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Complete List of Authors:	Deveza, Leticia; University of Sydney, Royal North Shore Hospital, Rheumatology Department Hunter, David; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department Wajon, Anne; Macquarie University Clinic, Macquarie Hand Therapy, Macquarie University, New South Wales, Australia Bennell, Kim; University of Melbourne, CHESM Vicenzino, Bill; The University of Queensland, Physiotherapy Hodges, Paul; School of Health and Rehabilitation Sciences: Physiotherapy, The University of Queensland Eyles, Jillian; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department Jongs, Ray; Royal North Shore Hospital, Physiotherapy Department Riordan, Edward; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department Duong, Vicky; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department Oo, Win; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department O'Connell, Rachel; National Health and Medical Research Council (NHMRC) Clinical Trial Centre, University of Sydney Meneses, Sarah; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department
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Efficacy of combined conservative therapies on clinical outcomes in patients with thumb base osteoarthritis: protocol for a randomised, controlled trial (COMBO)

Leticia A Deveza[1], David J Hunter[1], Anne Wajon[2], Kim L Bennell[3], Bill Vicenzino[4], Paul Hodges[4], Jillian P Eyles[1], Ray Jongs[5], Edward A Riordan[1], Vicky Duong[1], Win Min Oo[1], Rachel O'Connell[6], Sarah R F Meneses[1]

Affiliations

1. Rheumatology Department, Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, New South Wales, Australia.

2. Macquarie University Clinic, Macquarie Hand Therapy, Macquarie University, New South Wales, Australia.

3. Centre for Health, Exercise and Sports Medicine, Department of Physiotherapy, School of Health Sciences, The University of Melbourne, Melbourne, Victoria, Australia.

4. School of Health and Rehabilitation Sciences: Physiotherapy, The University of Queensland, Brisbane, St. Lucia, Australia.

5. Physiotherapy Department, Royal North Shore Hospital, Sydney, New South Wales, Australia.

6. National Health and Medical Research Council (NHMRC) Clinical Trial Centre, University of Sydney, Sydney, New South Wales, Australia.

Corresponding author

Dr Leticia A Deveza at Rheumatology Department, Royal North Shore Hospital - Reserve Road, St. Leonards, NSW 2065, Australia. Email: leticia.alle@sydney.edu.au Phone: 61 2 9463 1775

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ABSTRACT

Introduction: Management of thumb base osteoarthritis (OA) using a combination of therapies is common in clinical practice, however evidence for the efficacy of this approach is lacking. The aim of this study is to determine the effect of a combination of conservative therapies for the treatment of thumb base OA compared to an education control group.

Methods and analysis: This is a randomised, controlled, single centre, two-arm superiority trial with 1:1 allocation ratio; with assessor and statistician blinded. Participants are blinded to the trial's hypothesis and to the interventions received by the opposite group. A total of 204 participants will be recruited from the community and randomised using a computer generated schedule. The intervention group will receive education for joint protection and OA, a splint for the base of the thumb, hand exercises, and topical diclofenac sodium 1% gel over 6 weeks. The control group will receive education for joint protection and OA alone. Main inclusion criteria are pain ≥ 40 mm (VAS, 0-100) at the base of the thumb, impairment in hand function ≥ 6 (FIHOA , 0-30) and radiographic thumb base OA (KLG ≥ 2). Participants currently receiving any of the intervention components will be excluded. Outcomes will be measured at 2, 6 and 12 weeks. The primary outcome is change in pain and hand function from baseline to 6 weeks. Other outcomes include changes in grip and pinch strength, quality of life, presence of joint swelling and tenderness, duration of joint stiffness, patient's global assessment and use of rescue medication. Analysis will be performed according to the intention-to-treat principle. Adverse events will be monitored throughout the study.

Ethics and dissemination: This protocol is approved by the local ethics committee (HREC/15/HAWKE/479). Dissemination will occur through presentations at international conferences and publication in peer-reviewed journals.

Trial registration details: ACTRN12616000353493.

Keywords: Osteoarthritis, thumb, conservative, clinical trial

STRENGHTS AND LIMITATIONS OF THE STUDY

- There is currently no highly efficacious strategy for managing thumb base osteoarthritis (OA). A combination of non-pharmacological and pharmacological modalities is frequently used in practice but evidence of efficacy for this strategy is lacking.
- The 204 participants will be blinded to the treatment offered to the opposite group in order to minimize differences regarding expectations with the allocated treatment between groups.
- Interventions included in this study are usually easily available in practice which facilitates implementation.
- Results from the subgroup analysis will be used for hypothesis generation only, as the study was not powered for these analyses.

INTRODUCTION

Background and rationale

Osteoarthritis (OA) is a chronic and prevalent joint disorder with great impact on quality of life and high economic burden [1, 2]. The most common form of OA is that involving the hands, affecting three times more women than men and with greater prevalence following menopause [2, 3]. Overall prevalence of symptomatic hand OA is nearly 15% [4], while in the elderly (aged 70 years and over) the prevalence is about 26% in women and 13.4% in men [5].

Among the different subtypes of hand OA, that affecting the base of the thumb represents a particular challenge to clinicians due to associated disabling symptoms and the limited efficacy of treatment options [6]. Radiographic thumb base OA was reported to affect nearly 21% of the population over 40 years of age in the United States [7] and it is usually more frequently related to pain and disability than interphalangeal joint OA [6]. In addition to pain, it can cause deformity, stiffness, decreased range of motion and strength, resulting in difficulty performing common activities such as opening jars, carrying weights and writing [8].

While thumb base OA is primarily treated with non-surgical modalities, surgical treatment may be indicated for those whose debilitating symptoms persist despite adequate conservative management. Thumb base OA is one of the most common causes of hand surgery [9]. Surgical management, however,

is associated with a number of complications including tendon rupture, sensory changes and wound infection [10]. In addition, a 7-year prospective study found 70% of patients waiting for surgery for thumb base OA were able to postpone or avoid surgery following conservative treatment with joint protection and splinting [11].

Although a number of conservative therapies have proven to be effective for the management of hand OA, only modest treatment effects were reported for most individual interventions [12]. This is particularly true in the case of thumb base OA, with few high quality clinical trials in the literature to date and great heterogeneity across studies [13].

Among the non-surgical modalities, education about the disease, delivered along with instructions regarding joint protection techniques, has been demonstrated to have no clinically significant benefits for pain [8]. In contrast, a systematic review demonstrated that the use of splints for thumb base OA reduced pain, particularly in the long-term, based on data from two trials [14]. The same review found evidence that hand exercises might improve grip strength and hand function; however, evidence was based on individual trials using different exercise programmes. With regards to pharmacological management, there are insufficient data available to support the efficacy of intra-articular therapy with either corticosteroids or hyaluronic acid [15] and their use is not recommended by the 2012 American College of Rheumatology (ACR) guidelines [16]. On the other hand, non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to relieve pain associated with thumb base OA, and topical formulations are recommended over oral NSAIDs in the most recent guidelines, due to a superior safety profile [16-18]. However, their effect on function is small and transitory (no more effective than placebo after 2 weeks) [19].

Combining non-pharmacological and pharmacological modalities in the management of hand OA is recommended by the European League Against Rheumatism (EULAR) guidelines [17], supported by a literature review [8], and is frequently used in clinical practice. Despite this, direct evidence of efficacy of this strategy is lacking. A few trials evaluating combined treatment have been performed, although they have not generally been specific to thumb base OA [20, 21]. Moreover, the combinations investigated usually included exclusively non-pharmacological modalities [22] and to date no strategy has been found to be highly efficacious for improving pain and function for thumb base OA. Determining an evidence-based therapeutic approach with a clinically meaningful effect on clinical outcomes would provide health professionals with a basis for decision-making for treatment of patients with thumb base OA. This strategy does not yet exist, and decisions on the best combination of interventions are usually based on personal experience and personal opinion of health professionals.

Objective

The aim of this study is to determine the effect of a combination of conservative non-pharmacological and pharmacological modalities in the treatment of thumb base OA compared to education control. The intervention group will consist of education about the disease and joint protection techniques, hand exercises, a splint to support the base of the thumb, and topical NSAID. The control group will be provided with education about the disease and joint protection techniques only.

METHODS AND ANALYSIS

Trial design

The COMBO trial is designed as a randomised, controlled, assessor and statistician blinded, parallel, two-arm superiority trial with 1:1 allocation ratio. The trial will be conducted at a single centre in Australia. The interventions will take place from baseline to 6 weeks and follow-up assessments will occur at 2, 6 and 12 weeks (Figure 1). The protocol was designed in accordance with the principles of the Declaration of Helsinki.

Participants

Participants will be recruited from the community and from our research volunteer database composed of participants who have expressed their willingness to be involved in future studies. The recruitment strategies will include advertisements on social media networks and posters/flyers placed on notice boards and waiting room walls of medical practices and community areas. In the first instance, a preliminary screening will occur by phone/internet and for those participants who pass this initial screening, a face-to-face visit will be conducted to confirm their eligibility. All participants will receive verbal and written information about the trial and the blinded assessor will obtain a written informed consent before inclusion.

Inclusion criteria

Participants will be eligible for the study if they meet all the following inclusion criteria [23]: age ≥ 40 years; pain at the base of the thumb at least half of the days in the past month; average pain ≥ 40 on a 100-mm Visual Analogue Scale (VAS), where 0 is no pain and 100 is worst pain imaginable, over the past 30 days and in the 48 hours prior to the screening visit; scores ≥ 6 on the Functional Index for Hand Osteoarthritis (FIHOA, range 0 - 30) [24]; and radiographic evidence of thumb base OA read by a trained

rheumatologist (Kellgren Lawrence grade (KLG) ≥ 2) [25]. The most severely involved hand will be included (as defined by pain VAS) in cases of bilateral symptomatic thumb base OA. If the pain scores are the same for both hands, participants will be asked to nominate the worst hand, which will be included as the index.

Exclusion criteria

Participants will be excluded if they fulfil any of the following criteria: known diagnosis of crystal-related arthritis (e.g. gout, calcium pyrophosphate deposition disease), autoimmune arthritis (e.g. rheumatoid arthritis, psoriatic arthritis), hemochromatosis or fibromyalgia; hand surgery in the last 6 months or planning to undergo surgery in the next 6 months; use of concomitant medications potentially directed at OA, unless at a stable dosage for at least 1 month for analgesics and NSAIDs, or 3 months for slow acting symptomatic or structure modifying drugs (e.g. diacerein, chondroitin sulphate, avocado/soybean unsaponifiables); intra-articular hyaluronic acid injection in the affected joint in the past 6 months; intra-articular steroid injection in the affected joint in the past month; significant injury to the affected joint in the past 6 months; any other self-reported hand condition that is likely to be contributing to the pain at the base of the thumb (e.g. scaphoid fracture, carpal tunnel syndrome, DeQuervain's tendinopathy, trigger thumb, joint infection, diabetic neuropathy, pain referred from the neck, pain following hand or wrist trauma or surgery); poor general health likely to interfere with compliance or assessments, judged by the investigator; known hypersensitivity to diclofenac; current history of advanced renal failure; past or current history of gastrointestinal ulceration, bleeding and/or perforation; women who are pregnant or breastfeeding; current use of any of the study interventions.

Randomisation and allocation concealment

Individuals who consent to take part in the study and fulfil all study criteria will be assigned to either intervention or control group with a 1:1 allocation as per a computer generated randomisation schedule, stratified by OA severity using KLG (2 and 3 vs. 4) using random blocks of size 2, 4 and 6. The allocation sequence will be concealed from the researchers enrolling and assessing participants in sequentially numbered opaque, sealed and stapled envelopes. Aluminium foil inside the envelope will be used to render the envelope impermeable to intense light. Envelopes will be stored in a locked drawer and will be opened by the study coordinator only after the enrolled participant completes all baseline assessments.

The sequence generation will be prepared by a statistician and the envelopes will be prepared by an external investigator. The study blinded assessor will enrol participants and the study therapist (one single physiotherapist with experience in thumb base OA management) will open the envelope in front of the participant and execute the designated intervention.

Blinding

All clinical assessments will be conducted by an assessor blinded to treatment allocation. To reduce the potential for unblinding, participants will be instructed not to disclose any information about the treatment, not to wear the splint during the follow-up assessments, and not to use the topical NSAID just before the visit. The physiotherapist executing and supervising the treatments will not be blinded to the group allocation. The statistician involved in the main statistical analyses will be blinded to group allocation. Group allocation will be immediately unblinded if deemed necessary by the chief investigator in the case of serious adverse events potentially related to the study.

Participants will be naive to the treatments offered to the opposite group and hence blinded to the hypothesis of the study. In order to reduce the risk of bias, participants will be informed about the overall aspects involved in the treatment of both groups (i.e. conservative therapies not involving oral or intra-articular medications) but not told the specific treatments included in each one of them nor about the differences among groups. This procedure aims to minimize differences regarding expectations with the allocated treatment between groups.

Interventions

The intervention group will receive a combination of education about OA and joint protection techniques, a splint to support the base of the thumb, hand exercises and topical NSAID. The control group will receive education about the disease and education about joint protection techniques alone (standard care). All participants will attend two individual, face-to-face treatment sessions with the study physiotherapist of approximately 30 minutes each, at baseline and after two weeks (2-week visit). The 2-week visit aims at checking adherence to the programme while balancing the number of face-to-face visits and contact with the therapist between the control and intervention groups (2 visits for each group).

The intervention will be delivered over 6 weeks. After the 6-week visit, participants will be encouraged by the physiotherapist to continue the treatment throughout the follow-up period (from 6

to 12 weeks) but intervention use will be at the participants' discretion. This period aims to evaluate participant's choice in continuing using the interventions and to assess the outcomes after this period.

Education about OA and joint protection techniques

All participants in this study (both groups) will be provided with education about OA and joint protection techniques through a 9-page educational booklet delivered at baseline (Appendix 1) and through two face-to-face sessions with the study therapist at baseline and at the 2-week visit. Information about the disease will include: anatomy of the first carpometacarpal (CMC) joint, using the Acland's video atlas of human anatomy (Carpometacarpal joint of thumb) [26], diagnosis, disease course, objectives of treatment, self-management, and instruction on joint protection techniques and assistive devices. The booklet used in this study was adapted from an online resource produced by the hand therapy unit of James Cook University Hospital, United Kingdom [27]. Written permission was obtained to use the adapted version. The physiotherapist will have a script to follow to maintain consistency with all participants regarding the joint protection advice.

