study design in the field of musculoskeletal pain and sports medicine.

Author statement

MW, AW and RJV came up with the study idea. MW, ACV, AW, CLA, and RJV designed the study. MW, NJW and DMC designed the statistical analysis plan. MW, ACV, AW and RJV drafted the manuscript. All authors provided feedback and gave important intellectual input. All authors read and consented to the content of the article.

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This research received a grant from the Dutch Association of Medical Specialists to develop a clinical guideline for the treatment of patients with Achilles tendinopathy. This non-commercial association is not involved in the planning, conduct or reporting of this study.

Conflicts of interest

NJW leads a research project in collaboration with Pfizer plc. Pfizer part-funds a junior researcher. The projects is purely methodological, using historical data on treatments for pain relief. NJW has no other conflicts. All other authors report to have no conflicts of interest.

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Appendix I: Search Strategy

Embase.com

('achilles tendinitis'/exp OR ((tendinitis/de OR pathology/de) AND 'achilles tendon'/de) OR (((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*):ab,ti) AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti)

Medline Ovid

(((Tendinopathy/ OR Pathology/) AND "achilles tendon"/) OR "achilles tendon"/pa OR (((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*).ab,ti.) AND (Exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti.) NOT (Animals/ NOT Humans/)

CINAHL EBSCOhost

(((MH Tendinopathy OR MH Pathology) AND MH "achilles tendon") OR TI (((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*) OR AB (((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*)) AND (MH Clinical trials OR MH Randomized Controlled Trials OR MH Double-Blind Studies OR MH Single-Blind Studies OR MH Triple-Blind Studies OR MH Random Assignment OR TI (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) N1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups) OR AB (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) N1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups)) NOT (MH Animals+ NOT MH Humans+)

SportDiscuss EBSCOhost

(((MH TENDINITIS OR MH TENDINOSIS OR MH Pathology) AND MH "achilles tendon") OR TI (((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*) OR AB (((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*)) AND (TI (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) N1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups) OR AB (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) N1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups))

AMED EBSCOhost

(((MH Tendinopathy OR MH Pathology) AND MH "achilles tendon") OR TI (((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*) OR AB (((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*)) AND (MH Clinical trials OR MH Randomized Controlled Trials OR TI (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) N1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups) OR AB (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) N1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups)) NOT (MH Animals+ NOT MH Humans+)

Cochrane CENTRAL

((((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*):ab,ti)

Web of science

TS=(((((achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog* OR pain* OR injur*)) OR achillodyn*))) AND TS=(random* OR trial* OR rct)

Google scholar

"achilles|calcaneal tendinitis|tendinopathy|tendinosis|tendonitis" intitle:trial|randomized|randomized|rct

Open grey

(achilles OR calcaneal) AND (tendinitis OR tendinopathy OR tendinosis OR tendonitis) AND (rct OR randomized OR randomized)

Worldcat.org

kw:(achilles OR calcaneal) AND kw:(tendinitis OR tendinopathy OR tendinosis OR tendonitis) ti:(rct OR randomized OR randomized)

WHO ICTRP

"achilles tendinitis" OR "Achilles tendinopathy" in title

Clinicaltrials.gov

"achilles tendinitis" OR "Achilles tendinopathy"