Splint

While favourable results have been observed with different types of splints, prefabricated types are preferred over the custom-made version by most patients [13]. Moreover, different ways of using the splint have been studied. A systematic review of design and effects of splints identified two trials with low risk of bias in which best results were achieved with the use of splints during daily activities [14, 28]. Therefore, a prefabricated neoprene splint (Comfort Cool® Thumb CMC Restriction Splint) will be used in this study. This splint is readily commercially available, facilitating potential dissemination post study. The splint incorporates the base of the thumb and wrist and participants will receive recommendation to use it during activities of daily living (minimum of 4 hours/day) for 6 weeks (Figure 2). The splint will be removed during rest, sleep, exercises and bathing.

Hand exercises

The exercise programme will be the same for all participants in the intervention group and will consist of five exercises: thumb opposition, paper tearing, line tracing on ball, using chopsticks to pick up objects and squeezing a ball. The aim of the exercise programme will be to optimize range of motion (thumb opposition and line tracing on ball), to improve neuromuscular control of the alignment of the thumb and muscular endurance (paper tearing and squeezing a ball), and to train proprioception of the

thumb base joint (all 5 exercises). Specific attention will be drawn to performing the exercises in a way which prevents collapse (hyperextension) of the first metacarpophalangeal (MCP) joint while maintaining the web space (abduction). These exercises are based on recent evidence which emphasizes the importance of proprioceptive exercises and strengthening for the 1st dorsal interosseous muscles [29, 30], whilst aiming to be functional and similar to movements used for daily tasks. The exercise programme will be visually depicted using images from a website developed by physiotherapists from the New South Wales Department of Health, Sydney, Australia (Appendix 2) [31]. Consent was obtained to include the images into a written instruction to participants in the intervention group.

Participants will receive instructions on how to perform the exercises correctly during their supervised one-on-one session with the study physiotherapist at baseline. They will be further instructed to perform individual unsupervised at-home sessions, three times per week, from baseline to the 6-week visit, and adjustment to the programme will be checked at the 2-week visit. Each exercise should be repeated 10 times during the first week. The muscular endurance exercises (paper tearing and squeezing a ball) will be progressed by increasing the difficulty of the tasks (i.e. tearing a thicker paper and squeezing the ball harder, respectively). For the remaining exercises, the number of repetitions will be increased, aiming for 12 repetitions during the second week and 15 repetitions for the following 4 weeks, if tolerated, as judged by the patient.

Topical NSAID

The intervention group will receive *Diclofenac diethylammonium* gel (11.6 mg/g), a topical NSAID commonly used in clinical practice that has been studied in large, good quality trials with superiority over placebo [18]. Participants will be instructed to use the medication three times per day for 6 weeks on a daily basis. In order to standardize the amount used, participants will receive a small spatula with a permanent pen mark showing exactly how much product they should use. The advised amount corresponds with approximately 200 mg to be applied in an area of 40 cm^2, as recommended by the dosage guidelines.

Outcomes

Outcome measures used in this study are validated instruments that were promoted in recent recommendations for clinical trials for hand OA [23]. The primary outcomes are change in pain scores at the base of the thumb, assessed by VAS (0-100 mm), and change in hand function, assessed by FIHOA (0-30) from baseline to 6 weeks. The FIHOA tool is composed of 10 items scored using a semi-quantitative

4-point scale. It is a self-reported questionnaire evaluating the functional performance of 10 distinct activities involving the hand that has demonstrated good measurement properties including reliability, feasibility and sensitivity to change [32].

Secondary outcomes are change in pain scores at the base of thumb, assessed by VAS, and in hand function assessed by FIHOA from baseline to 2 and 12 weeks as well as the following outcomes assessed from baseline to 2, 6 and 12 weeks: change in grip strength (Jamar hand dynamometer (in kg)) and tip pinch strength (B&L pinch gauge (in kg)), assessed with participants with feet flat on the ground and elbow flexed at 90 degrees; change in patient global disease assessment, assessed in response to the question " Considering all the ways your thumb arthritis affects you, how have you been during the last 48 hours?" (on a VAS (0-100 mm, where 0 is very well and 100 is the very poor)); change in duration of thumb base stiffness, assessed by the question "What is the duration of stiffness at the base of your thumb in the morning?" (expressed in minutes); change in health related quality of life assessed by the Assessment of Quality of Life – 4D instrument (AqoL-4D), a 12-item tool with good validity and reliability [33], including questions related to independent living, mental health, relationship and senses, and scored from -0.04 to 1.00, with 1.00 indicating full health [34]; use of rescue medications for pain at the base of the thumb (Paracetamol, up to 3000 mg per day), assessed by inspection of participant's diary; change in presence of swelling and tenderness, assessed by joint examination (scored as present or absent); participant's global rating of change for pain, function and overall change, assessed by the question "Which option best represents the change in pain/ change in function/overall change in your thumb since you began the study?", scored using a 5-point Likert scale ranging from much better to much worse; percentage of treatment responders at 6 and 12 weeks according to the OMERACT-OARSI criteria; and change in impairments in work and other activities, assessed by the Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH), consisted of 6 questions related to impairments in both work and daily activities over the past 7 days, which has been used in patients with rheumatoid arthritis and other rheumatic diseases [35-37].

As tertiary/correlative outcomes, the participants will be required to fill out the credibility/expectancy questionnaire at baseline in order to assess expectation related to the assigned treatment [38]. The questionnaire is composed of 6 questions and higher scores demonstrated higher expectation/credibility. In addition, range of motion of the first MCP joint will be measured with a goniometer and presence of first MCP joint collapse pattern on pinch will be recorded at baseline.

Procedures

An outline of the protocol visits and procedures is provided in Table 1.

Table 1. Schedule of study's events.

	Screening Visit	Baseline Visit	2-week visit	6-week visit	12-week visit
Informed consent	X				
Demographics	X				
Medical history	X				
Medication form	X				
Co-morbidity assessment	X				
VAS for pain	X	X	X	X	X
FIHOA	X	X	X	X	X
Assessment of stiffness		X	X	X	X
Patient global assessment		X	X	X	X
Aqol-4D		X	X	X	X
Use of rescue medication			X	X	X
Joint examination		X	X	X	X
Grip and pinch strength		X	X	X	X
WPAI-GH		X	X	X	X
Global rating of change				X	X
First MCP joint assessment		X			
Treatment expectation		X			
Treatment adherence			X	X	X
Clinical safety assessment					
Blood pressure		X	X	X	X
Adverse events			X	X	X

Radiology/Imaging					
PA view radiograph	X				
Eaton stress view radiograph	X				
Hand ultrasonography		X			

VAS = Visual Analogue Scale; FIHOA = Functional Index for Hand Osteoarthritis; AqoL-4D = Assessment of Quality of Life – 4D.

Screening visit

After an initial screening phone call, potential participants will attend a screening visit that will consist of collection of demographic data such as: age, date of birth, gender, ethnicity, financial status, marital status, symptom duration, current or past activities involving intensive use of the hands (e.g. sports, gardening, playing specific musical instruments), previous and concomitant therapies, height, weight, years of formal education, primary occupation, comorbidities, menopausal status in women, and OA at other joints (such as knee or hip). The key inclusion/exclusion criteria will be assessed to confirm the participant's eligibility. Participants will be allowed to continue using current pain medications provided the dose has been stable at study entry as per exclusion criteria. They will be permitted to use Paracetamol (maximum 3000 mg per day) as rescue medication for any symptom exacerbation.

Radiographic assessment

All potential participants will be referred for a postero-anterior (PA) view and an Eaton stress view radiograph of both hands. The protocol for acquisition of the Eaton stress view is presented in Appendix 3 and is based on a previous paper describing this technique [39]. The PA view will be used to assess eligibility and thumb base OA severity using KLG, in addition to radiographic severity using both the Osteoarthritis Research Society International (OARSI) atlas [40] and the Eaton classification criteria [41]. The degree of subluxation of the first CMC joint will be assessed on the Eaton stress view [39].

Baseline Assessment

At the baseline visit, an ultrasound of the first CMC joint will be performed by a physiatrist with experience in musculoskeletal ultrasound, in order to assess presence of synovitis and other structural features including osteophytes, cartilage damage, erosions and stability of the first CMC joint. The

protocol for the ultrasound assessment is detailed in Appendix 4. Assessment of tenderness and swelling on physical examination by the blinded assessor will be first calibrated with the study's rheumatologist and inter-rater reliability will be assessed later in the study.

After the assessment, the blinded assessor will introduce the physiotherapist to the participant and leave the assessment room. At the end of the visit the physiotherapist will deliver an envelope containing the credibility/expectancy questionnaire to assess the treatment expectation [38]. The participant will be instructed to place the completed questionnaire back into the envelope and to seal it. The envelopes will not be opened until the study is complete.

2, 6 and 12-week visits

The outcome measures will be reassessed at the 2, 6 and 12-week visits by the blinded assessor. At the end of each visit the study physiotherapist will record adverse events, use of rescue medication and treatment adherence from the participant diaries (see below). The physiotherapist will also ensure the correct performance of exercises by participants in the intervention group. Participants' global rating of change for pain, function and overall change will be concealed from the physiotherapist until the study is complete.

Treatment adherence

To monitor adherence to the treatments, participants from the intervention group will receive a diary and will be asked to record the hours of splint use and the use of topical NSAIDs on a daily basis. In addition, participants will be requested to report which exercises were performed and the frequency of these on a weekly basis. Adherence will be monitored using the diary from week 6 to 12, to assess whether participants continued the intervention following the 6-week visit. Control participants will also be provided with the diaries as all participants will be asked to record the use of rescue medication. Participants in the intervention group will be asked to record any adverse events relating to exercises, splint wear or use of topical NSAID in their diary.

Participant Safety and Withdrawal

Risk Management and Safety

Adverse events will be assessed by inspection of participants' diaries at 2, 6 and 12 weeks after intervention commencement. The risks for participants involved in this study are minimal. Topical

NSAIDs have demonstrated a good safety profile and good tolerability, with no higher gastrointestinal, cardiovascular, renal and hepatic adverse events than placebo [18]. Nevertheless, due to theoretical concerns related to the use of NSAIDs, adverse events will be monitored. To ensure the safety of participants, blood pressure will be monitored and systemic symptoms (new or worsening of previous symptoms) will be assessed at 2, 6 and 12 weeks after study commencement. Symptoms suspected to be related to the topical NSAIDs will be assessed by a physician involved in the study and, if necessary, the medication will be discontinued and further medical evaluation will be arranged. Local skin dermatitis may occur; however, these will most likely be minor local skin reactions. Participants who have local adverse reactions will cease the topical medication and will be followed to certify resolution of their rash. The same procedure will be applied if participants report local adverse skin reactions associated with the splint use. All adverse events will be reported.

Participants currently taking warfarin that are allocated to the intervention group will be required to consult their treating physician during the study due to the potential interaction between this drug and NSAIDs. Participants will be exposed to a small amount of radiation (0.001mSV) for the acquisition of the radiograph, which is much lower than the annual average radiation dose (around 2mSV) [42].

Handling of Withdrawals

If a participant withdraws from the study, they will have their reasons for withdrawal recorded and any information provided or recorded up to the point of withdrawal will be kept in accordance with the data security and handling protocol of this study (see below). Strategies to maximize follow-up and prevent missing data will be used, including adhering to the assessment schedule in the event of participant withdrawal. In the event that the participant is unable to attend a study visit, the questionnaires will be administered over the phone. Participants who withdraw from the study will not be replaced.

Statistical Methods

Sample size estimation and justification

The two primary outcome measures (VAS and FIHOA) were used to estimate the sample size. For the FIHOA, the minimal clinically important difference (MCID) is not known, thus the calculation was based on detecting a mean difference of 3 points (defined arbitrarily) on the FIHOA (range 0 - 30). The standard deviation (SD) used was based on the baseline scores presented in the FIHOA's validation study

(SD 6.2) [43]. For pain intensity, the calculation was based on detecting a MCID of 20 mm on a 100mm VAS, assuming a SD of 20 mm as was used in a previous study [44]. The two primary outcomes are correlated (r=0.49) [24], hence an alpha of 0.027 was used as the level of significance for both outcomes which preserves an overall 5% level of significance. To achieve a sample power of at least 80% for both outcomes, a sample size of 81 individuals per group will be required. To accommodate expected dropouts of 20% before study completion, we aim to include 102 participants in each group.

Statistical analysis

Data will be analysed according to the intention-to-treat principle. Demographic characteristics and baseline scores will be presented to assess comparability of treatment groups at baseline. Participants' characteristics will be described using mean and SD for continuous variables or medians (quartiles) if the distribution is skewed. Counts with percentages will be presented for categorical variables.

For continuous outcomes, the mean scores (SD) will be presented at each time-point by treatment group. The between-group difference in mean change from baseline with 95% confidence interval will be presented for all primary and secondary outcomes and compared using independent t-test or the Wilcoxon rank-sum test as appropriate. Categorical outcomes will be examined by $\chi 2$ test or Fisher's exact test, if expected cell counts are small. Analysis adjusted for baseline score and other relevant demographic and clinical characteristics will also be performed using analysis of covariance models fitted separately at 2, 6 and 12 weeks for all outcomes with the change from baseline as the dependent variable. Furthermore, standardized mean differences (95% CI) will be computed as the adjusted between-group difference in scores divided by the pooled SD of the baseline scores.

In addition, outcomes will be analysed on a categorical basis. The basis for categorization will be the participant's score on the perceived ratings of change (participants reporting feeling much better and slightly better will be considered to have undergone meaningful change), and the OMERACT-OARSI criteria [45]. Logistic regression models adjusted for age, gender, BMI and KLG will be used to compare response between treatment groups. The OMERACT-OARSI criteria for a meaningful change (improvement) are one of the following:

1) High improvement:

- ≥ 50% improvement + absolute change of ≥ 20 in self-reported pain intensity (VAS, 0 – 100mm), OR
- ≥ 50% improvement + absolute change of ≥ 6 in self-reported hand function (FIHOA, 0 – 30);

OR

2) Improvement in at least 2 of the 3 following:

- ≥ 20% improvement + absolute change ≥ 10 in self-reported pain intensity (VAS, 0 – 100mm)
- ≥ 20% improvement + absolute change ≥ 10 in Patient Global Assessment of disease activity (VAS, 0 – 100mm)
- ≥ 20% improvement + absolute change ≥ 3 in self-reported hand function (FIHOA, 0 – 30).

Post-hoc subgroup analyses will be performed examining whether there is heterogeneity in treatment effect according to presence of the following: concomitant symptomatic interphalangeal joint OA, presence of erosive hand OA (defined based on radiographic score), presence of CMC joint subluxation (assessed by the ratio of the radial subluxation of the base of the first metacarpal to the total articular width of the first metacarpal, on the Eaton stress view radiograph [39]), and by baseline OA severity according to KLG.

DATA SECURITY & HANDLING

Study data will be collected and managed using Research Electronic Data Capture (REDCap) tool hosted at the University of Sydney. This tool is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Back-up re-identified information will be kept in password protected electronic files. These files will be saved into an external hard drive that will be stored in a locked cabinet at the Principal Investigator's office. The privacy, security and ownership of the research data will be maintained and will not be stored or accessible by another organization.

The archiving period for clinical research records will be 15 years. After this period, the electronic files will be deleted and paper forms will be destroyed. No information which could lead to the identification of a participant will be included in the dissemination of results.

ETHICS AND DISSEMINATION

This protocol was approved by the local ethics committee (HREC/15/HAWKE/479). Any protocol modification will be sent to review by the research ethics committee and will be amended at the trial registry. Dissemination is planned to occur through presentations at international conferences and

publication in peer-reviewed journals.

AUTHORS' CONTRIBUTION

LAD, DJH, AW, KLB, BV, PH, EAR, JPE, RJ and SRFM contributed to study conception and design. VD, ROC and WMO contributed to study design. DJH, KLB, BV and PH attained project funding. LAD drafted the first version of the manuscript. ROC will have access to the final trial dataset and perform the statistical analysis. All authors revised the protocol critically for important intellectual content and read and approved the final version of the protocol. All authors agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

DJH is a consultant to Flexion, Nestle and Merck Serono.

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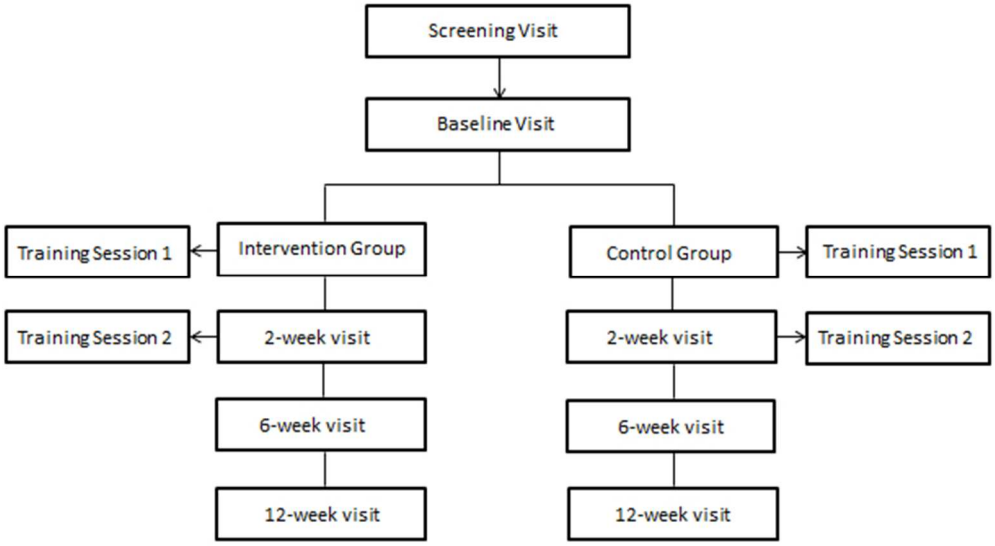
Figure legends

Figure 1. Trial design and visits.

Figure 2. Comfort Cool® Thumb CMC Restriction Splint.



Trial design and visits.

129x77mm (120 x 120 DPI)

Comfort Cool® Thumb CMC Restriction Splint.

73x53mm (120 x 120 DPI)

Appendix 1. Participant's booklet.

Osteoarthritis of the Carpometacarpal Thumb Joint

Patient Information Booklet

Study Coordinator: Sarah Meneses
sarah.meneses@sydney.edu.au
(02) 9463 1855

For more information about osteoarthritis,
visit www.myjointpain.com.au

Version 1 - 21/04/16

Osteoarthritis of the carpometacarpal thumb joint

This booklet has been written to provide you with information about your thumb arthritis and give you a better understanding of your thumb joint, why you experience pain, and how you can manage your symptoms.

It contains information about:

- Anatomy of the thumb carpometacarpal joint
- Osteoarthritis of the thumb carpometacarpal joint
- Joint protection
- Assistive devices
- Heat and cold
- Pain relief

Anatomy of the carpometacarpal thumb joint

The thumb carpometacarpal (CMC) joint is where the metacarpal bone of the thumb attaches to the trapezium (carpal) bone of the wrist (see diagram on the following page).

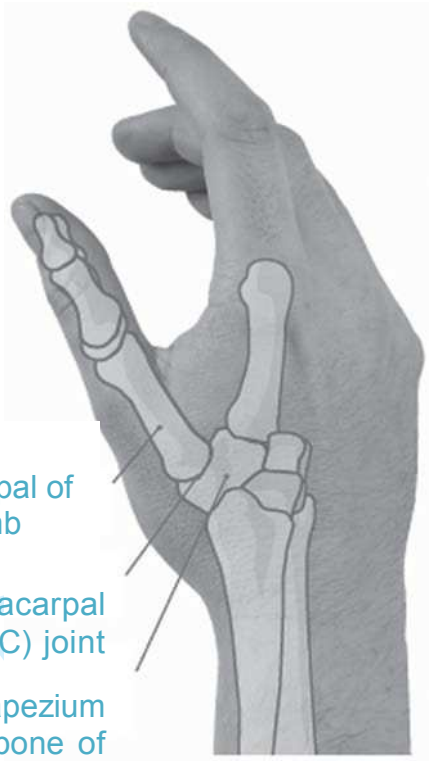
What is OA?

Osteoarthritis (OA) is the most common form of arthritis and affects mainly the joint's cartilage and surrounding bone tissue.

There are many factors that can increase the risk of the developing OA; for example it is more common in females over the age of forty, and is more likely to develop in a joint that has had a previous injury or operation.

A joint is where two bones meet to allow movement. Muscles pull on tendons, which are attached to the bone to produce movement.

CMC joint arthritis



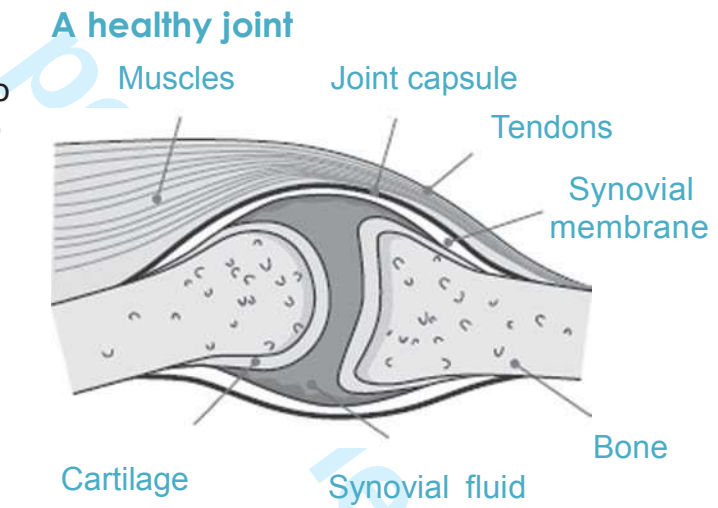
The ends of the bones are covered in a smooth tissue called cartilage that cushions the joint. There is a space between the two ends of bone making up the joint.

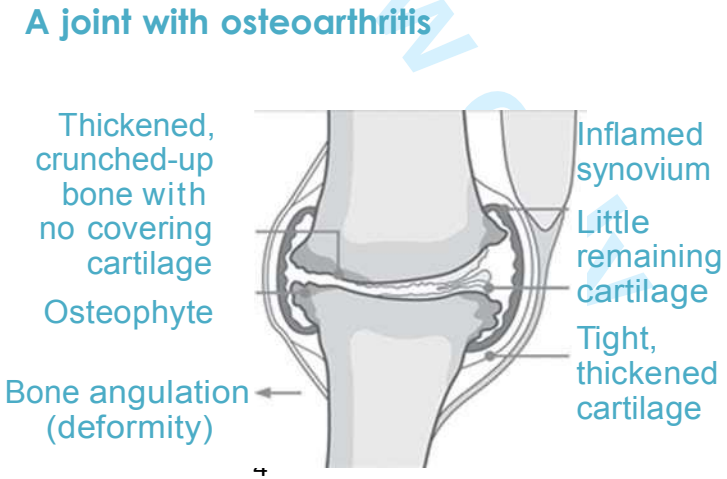
The joint is held together within a joint capsule, which contains a thick fluid (synovial fluid) providing lubrication to allow smooth movement. Surrounding ligaments and muscles also maintain the stability of the joint.

When OA develops in a joint, the cartilage gradually roughens and becomes thin, and the bone underneath thickens. The bones at the edge of the joint grow outwards in bony 'spurs' (see diagrams) and excess synovial fluid can be produced, causing the joint to swell.

This can mean that you avoid using these joints, subsequently causing the surrounding muscles to weaken.

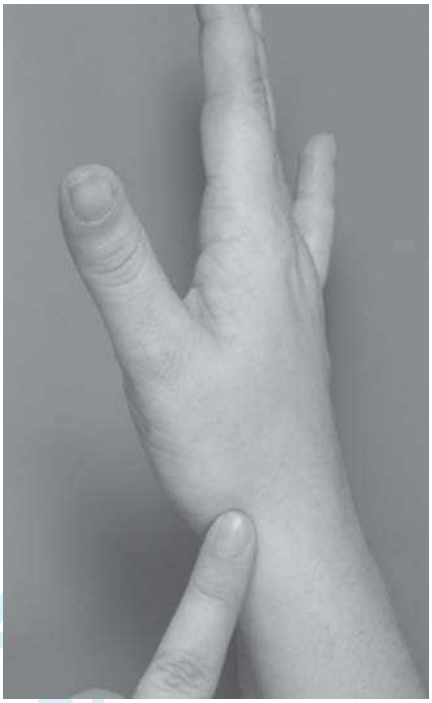
In severe OA, the cartilage can become so thin that it no longer covers the joint surfaces, and damage is caused to the bone ends by them grinding against each other during movement. This can, over time, change the shape of the joint creating a deformity, as the joint is no longer held in its natural position.





Common symptoms of CMC OA

Pain: Usually felt as a sharp or aching pain at the base of the thumb. The pain is usually worse during movement and relieved by rest.



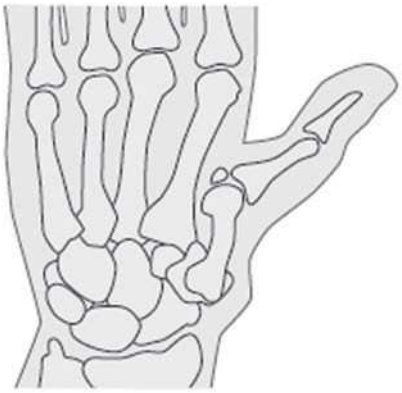
Reduced grip strength: It may be difficult to grip or pick up objects.

Stiffness: Following periods of rest (eg in mornings).

Swelling: Around the base of the thumb.

Muscle Weakness and Instability

Deformity: In the later stages of the condition the thumb joint may collapse inwards into a subluxed position (see diagram).



The joint protection techniques and the use of assistive devices (as described in this booklet) can help to relieve these symptoms and slow the progression of this condition.

Joint protection

Most people find their own ways of doing activities that are less painful. It is important that you are aware of the activities that cause your thumb joint to be painful so that you can consider other ways to perform these activities that place less strain on the painful joints.

Each time you experience thumb pain when doing an activity, stop and consider whether the way you are doing it is causing stress on the joint. Think about if there is another way the activity can be performed that is better for your joints.

For example:

- When doing activities that involve a pinch grip (eg writing) keep the top joint of the thumb bent and the wrist extended.
- When doing activities that involve turning or twisting avoid fully straightening the top joint of the thumb and the thumb crossing in front of the palm.

The following are joint protection techniques that may help to reduce the pain you experience when doing activities and prevent further damage to the joints:

- Take notice of any pain you feel, it can serve as a warning that the way you are performing the activity is causing damage to the joint.
- Spread the load over several joints (eg by carrying items on two flat hands rather than gripping with your thumb).
- Use larger stronger joints rather than putting the strain through your thumb joints.
- Use less effort (eg push or slide heavy items rather than carrying).

Examples of joint protection techniques

Instead of this ...

... try this

Instead of this (holding a pile of papers with one hand) ...

... try this (holding it with two hands)

Hug large objects close to your body

'Shift not lift' - slide a plastic jug of water to the kettle - only use as much water as you need

Assistive devices

There are a variety of small aids that are available to assist you in maintaining your independence completing daily activities.

For example:

Jar twisters: Jar twisters to help you open tight jars.

Wide grip cutlery: Wide grip cutlery if you find it difficult or painful to hold cutlery.

Pen grips: Pen grips to support your grip or writing.

Tap turners: Attach onto your taps to make them easier to turn on and off.

Key turners: Key turners if you have difficulty turning key in door.

Plug pulls: Assists grip if you have difficulty removing plugs.

An occupational therapist (OT) can discuss specific activities that you are finding difficult or painful and advise you whether any assistive devices are available to help.

Heat and cold

Applying heat, such as a hot pack (microwaveable wheat pack), heating pad or hot water bottle to stiff, painful joints may help relieve these symptoms. If your joints are hot and swollen you may find it useful to apply an ice pack.

Try applying heat or cold to the painful area for 15 minutes. Always have a layer (such as a tea towel) between your skin and the heat or ice pack. You can repeat this whenever you need to throughout the day. Make sure the temperature of the skin returns to normal in between applying heat or ice packs to prevent damage to the tissues.

Pain relief

Some people find that paracetamol or anti-inflammatory medications (such as aspirin and ibuprofen) can help to reduce the pain experienced.

This should always be discussed with your GP or consultant as they will be able to recommend what type of pain relief and what dose is appropriate for you, depending upon any other medical conditions you have.

Acknowledgments

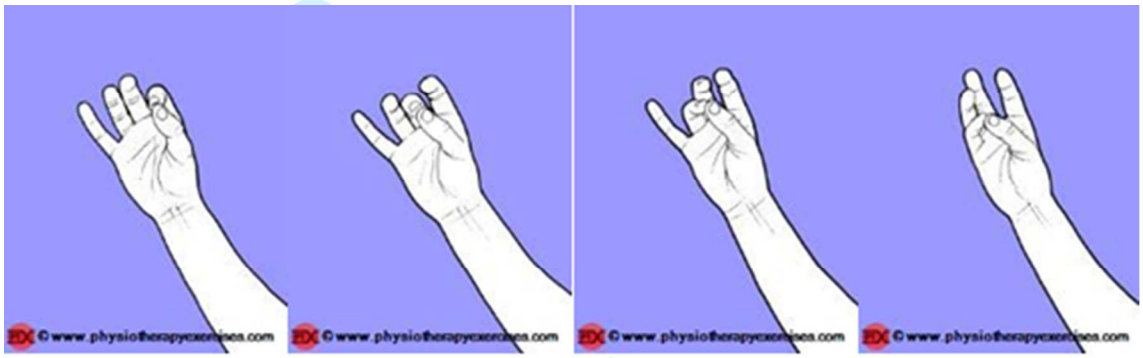
This booklet has been adapted with permission from the Hand Therapy Unit at James Cook University Hospital.

Appendix 2. Written instructions on how to perform the exercises provided to participants in the intervention group.

Week 1

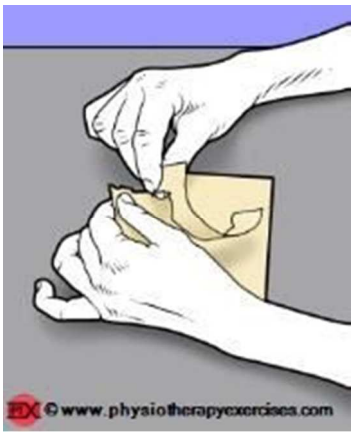
Perform the following exercises as taught by your therapist three days a week. Exercises should not aggravate the pain. You should stop short of aggravating pain.

1. Thumb Opposition



Position yourself with your hand resting in front of you. Practice touching the tip of your thumb to the tip of your index finger, then to the tip of your middle finger and then to the tip of your ring finger. If pain free, you can aim to touch the tip of your thumb to the tip of your little finger.
Repeat this movement 10 times.

2. Tearing paper

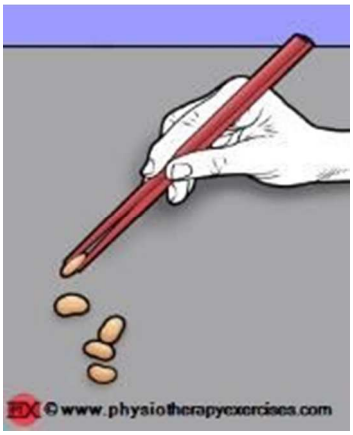


Position yourself with a piece of paper in front of you. Tear the paper.
Repeat 10 times.

3. Tracing line on ball

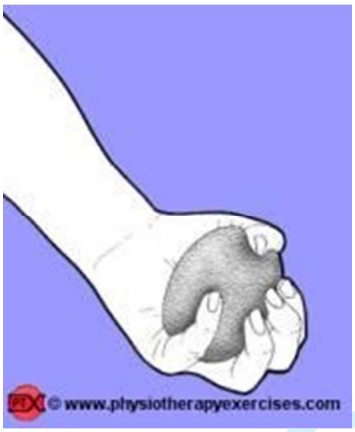
Position yourself with your hand resting on the ball in front of you. Slide your thumb along the line of the ball, while moving the ball with your finger tips.
Trace the line on the ball 10 times.

4. Using chopsticks



Position yourself with the chopsticks in your hand. Use the chopsticks to pick up a bean and place into the container.
Repeat 10 times.

5. Squeezing ball

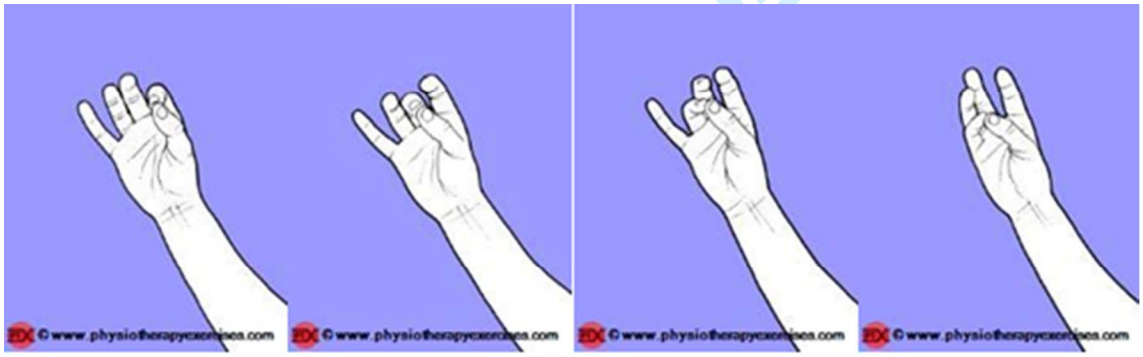


Position yourself sitting with a stress ball held in your hand. Practice squeezing the ball until it is about a third compressed.
Repeat 10 times.

Week 2

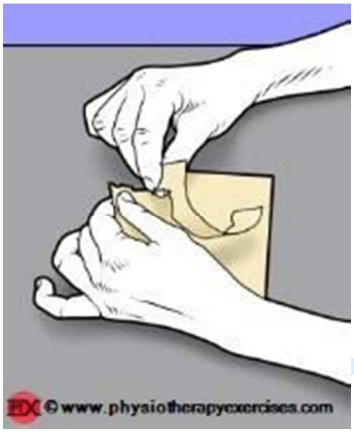
Perform the following exercises as taught by your therapist three days a week. Exercises should not aggravate the pain. You should stop short of aggravating pain.

1. Thumb Opposition



Position yourself with your hand resting in front of you. Practice touching the tip of your thumb to the tip of your index finger, then to the tip of your middle finger and then to the tip of your ring finger. If pain free, you can aim to touch the tip of your thumb to the tip of your little finger.
Repeat this movement 12 times.

2. Tearing paper



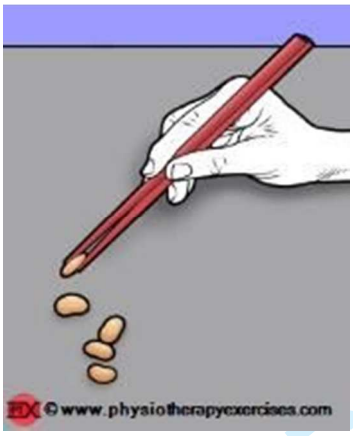
Position yourself with a piece of paper in front of you. Fold the paper in half and tear the paper.

Repeat 10 times.

3. Tracing line on ball

Position yourself with your hand resting on the ball in front of you. Slide your thumb along the line of the ball, while moving the ball with your finger tips.
Trace the line on the ball 12 times.

4. Using chopsticks



Position yourself with the chopsticks in your hand. Use the chopsticks to pick up a bean and place into the container.
Repeat 12 times.

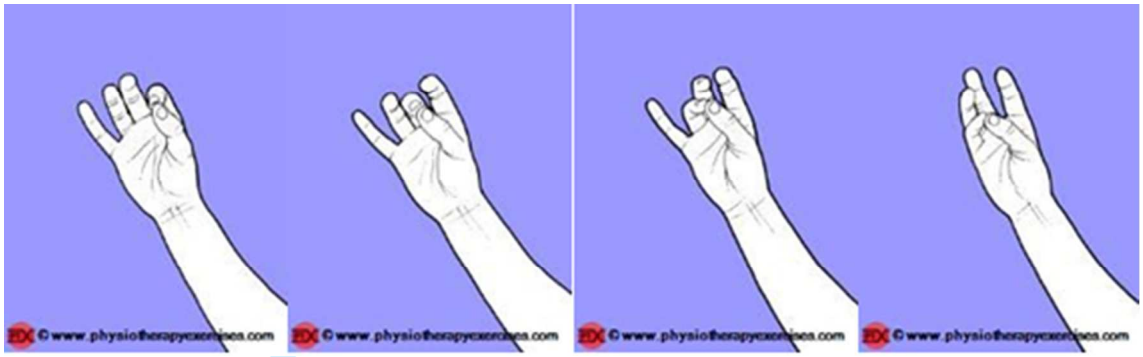
5. Squeezing ball

Position yourself sitting with a stress ball held in your hand. Practice squeezing the ball until it is about half compressed.
Repeat 10 times.

Week 3 to 6

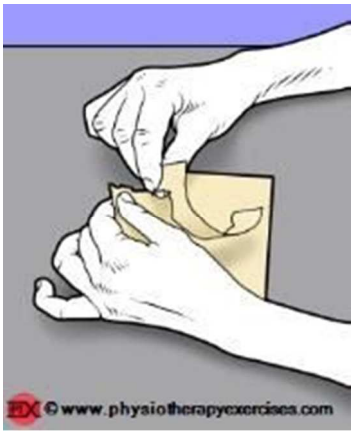
Perform the following exercises as taught by your therapist three days a week. Exercises should not aggravate the pain. You should stop short of aggravating pain.

1. Thumb Opposition



Position yourself with your hand resting in front of you. Practice touching the tip of your thumb to the tip of your index finger, then to the tip of your middle finger and then to the tip of your ring finger. If pain free, you can aim to touch the tip of your thumb to the tip of your little finger.
Repeat this movement 15 times.

2. Tearing paper



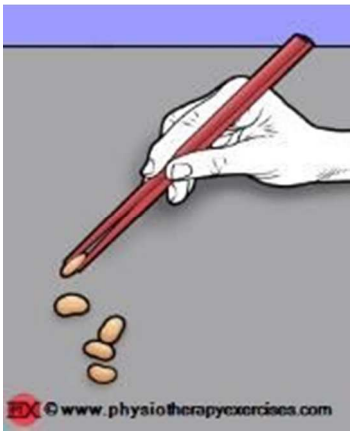
Position yourself with a piece of paper in front of you. Fold the paper into quarters. Tear the paper.

Repeat 10 times.

3. Tracing line on ball

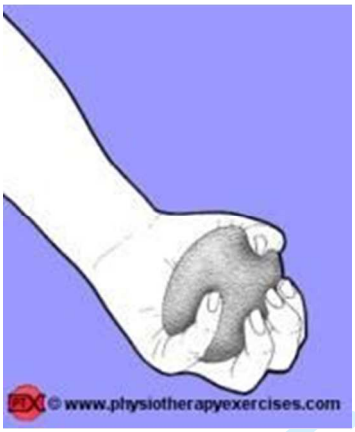
Position yourself with your hand resting on the ball in front of you. Slide your thumb along the line of the ball, while moving the ball with your finger tips.
Trace the line on the ball 15 times.

4. Using chopsticks



Position yourself with the chopsticks in your hand. Use the chopsticks to pick up a bean and place into the container.
Repeat 15 times.

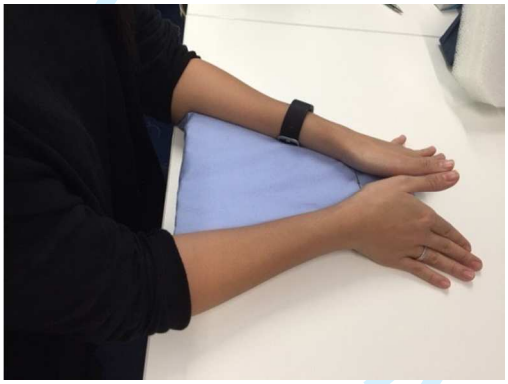
5. Squeezing ball



Position yourself sitting with a stress ball held in your hand. Practice squeezing the ball until it is about three-quarters compressed. Repeat 10 times.

Appendix 3. Technique for the acquisition of the Eaton stress view radiograph.

The radiographs will be obtained in the PA projection with the hand and stress view of the trapeziometacarpal joint placed over an X-ray cassette (the volar aspect of the hand touching the cassette), with the forearms held about 10 cm apart and pronated approximately 45° in neutral deviation. The participants will be instructed to place the thumbs parallel (nails symmetric without tilt) and to actively press them together (inwards and down) with the metacarpophalangeal (MCP) and interphalangeal (IP) joints touching. The wrists are held in neutral alignment and the elbows flexed to 90° bilaterally with the subject seated. The top of the foam piece is placed under both thumbs and the rest of the foam is used to keep the forearms apart as shown in the images provided in this Appendix. The study coordinator will provide this protocol to the radiographer and assure that the technique is being correctly executed.



Appendix 4. Ultrasound scanning protocol.

Lateral longitudinal scans on both the radio-dorsal and radio-palmar side of the first CMC joint will be used to assess inflammatory and structural ultrasonographic findings (i.e. synovitis, Power Doppler signal, osteophytes, articular cartilage damage, joint space narrowing, and bone erosion). Dichotomous grading scales will be used to score all features, in addition to semi-quantitative grading scales for synovitis, Power Doppler signal, and osteophytes. The OMERACT US group has shown the reliability of these scales [1, 2]. In addition, joint space narrowing will be assessed using a quantitative scale, measured in mm, as the distance from the edge of trapezium to the edge of first metacarpal.

In addition, we will examine the ability of high-resolution ultrasonography to delineate morphological characteristics of anterior oblique ligament and radio-dorsal ligaments, the main stabilizing ligaments of this joint.

Subluxation of the first CMC joint is not an uncommon finding in OA due to specific ligament instability, as the anterior oblique ligament plays an important role in preventing volar metacarpal subluxation. The role of dynamic ultrasonographic stress test in detecting the instability of first CMC joint will be assessed. To replicate a clinical test used to detect anterior oblique ligament insufficiency [3], the joint will be held in palmar abduction position, and maximal volarly directed stress will be applied to the base of the first metacarpal, as the methods described to test the stability of this ligament in normal healthy joints [4].

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3. Takwale VJ, Stanley JK, Shahane SA. Post-traumatic instability of the trapeziometacarpal joint

of the thumb: diagnosis and the results of reconstruction of the beak ligament. J Bone Joint Surg Br 2004; 86:541–545.

4. Chiavaras, M.M., et al., Sonography of the anterior oblique ligament of the trapeziometacarpal joint: a study of cadavers and asymptomatic volunteers. AJR Am J Roentgenol, 2010. 195(6): p. W428-34.

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

Section/item	Item No	Description	Addressed on page number
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	____yes_____
Protocol version	3	Date and version identifier	____N/A_____
Funding	4	Sources and types of financial, material, and other support	____17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1_____
	5b	Name and contact information for the trial sponsor	____N/A_____
	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	____17_____
	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	3,4
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	4
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)	4
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	5
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)	5,6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8,9
	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)	14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10,11
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	9,10
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 Figure)	11,12

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	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6,7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	9,10,12
	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	14

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	16
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	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15,16
	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)	15
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	13,14
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	16
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)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____5_____
	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	_____16_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17_____
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	____16_____
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	____16_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___16,17_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____yes_____
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_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of combined conservative therapies on clinical outcomes in patients with thumb base osteoarthritis: protocol for a randomised, controlled trial (COMBO)

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Complete List of Authors:	Deveza, Leticia; University of Sydney, Royal North Shore Hospital, Rheumatology Department Hunter, David; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department Wajon, Anne; Macquarie University Clinic, Macquarie Hand Therapy, Macquarie University, New South Wales, Australia Bennell, Kim; University of Melbourne, CHESM Vicenzino, Bill; The University of Queensland, Physiotherapy Hodges, Paul; School of Health and Rehabilitation Sciences: Physiotherapy, The University of Queensland Eyles, Jillian; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department Jongs, Ray; Royal North Shore Hospital, Physiotherapy Department Riordan, Edward; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department Duong, Vicky; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department Oo, Win; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department O'Connell, Rachel; National Health and Medical Research Council (NHMRC) Clinical Trial Centre, University of Sydney Meneses, Sarah; Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Evidence based practice, Medical management
Keywords:	osteoarthritis, thumb, Clinical trials < THERAPEUTICS, conservative

Efficacy of combined conservative therapies on clinical outcomes in patients with thumb base osteoarthritis: protocol for a randomised, controlled trial (COMBO)

Leticia A Deveza[1], David J Hunter[1], Anne Wajon[2], Kim L Bennell[3], Bill Vicenzino[4], Paul Hodges[4], Jillian P Eyles[1], Ray Jongs[5], Edward A Riordan[1], Vicky Duong[1], Win Min Oo[1], Rachel O'Connell[6], Sarah R F Meneses[1]

Affiliations

1. Rheumatology Department, Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, New South Wales, Australia.

2. Macquarie University Clinic, Macquarie Hand Therapy, Macquarie University, New South Wales, Australia.

3. Centre for Health, Exercise and Sports Medicine, Department of Physiotherapy, School of Health Sciences, The University of Melbourne, Melbourne, Victoria, Australia.

4. School of Health and Rehabilitation Sciences: Physiotherapy, The University of Queensland, Brisbane, St. Lucia, Australia.

5. Physiotherapy Department, Royal North Shore Hospital, Sydney, New South Wales, Australia.

6. National Health and Medical Research Council (NHMRC) Clinical Trial Centre, University of Sydney, Sydney, New South Wales, Australia.

Corresponding author

Dr Leticia A Deveza at Rheumatology Department, Royal North Shore Hospital - Reserve Road, St. Leonards, NSW 2065, Australia. Email: leticia.alle@sydney.edu.au Phone: 61 2 9463 1775

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ABSTRACT

Introduction: Management of thumb base osteoarthritis (OA) using a combination of therapies is common in clinical practice, however evidence for the efficacy of this approach is lacking. The aim of this study is to determine the effect of a combination of conservative therapies for the treatment of thumb base OA compared to an education control group.

Methods and analysis: This is a randomised, controlled, single centre, two-arm superiority trial with 1:1 allocation ratio; with assessor and statistician blinded. Participants are blinded to the trial's hypothesis and to the interventions received by the opposite group. A total of 204 participants will be recruited from the community and randomised using a computer generated schedule. The intervention group will receive education for joint protection and OA, a splint for the base of the thumb, hand exercises, and topical diclofenac sodium 1% gel over 6 weeks. The control group will receive education for joint protection and OA alone. Main inclusion criteria are pain ≥ 40 mm (VAS, 0-100) at the base of the thumb, impairment in hand function ≥ 6 (FIHOA , 0-30) and radiographic thumb base OA (KLG ≥ 2). Participants currently receiving any of the intervention components will be excluded. Outcomes will be measured at 2, 6 and 12 weeks. The primary outcome is change in pain and hand function from baseline to 6 weeks. Other outcomes include changes in grip and pinch strength, quality of life, presence of joint swelling and tenderness, duration of joint stiffness, patient's global assessment and use of rescue medication. Analysis will be performed according to the intention-to-treat principle. Adverse events will be monitored throughout the study.

Ethics and dissemination: This protocol is approved by the local ethics committee (HREC/15/HAWKE/479). Dissemination will occur through presentations at international conferences and publication in peer-reviewed journals.

Trial registration details: ACTRN12616000353493.

Keywords: Osteoarthritis, thumb, conservative, clinical trial

STRENGHTS AND LIMITATIONS OF THE STUDY

- There is currently no highly efficacious strategy for managing thumb base osteoarthritis (OA). A combination of non-pharmacological and pharmacological modalities is frequently used in practice but evidence of efficacy for this strategy is lacking.
- The 204 participants will be blinded to the treatment offered to the opposite group in order to minimize differences regarding expectations with the allocated treatment between groups.
- Interventions included in this study are usually easily available in practice which facilitates implementation.
- Results from the subgroup analysis will be used for hypothesis generation only, as the study was not powered for these analyses.

INTRODUCTION

Background and rationale

Osteoarthritis (OA) is a chronic and prevalent joint disorder with great impact on quality of life and high economic burden [1, 2]. The most common form of OA is that involving the hands, affecting three times more women than men and with greater prevalence following menopause [2, 3]. Overall prevalence of symptomatic hand OA is nearly 15% [4], while in the elderly (aged 70 years and over) the prevalence is about 26% in women and 13.4% in men [5].

Among the different subtypes of hand OA, that affecting the base of the thumb represents a particular challenge to clinicians due to associated disabling symptoms and the limited efficacy of treatment options [6]. Radiographic thumb base OA was reported to affect nearly 21% of the population over 40 years of age in the United States [7] and it is usually more frequently related to pain and disability than interphalangeal joint OA [6]. In addition to pain, it can cause deformity, stiffness, decreased range of motion and strength, resulting in difficulty performing common activities such as opening jars, carrying weights and writing [8].

While thumb base OA is primarily treated with non-surgical modalities, surgical treatment may be indicated for those whose debilitating symptoms persist despite adequate conservative management. Thumb base OA is one of the most common causes of hand surgery [9]. Surgical management, however,

is associated with a number of complications including tendon rupture, sensory changes and wound infection [10]. In addition, a 7-year prospective study found 70% of patients waiting for surgery for thumb base OA were able to postpone or avoid surgery following conservative treatment with joint protection and splinting [11].

Although a number of conservative therapies have proven to be effective for the management of hand OA, only modest treatment effects were reported for most individual interventions [12]. This is particularly true in the case of thumb base OA, with few high quality clinical trials in the literature to date and great heterogeneity across studies [13].

Among the non-surgical modalities, education about the disease, delivered along with instructions regarding joint protection techniques, has been demonstrated to have no clinically significant benefits for pain [8]. In contrast, a systematic review demonstrated that the use of splints for thumb base OA reduced pain, particularly in the long-term, based on data from two trials [14]. The same review found evidence that hand exercises might improve grip strength and hand function; however, evidence was based on individual trials using different exercise programmes. With regards to pharmacological management, there are insufficient data available to support the efficacy of intra-articular therapy with either corticosteroids or hyaluronic acid [15] and their use is not recommended by the 2012 American College of Rheumatology (ACR) guidelines [16]. On the other hand, non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to relieve pain associated with thumb base OA, and topical formulations are recommended over oral NSAIDs in the most recent guidelines, due to a superior safety profile [16-18]. However, their effect on function is small and transitory (no more effective than placebo after 2 weeks) [19].

Combining non-pharmacological and pharmacological modalities in the management of hand OA is recommended by the European League Against Rheumatism (EULAR) guidelines [17], supported by a literature review [8], and is frequently used in clinical practice. Despite this, direct evidence of efficacy of this strategy is lacking. A few trials evaluating combined treatment have been performed, although they have not generally been specific to thumb base OA [20, 21]. Moreover, the combinations investigated usually included exclusively non-pharmacological modalities [22] and to date no strategy has been found to be highly efficacious for improving pain and function for thumb base OA. Determining an evidence-based therapeutic approach with a clinically meaningful effect on clinical outcomes would provide health professionals with a basis for decision-making for treatment of patients with thumb base OA. This strategy does not yet exist, and decisions on the best combination of interventions are usually based on personal experience and personal opinion of health professionals.

Objective

The aim of this study is to determine the effect of a combination of conservative non-pharmacological and pharmacological modalities in the treatment of thumb base OA compared to education control (standard care). The intervention group will consist of education about the disease and joint protection techniques, hand exercises, a splint to support the base of the thumb, and topical NSAID. The control group will be provided with education about the disease and joint protection techniques alone.

METHODS AND ANALYSIS

Trial design

The COMBO trial is designed as a randomised, controlled, assessor and statistician blinded, parallel, two-arm superiority trial with 1:1 allocation ratio. The trial will be conducted at a single centre in Australia. The interventions will take place from baseline to 6 weeks and follow-up assessments will occur at 2, 6 and 12 weeks (Figure 1). The protocol was designed in accordance with the principles of the Declaration of Helsinki.

Consumer involvement

Our consumer focus group has been involved in discussions during the genesis of this trial, which consisted of the selection of interventions, outcomes, and the duration and frequency of the study assessments.

Participants

Participants will be recruited from the community and from our research volunteer database composed of participants who have expressed their willingness to be involved in future studies. The recruitment strategies will include advertisements on social media networks and posters/flyers placed on notice boards and waiting room walls of medical practices and community areas. In the first instance, a preliminary screening will occur by phone/internet and for those participants who pass this initial screening, a face-to-face visit will be conducted to confirm their eligibility. All participants will receive verbal and written information about the trial and the blinded assessor will obtain a written informed consent before inclusion.

Inclusion criteria

Participants will be eligible for the study if they meet all the following inclusion criteria [23]: age ≥ 40 years; pain at the base of the thumb at least half of the days in the past month; average pain ≥ 40 on a 100-mm Visual Analogue Scale (VAS), where 0 is no pain and 100 is worst pain imaginable, over the past 30 days and in the 48 hours prior to the screening visit; scores ≥ 6 on the Functional Index for Hand Osteoarthritis (FIHOA, range 0 - 30) [24]; and radiographic evidence of thumb base OA read by a trained rheumatologist (Kellgren Lawrence grade (KLG) ≥ 2) [25]. The most severely involved hand will be included (as defined by pain VAS) in cases of bilateral symptomatic thumb base OA. If the pain scores are the same for both hands, participants will be asked to nominate the worst hand (i.e., the one that causes more problems to the participant, either the dominant or non-dominant hand), which will be included as the index.

Exclusion criteria

Participants will be excluded if they fulfil any of the following criteria: known diagnosis of crystal-related arthritis (e.g. gout, calcium pyrophosphate deposition disease), autoimmune arthritis (e.g. rheumatoid arthritis, psoriatic arthritis), hemochromatosis or fibromyalgia; hand surgery in the last 6 months or planning to undergo surgery in the next 6 months; use of concomitant medications potentially directed at OA, unless at a stable dosage for at least 1 month for analgesics and NSAIDs, or 3 months for slow acting symptomatic or structure modifying drugs (e.g. diacerein, chondroitin sulphate, avocado/soybean unsaponifiables); intra-articular hyaluronic acid injection in the affected joint in the past 6 months; intra-articular steroid injection in the affected joint in the past month; significant injury to the affected joint in the past 6 months; any other self-reported hand condition that is likely to be contributing to the pain at the base of the thumb (e.g. scaphoid fracture, carpal tunnel syndrome, DeQuervain's tendinopathy, trigger thumb, joint infection, diabetic neuropathy, pain referred from the neck, pain following hand or wrist trauma or surgery); poor general health likely to interfere with compliance or assessments, judged by the investigator; known hypersensitivity to diclofenac; current history of advanced renal failure; past or current history of gastrointestinal ulceration, bleeding and/or perforation; women who are pregnant or breastfeeding; current use of any of the study interventions.

Randomisation and allocation concealment

Individuals who consent to take part in the study and fulfil all study criteria will be assigned to either intervention or control group with a 1:1 allocation as per a computer generated randomisation schedule, stratified by OA severity using KLG (2 and 3 vs. 4) using random blocks of size 2, 4 and 6. The allocation sequence will be concealed from the researchers enrolling and assessing participants in sequentially numbered opaque, sealed and stapled envelopes. Aluminium foil inside the envelope will be used to render the envelope impermeable to intense light. Envelopes will be stored in a locked drawer and will be opened by the study coordinator only after the enrolled participant completes all baseline assessments.

The sequence generation will be prepared by a statistician and the envelopes will be prepared by an external investigator not involved in the trial. The study blinded assessor will enrol participants and the study therapist (one single physiotherapist with experience in thumb base OA management) will open the envelope in front of the participant and execute the designated intervention.

Blinding

All clinical assessments will be conducted by an assessor blinded to treatment allocation. To reduce the potential for unblinding, participants will be instructed not to disclose any information about the treatment, not to wear the splint during the follow-up assessments, and not to use the topical NSAID just before the visit. Any occurrence of unblinding of the assessor will be recorded with its reason and reported along with the trial's results. The physiotherapist executing and supervising the treatments will not be blinded to the group allocation. The statistician involved in the main statistical analyses will be blinded to group allocation. Group allocation will be immediately unblinded if deemed necessary by the chief investigator in the case of serious adverse events potentially related to the study.

Participants will be naive to the treatments offered to the opposite group and hence blinded to the hypothesis of the study. In order to reduce the risk of bias, participants will be informed about the overall aspects involved in the treatment of both groups (i.e. conservative therapies not involving oral or intra-articular medications) but not told the specific treatments included in each one of them nor about the differences among groups. This procedure aims to minimize differences regarding expectations with the allocated treatment between groups.

Interventions

The intervention group will receive a combination of education about OA and joint protection techniques, a splint to support the base of the thumb, hand exercises and topical NSAID. The control

group will receive education about the disease and education about joint protection techniques alone (standard care). All participants will attend two individual, face-to-face treatment sessions with the study physiotherapist of approximately 30 minutes each. The first will occur at the baseline visit and the second will occur after two weeks (2-week visit). Both treatment sessions will occur after the assessment by the blinded assessor. The 2-week visit aims at checking adherence to the programme while balancing the number of face-to-face visits and contact with the therapist between the control and intervention groups (2 visits for each group).

The intervention will be delivered over 6 weeks. After the 6-week visit, participants will be encouraged by the physiotherapist to continue the treatment throughout the follow-up period (from 6 to 12 weeks) but intervention use will be at the participants' discretion. This period aims to evaluate participant's choice in continuing using the interventions and to assess the outcomes after this period.

Participants will be allowed to continue using current pain medications throughout the study provided the dose has been stable at study entry as per exclusion criteria. They will be permitted to use acetaminophen (paracetamol) as rescue medication for any symptom exacerbation, up to a maximum of 3000 mg per day.

Education about OA and joint protection techniques

All participants in this study (both groups) will be provided with education about OA and joint protection techniques through a 9-page educational booklet delivered at baseline (Appendix 1) and through two face-to-face sessions with the study therapist at baseline and at the 2-week visit. Information about the disease will include: anatomy of the first carpometacarpal (CMC) joint, using the Acland's video atlas of human anatomy (Carpometacarpal joint of thumb) [26], diagnosis, disease course, objectives of treatment, self-management, and instruction on joint protection techniques and assistive devices. The booklet used in this study was adapted from an online resource produced by the hand therapy unit of James Cook University Hospital, United Kingdom [27]. Written permission was obtained to use the adapted version. The physiotherapist will have a script to follow to maintain consistency with all participants regarding the joint protection advice.

Splint

While favourable results have been observed with different types of splints, prefabricated types are preferred over the custom-made version by most patients [13]. Moreover, different ways of using the splint have been studied. A systematic review of design and effects of splints identified two trials

with low risk of bias in which best results were achieved with the use of splints during daily activities [14, 28]. A prefabricated neoprene splint (Comfort Cool® Thumb CMC Restriction Splint) will be used in this study. This splint is readily commercially available and does not require any customization, facilitating potential dissemination post study, generalizability of our findings and application in routine clinical practice. The splint incorporates the base of the thumb and wrist and participants will receive recommendation to use it during activities of daily living (minimum of 4 hours/day) for 6 weeks (Figure 2). The splint will be removed during rest, sleep, exercises and bathing.

Hand exercises

The exercise programme will be the same for all participants in the intervention group and will consist of five exercises: thumb opposition, paper tearing, line tracing on ball, using chopsticks to pick up objects and squeezing a ball. The aim of the exercise programme will be to optimize range of motion (thumb opposition and line tracing on ball), to improve neuromuscular control of the alignment of the thumb and muscular endurance (paper tearing and squeezing a ball), and to train proprioception of the thumb base joint (all 5 exercises). Specific attention will be drawn to performing the exercises in a way which prevents collapse (hyperextension) of the first metacarpophalangeal (MCP) joint while maintaining the web space (abduction). These exercises are based on recent evidence which emphasizes the importance of proprioceptive exercises and strengthening for the 1st dorsal interosseous muscles [29, 30], whilst aiming to be functional and similar to movements used for daily tasks. The exercise programme will be visually depicted using images from a website developed by physiotherapists from the New South Wales Department of Health, Sydney, Australia (Appendix 2) [31]. Consent was obtained to include the images into a written instruction to participants in the intervention group. The exercise programme was designed with emphasis on the first CMC joint in particular in order to optimize potential generalizability of the intervention for patients with this condition in clinical practice.

Participants will receive instructions on how to perform the exercises correctly during their supervised one-on-one session with the study physiotherapist at baseline. They will be further instructed to perform individual unsupervised at-home sessions, three times per week, from baseline to the 6-week visit, and adjustment to the programme will be checked at the 2-week visit. Each exercise should be repeated 10 times during the first week. The muscular endurance exercises (paper tearing and squeezing a ball) will be progressed by increasing the difficulty of the tasks (i.e. tearing a thicker paper and squeezing the ball harder [compressing the ball until it is about a third compressed (first week), half compressed (second week), and about three quarters compressed (weeks 3 to 6)], respectively). For the

remaining exercises, the number of repetitions will be increased, aiming for 12 repetitions during the second week and 15 repetitions for the following 4 weeks, if tolerated, as judged by the patient.

Topical NSAID

The intervention group will receive *Diclofenac diethylammonium* gel (11.6 mg/g) (diclofenac sodium 1% gel; Voltaren Emulgel®), a topical NSAID commonly used in clinical practice that has been studied in large, good quality trials with superiority over placebo [18]. Participants will be instructed to use the medication three times per day for 6 weeks on a daily basis. In order to standardize the amount used, participants will receive a small spatula with a permanent pen mark showing exactly how much product they should use. The advised amount corresponds with approximately 200 mg to be applied in an area of 40 cm^2, as recommended by the dosage guidelines.

Outcomes

Outcome measures used in this study are validated instruments that were promoted in recent recommendations for clinical trials for hand OA [23]. The primary outcomes are change in pain scores at the base of the thumb, assessed by VAS (0-100 mm), and change in hand function, assessed by FIHOA (0-30) from baseline to 6 weeks. The FIHOA tool is composed of 10 items scored using a semi-quantitative 4-point scale. It is a self-reported questionnaire evaluating the functional performance of 10 distinct activities involving the hand that has demonstrated good measurement properties including reliability, feasibility and sensitivity to change [32].

Secondary outcomes are change in pain scores at the base of thumb, assessed by VAS, and in hand function assessed by FIHOA from baseline to 2 and 12 weeks as well as the following outcomes assessed from baseline to 2, 6 and 12 weeks: change in grip strength (Jamar hand dynamometer (in kg)) and tip pinch strength (B&L pinch gauge (in kg)), assessed with participants with feet flat on the ground and elbow flexed at 90 degrees; change in patient global disease assessment, assessed in response to the question " Considering all the ways your thumb arthritis affects you, how have you been during the last 48 hours?" (on a VAS (0-100 mm, where 0 is very well and 100 is the very poor)); change in duration of thumb base stiffness, assessed by the question "What is the duration of stiffness at the base of your thumb in the morning?" (expressed in minutes); change in health related quality of life assessed by the Assessment of Quality of Life – 4D instrument (AqoL-4D), a 12-item tool with good validity and reliability [33], including questions related to independent living, mental health, relationship and senses, and scored from -0.04 to 1.00, with 1.00 indicating full health [34]; use of rescue medications for pain at the

base of the thumb (p, up to 3000 mg per day), assessed by inspection of participant's diary; change in presence of swelling and tenderness, assessed by joint examination (scored as present or absent); participant's global rating of change for pain, function and overall change, assessed by the question "Which option best represents the change in pain/ change in function/overall change in your thumb since you began the study?", scored using a 5-point Likert scale ranging from much better to much worse; percentage of treatment responders at 6 and 12 weeks according to the OMERACT-OARSI criteria; and change in impairments in work and other activities, assessed by the Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH), consisted of 6 questions related to impairments in both work and daily activities over the past 7 days, which has been used in patients with rheumatoid arthritis and other rheumatic diseases [35-37].

As tertiary/correlative outcomes, the participants will be required to fill out the credibility/expectancy questionnaire at baseline in order to assess expectation related to the assigned treatment [38]. The questionnaire is composed of 6 questions and higher scores demonstrated higher expectation/credibility. In addition, range of motion of the first MCP joint will be measured with a goniometer and presence of first MCP joint collapse pattern on pinch will be recorded at baseline.

Procedures

An outline of the protocol visits and procedures is provided in Table 1.

Table 1. Schedule of study's events.

	Screening Visit	Baseline Visit	2-week visit	6-week visit	12-week visit
Informed consent	X				
Demographics	X				
Medical history	X				
Medication form	X				
Co-morbidity assessment	X				
VAS for pain	X	X	X	X	X
FIHOA	X	X	X	X	X

Assessment of stiffness		X	X	X	X
Patient global assessment		X	X	X	X
Aqol-4D		X	X	X	X
Use of rescue medication			X	X	X
Joint examination		X	X	X	X
Grip and pinch strength		X	X	X	X
WPAI-GH		X	X	X	X
Global rating of change				X	X
First MCP joint assessment		X			
Treatment expectation		X			
Treatment adherence			X	X	X
Clinical safety assessment					
Blood pressure		X	X	X	X
Adverse events			X	X	X
Radiology/Imaging					
PA view radiograph	X				
Eaton stress view radiograph	X				
Hand ultrasonography		X			

VAS = Visual Analogue Scale; FIHOA = Functional Index for Hand Osteoarthritis; AqoL-4D = Assessment of Quality of Life – 4D.

Screening visit

After an initial screening phone call, potential participants will attend a screening visit that will consist of collection of demographic data such as: age, date of birth, gender, ethnicity, financial status, marital status, symptom duration, current or past activities involving intensive use of the hands (e.g. sports, gardening, playing specific musical instruments), previous and concomitant therapies, height, weight, years of formal education, primary occupation, comorbidities, menopausal status in women,

and OA at other joints (such as knee or hip). The key inclusion/exclusion criteria will be assessed to confirm the participant's eligibility.

Radiographic assessment

All potential participants will be referred for a postero-anterior (PA) view and an Eaton stress view radiograph of both hands. The protocol for acquisition of the Eaton stress view is presented in Appendix 3 and is based on a previous paper describing this technique [39]. The PA view will be used to assess eligibility and thumb base OA severity using KLG, in addition to radiographic severity using both the Osteoarthritis Research Society International (OARSI) atlas [40] and the Eaton classification criteria [41]. The degree of subluxation of the first CMC joint will be assessed on the Eaton stress view [39].

Baseline Assessment

At the baseline visit, an ultrasound of the first CMC joint will be performed by a physiatrist with experience in musculoskeletal ultrasound, in order to assess presence of synovitis and other structural features including osteophytes, cartilage damage, erosions and stability of the first CMC joint. The protocol for the ultrasound assessment is detailed in Appendix 4. Assessment of tenderness and swelling on physical examination by the blinded assessor will be first calibrated with the study's rheumatologist and inter-rater reliability will be assessed later in the study.

After the assessment, the blinded assessor will introduce the physiotherapist to the participant and leave the assessment room. At the end of the visit the physiotherapist will deliver an envelope containing the credibility/expectancy questionnaire to assess the treatment expectation [38]. The participant will be instructed to place the completed questionnaire back into the envelope and to seal it. The envelopes will not be opened until the study is complete.

2, 6 and 12-week visits

The outcome measures will be reassessed at the 2, 6 and 12-week visits by the blinded assessor. At the end of each visit the study physiotherapist will record adverse events, use of rescue medication and treatment adherence from the participant diaries (see below). The physiotherapist will also ensure the correct performance of exercises by participants in the intervention group. Participants' global rating of change for pain, function and overall change will be concealed from the physiotherapist until the study is complete.

6-month contact with participants

After completion of the study at week 12, participants in the intervention group will be encouraged to continue the treatment and participants in the control group will be given advice about the interventions received by the treatment group (i.e. hand exercises, splint and topical diclofenac), with the same recommendations as those used in the study for each intervention. All participants will be contacted by phone or through an online survey at 6 months to assess: 1) Participants' choice in continue using the interventions (yes vs. no); 2) The frequency of intervention use (as recommended by the physiotherapist vs. less than the recommended by the physiotherapist); 3) Primary outcomes (pain at the base of the thumb, assessed by VAS (0-100 mm); and hand function, assessed by FIHOA (0-30)). The reason for non-compliance (e.g. lack of benefit, side effect, forgot to use intervention/do the exercise) will be recorded. This assessment aims at evaluating the effectiveness of the intervention in a longer-term follow-up and will not be used for assessing between-group differences in treatment effects.

Treatment adherence

To monitor adherence to the treatments, participants from the intervention group will receive a diary and will be asked to record the hours of splint use and the use of topical NSAIDs on a daily basis. In addition, participants will be requested to report which exercises were performed and the frequency of these on a weekly basis. Adherence will be monitored using the diary from week 6 to 12, to assess whether participants continued the intervention following the 6-week visit. Control participants will also be provided with the diaries as all participants will be asked to record the use of rescue medication. Participants in the intervention group will be asked to record any adverse events relating to exercises, splint wear or use of topical NSAID in their diary.

Participant Safety and Withdrawal

Risk Management and Safety

Adverse events will be assessed by inspection of participants' diaries at 2, 6 and 12 weeks after intervention commencement. The risks for participants involved in this study are minimal. Topical NSAIDs have demonstrated a good safety profile and good tolerability, with no higher gastrointestinal, cardiovascular, renal and hepatic adverse events than placebo [18]. Nevertheless, due to theoretical concerns related to the use of NSAIDs, adverse events will be monitored. To ensure the safety of

participants, blood pressure will be monitored and systemic symptoms (new or worsening of previous symptoms) will be assessed at 2, 6 and 12 weeks after study commencement. Symptoms suspected to be related to the topical NSAIDs will be assessed by a physician involved in the study and, if necessary, the medication will be discontinued and further medical evaluation will be arranged. Local skin dermatitis may occur; however, these will most likely be minor local skin reactions. Participants who have local adverse reactions will cease the topical medication and will be followed to certify resolution of their rash. The same procedure will be applied if participants report local adverse skin reactions associated with the splint use. All adverse events will be reported.

Participants currently taking warfarin that are allocated to the intervention group will be required to consult their treating physician during the study due to the potential interaction between this drug and NSAIDs. Participants will be exposed to a small amount of radiation (0.001mSV) for the acquisition of the radiograph, which is much lower than the annual average radiation dose (around 2mSV) [42].

Handling of Withdrawals

If a participant withdraws from the study, they will have their reasons for withdrawal recorded and any information provided or recorded up to the point of withdrawal will be kept in accordance with the data security and handling protocol of this study (see below). Strategies to maximize follow-up and prevent missing data will be used, including adhering to the assessment schedule in the event of participant withdrawal. In the event that the participant is unable to attend a study visit, the questionnaires will be administered over the phone. Participants who withdraw from the study will not be replaced.

Statistical Methods

Sample size estimation and justification

The two primary outcome measures (VAS and FIHOA) were used to estimate the sample size. For the FIHOA, the minimal clinically important difference (MCID) is not known, thus the calculation was based on detecting a mean difference of 3 points (defined arbitrarily) on the FIHOA (range 0 - 30). The standard deviation (SD) used was based on the baseline scores presented in the FIHOA's validation study (SD 6.2) [43]. For pain intensity, the calculation was based on detecting a MCID of 20 mm on a 100mm VAS, assuming a SD of 20 mm as was used in a previous study [44]. The two primary outcomes are correlated (r=0.49) [24], hence an alpha of 0.027 was used as the level of significance for both outcomes

which preserves an overall 5% level of significance. To achieve a sample power of at least 80% for both outcomes, a sample size of 81 individuals per group will be required. To accommodate expected dropouts of 20% before study completion, we aim to include 102 participants in each group.

Statistical analysis

Data will be analysed according to the intention-to-treat principle. Demographic characteristics and baseline scores will be presented to assess comparability of treatment groups at baseline. Participants' characteristics will be described using mean and SD for continuous variables or medians (quartiles) if the distribution is skewed. Counts with percentages will be presented for categorical variables.

For continuous outcomes, the mean scores (SD) will be presented at each time-point by treatment group. The between-group difference in mean change from baseline with 95% confidence interval will be presented for all primary and secondary outcomes and compared using independent t-test or the Wilcoxon rank-sum test as appropriate. Categorical outcomes will be examined by $\chi 2$ test or Fisher's exact test, if expected cell counts are small. Analysis adjusted for baseline score and other relevant demographic and clinical characteristics will also be performed using analysis of covariance models fitted separately at 2, 6 and 12 weeks for all outcomes with the change from baseline as the dependent variable. Furthermore, standardized mean differences (95% CI) will be computed as the adjusted between-group difference in scores divided by the pooled SD of the baseline scores.

In addition, outcomes will be analysed on a categorical basis. The basis for categorization will be the participant's score on the perceived ratings of change (participants reporting feeling much better and slightly better will be considered to have undergone meaningful change), and the OMERACT-OARSI criteria [45]. Logistic regression models adjusted for age, gender, BMI and KLG will be used to compare response between treatment groups. The OMERACT-OARSI criteria for a meaningful change (improvement) are one of the following:

1) High improvement:

- ≥ 50% improvement + absolute change of ≥ 20 in self-reported pain intensity (VAS, 0 – 100mm), OR
- ≥ 50% improvement + absolute change of ≥ 6 in self-reported hand function (FIHOA, 0 – 30);

OR

2) Improvement in at least 2 of the 3 following:

- ≥ 20% improvement + absolute change ≥ 10 in self-reported pain intensity (VAS, 0 – 100mm)

- ≥ 20% improvement + absolute change ≥ 10 in Patient Global Assessment of disease activity (VAS, 0 – 100mm)
- ≥ 20% improvement + absolute change ≥ 3 in self-reported hand function (FIHOA, 0 – 30).

Post-hoc subgroup analyses will be performed examining whether there is heterogeneity in treatment effect according to presence of the following: concomitant symptomatic interphalangeal joint OA, presence of erosive hand OA (defined based on radiographic score), presence of CMC joint subluxation (assessed by the ratio of the radial subluxation of the base of the first metacarpal to the total articular width of the first metacarpal, on the Eaton stress view radiograph [39]), and by baseline OA severity according to KLG.

DATA SECURITY & HANDLING

Study data will be collected and managed using Research Electronic Data Capture (REDCap) tool hosted at the University of Sydney. This tool is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Back-up re-identified information will be kept in password protected electronic files. These files will be saved into an external hard drive that will be stored in a locked cabinet at the Principal Investigator's office. The privacy, security and ownership of the research data will be maintained and will not be stored or accessible by another organization.

The archiving period for clinical research records will be 15 years. After this period, the electronic files will be deleted and paper forms will be destroyed. No information which could lead to the identification of a participant will be included in the dissemination of results.

ETHICS AND DISSEMINATION

This protocol was approved by the local ethics committee (HREC/15/HAWKE/479). Any protocol modification will be sent to review by the research ethics committee and will be amended at the trial registry. Dissemination is planned to occur through presentations at international conferences and publication in peer-reviewed journals.

AUTHORS' CONTRIBUTION

LAD, DJH, AW, KLB, BV, PH, EAR, JPE, RJ and SRFM contributed to study conception and design. VD, ROC and WMO contributed to study design. DJH, KLB, BV and PH attained project funding. LAD drafted the first version of the manuscript. ROC will have access to the final trial dataset and perform the statistical analysis. All authors revised the protocol critically for important intellectual content and read and approved the final version of the protocol. All authors agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

DJH is a consultant to Flexion, Nestle and Merck Serono.

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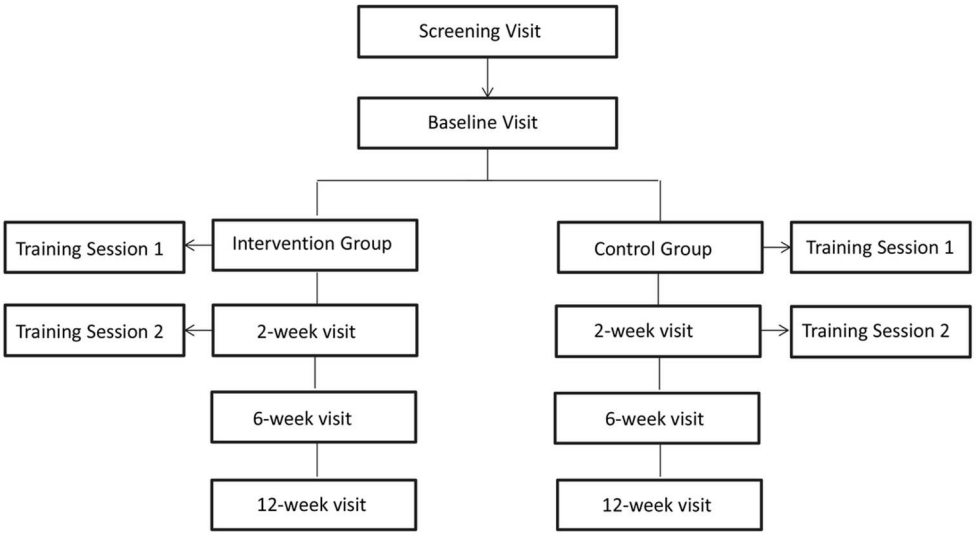
Figure legends

Figure 1. Trial design and visits.

Figure 2. Comfort Cool® Thumb CMC Restriction Splint.



Trial design and visits

106x65mm (300 x 300 DPI)

Comfort Cool® Thumb CMC Restriction Splint

127x127mm (300 x 300 DPI)

Appendix 1. Participant's booklet.

Osteoarthritis of the Carpometacarpal Thumb Joint

Patient Information Booklet

Study Coordinator: Sarah Meneses
sarah.meneses@sydney.edu.au
(02) 9463 1855

For more information about osteoarthritis,
visit www.myjointpain.com.au

Version 1 - 21/04/16

Osteoarthritis of the carpometacarpal thumb joint

This booklet has been written to provide you with information about your thumb arthritis and give you a better understanding of your thumb joint, why you experience pain, and how you can manage your symptoms.

It contains information about:

- Anatomy of the thumb carpometacarpal joint
- Osteoarthritis of the thumb carpometacarpal joint
- Joint protection
- Assistive devices
- Heat and cold
- Pain relief

Anatomy of the carpometacarpal thumb joint

The thumb carpometacarpal (CMC) joint is where the metacarpal bone of the thumb attaches to the trapezium (carpal) bone of the wrist (see diagram on the following page).

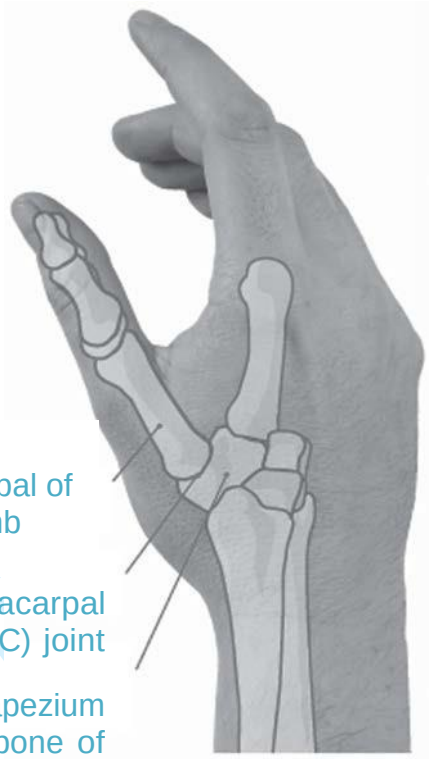
What is OA?

Osteoarthritis (OA) is the most common form of arthritis and affects mainly the joint's cartilage and surrounding bone tissue.

There are many factors that can increase the risk of the developing OA; for example it is more common in females over the age of forty, and is more likely to develop in a joint that has had a previous injury or operation.

A joint is where two bones meet to allow movement. Muscles pull on tendons, which are attached to the bone to produce movement.

CMC joint arthritis



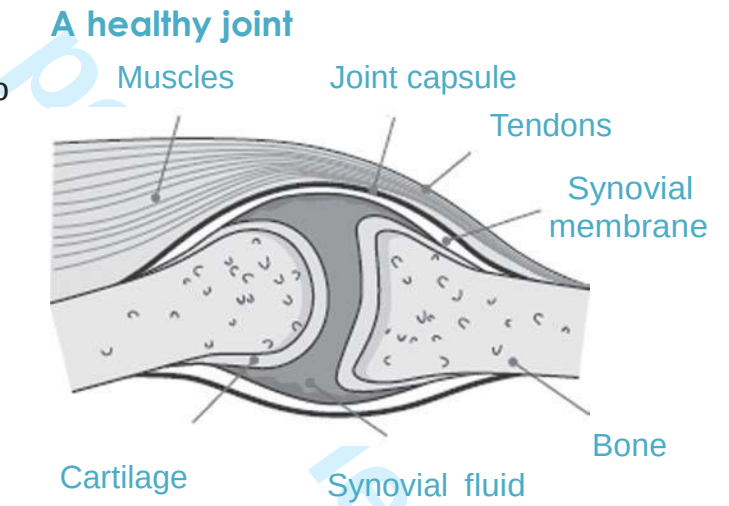
The ends of the bones are covered in a smooth tissue called cartilage that cushions the joint. There is a space between the two ends of bone making up the joint.

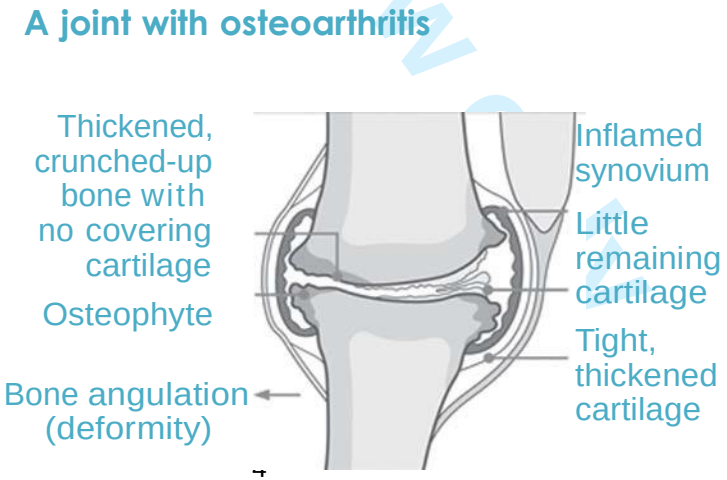
The joint is held together within a joint capsule, which contains a thick fluid (synovial fluid) providing lubrication to allow smooth movement. Surrounding ligaments and muscles also maintain the stability of the joint.

When OA develops in a joint, the cartilage gradually roughens and becomes thin, and the bone underneath thickens. The bones at the edge of the joint grow outwards in bony 'spurs' (see diagrams) and excess synovial fluid can be produced, causing the joint to swell.

This can mean that you avoid using these joints, subsequently causing the surrounding muscles to weaken.

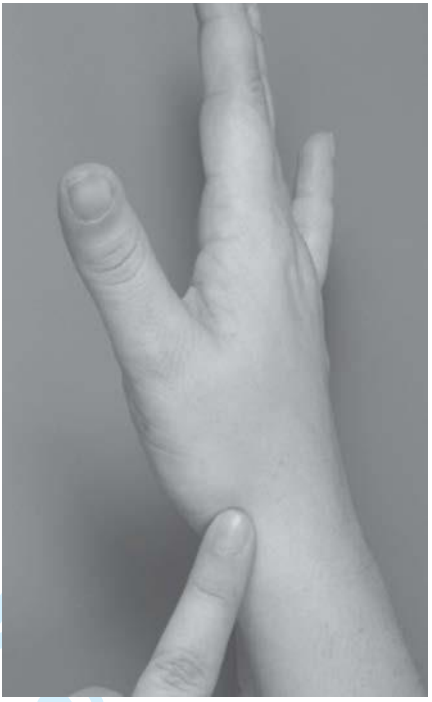
In severe OA, the cartilage can become so thin that it no longer covers the joint surfaces, and damage is caused to the bone ends by them grinding against each other during movement. This can, over time, change the shape of the joint creating a deformity, as the joint is no longer held in its natural position.





Common symptoms of CMC OA

Pain: Usually felt as a sharp or aching pain at the base of the thumb. The pain is usually worse during movement and relieved by rest.



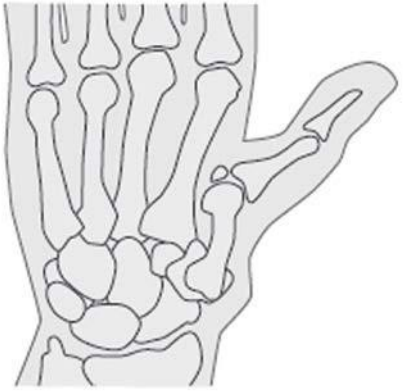
Reduced grip strength: It may be difficult to grip or pick up objects.

Stiffness: Following periods of rest (eg in mornings).

Swelling: Around the base of the thumb.

Muscle Weakness and Instability

Deformity: In the later stages of the condition the thumb joint may collapse inwards into a subluxed position (see diagram).



The joint protection techniques and the use of assistive devices (as described in this booklet) can help to relieve these symptoms and slow the progression of this condition.

Joint protection

Most people find their own ways of doing activities that are less painful. It is important that you are aware of the activities that cause your thumb joint to be painful so that you can consider other ways to perform these activities that place less strain on the painful joints.

Each time you experience thumb pain when doing an activity, stop and consider whether the way you are doing it is causing stress on the joint. Think about if there is another way the activity can be performed that is better for your joints.

For example:

- When doing activities that involve a pinch grip (eg writing) keep the top joint of the thumb bent and the wrist extended.
- When doing activities that involve turning or twisting avoid fully straightening the top joint of the thumb and the thumb crossing in front of the palm.

The following are joint protection techniques that may help to reduce the pain you experience when doing activities and prevent further damage to the joints:

- Take notice of any pain you feel, it can serve as a warning that the way you are performing the activity is causing damage to the joint.
- Spread the load over several joints (eg by carrying items on two flat hands rather than gripping with your thumb).
- Use larger stronger joints rather than putting the strain through your thumb joints.
- Use less effort (eg push or slide heavy items rather than carrying).

Examples of joint protection techniques

Instead of this ...

... try this

Instead of this (holding a pile of papers with one hand) ...

... try this (holding it with two hands)

Hug large objects close to your body

'Shift not lift' - slide a plastic jug of water to the kettle - only use as much water as you need

Assistive devices

There are a variety of small aids that are available to assist you in maintaining your independence completing daily activities.

For example:

Jar twisters: Jar twisters to help you open tight jars.

Wide grip cutlery: Wide grip cutlery if you find it difficult or painful to hold cutlery.

Pen grips: Pen grips to support your grip or writing.

Tap turners: Attach onto your taps to make them easier to turn on and off.

Key turners: Key turners if you have difficulty turning key in door.

Plug pulls: Assists grip if you have difficulty removing plugs.

An occupational therapist (OT) can discuss specific activities that you are finding difficult or painful and advise you whether any assistive devices are available to help.

Heat and cold

Applying heat, such as a hot pack (microwaveable wheat pack), heating pad or hot water bottle to stiff, painful joints may help relieve these symptoms. If your joints are hot and swollen you may find it useful to apply an ice pack.

Try applying heat or cold to the painful area for 15 minutes. Always have a layer (such as a tea towel) between your skin and the heat or ice pack. You can repeat this whenever you need to throughout the day. Make sure the temperature of the skin returns to normal in between applying heat or ice packs to prevent damage to the tissues.

Pain relief

Some people find that paracetamol or anti-inflammatory medications (such as aspirin and ibuprofen) can help to reduce the pain experienced.

This should always be discussed with your GP or consultant as they will be able to recommend what type of pain relief and what dose is appropriate for you, depending upon any other medical conditions you have.

Acknowledgments

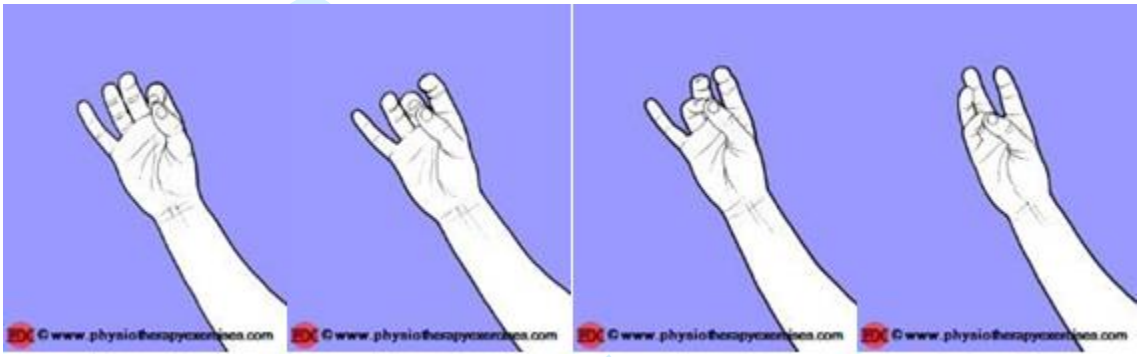
This booklet has been adapted with permission from the Hand Therapy Unit at James Cook University Hospital.

Appendix 2. Written instructions on how to perform the exercises provided to participants in the intervention group.

Week 1

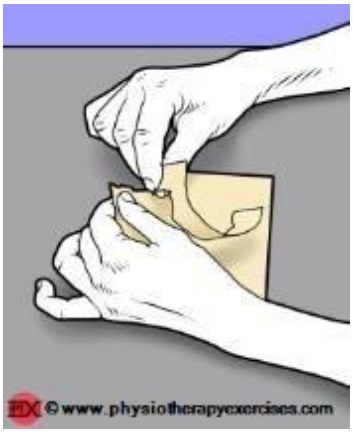
Perform the following exercises as taught by your therapist three days a week. Exercises should not aggravate the pain. You should stop short of aggravating pain.

1. Thumb Opposition



Position yourself with your hand resting in front of you. Practice touching the tip of your thumb to the tip of your index finger, then to the tip of your middle finger and then to the tip of your ring finger. If pain free, you can aim to touch the tip of your thumb to the tip of your little finger.
Repeat this movement 10 times.

2. Tearing paper

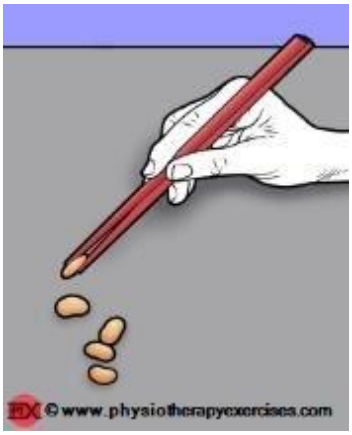


Position yourself with a piece of paper in front of you. Tear the paper.
Repeat 10 times.

3. Tracing line on ball

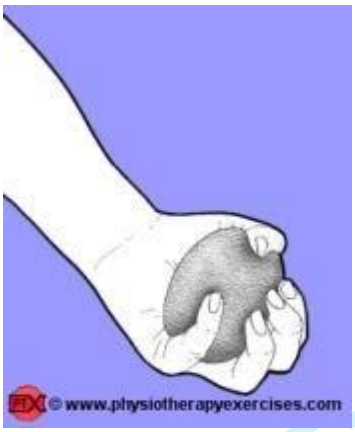
Position yourself with your hand resting on the ball in front of you. Slide your thumb along the line of the ball, while moving the ball with your finger tips.
Trace the line on the ball 10 times.

4. Using chopsticks



Position yourself with the chopsticks in your hand. Use the chopsticks to pick up a bean and place into the container.
Repeat 10 times.

5. Squeezing ball

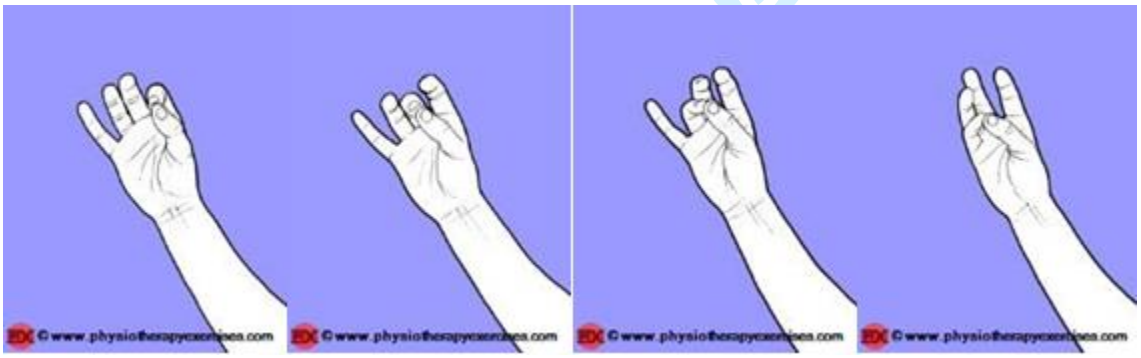


Position yourself sitting with a stress ball held in your hand. Practice squeezing the ball until it is about a third compressed.
Repeat 10 times.

Week 2

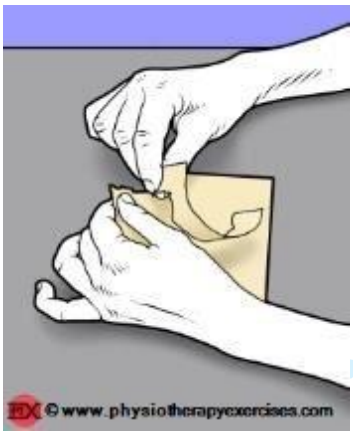
Perform the following exercises as taught by your therapist three days a week. Exercises should not aggravate the pain. You should stop short of aggravating pain.

1. Thumb Opposition



Position yourself with your hand resting in front of you. Practice touching the tip of your thumb to the tip of your index finger, then to the tip of your middle finger and then to the tip of your ring finger. If pain free, you can aim to touch the tip of your thumb to the tip of your little finger.
Repeat this movement 12 times.

2. Tearing paper



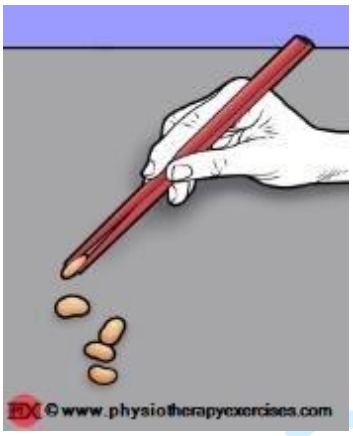
Position yourself with a piece of paper in front of you. Fold the paper in half and tear the paper.

Repeat 10 times.

3. Tracing line on ball

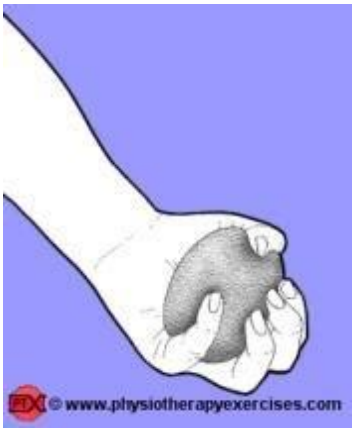
Position yourself with your hand resting on the ball in front of you. Slide your thumb along the line of the ball, while moving the ball with your finger tips.
Trace the line on the ball 12 times.

4. Using chopsticks



Position yourself with the chopsticks in your hand. Use the chopsticks to pick up a bean and place into the container.
Repeat 12 times.

5. Squeezing ball

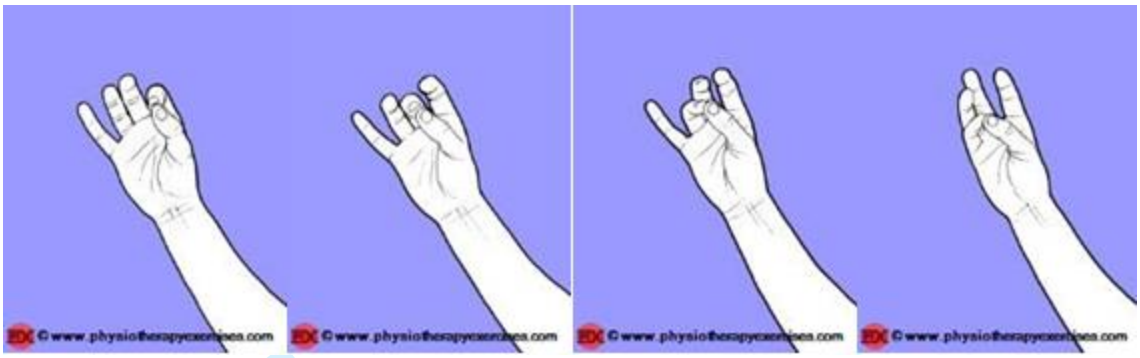


Position yourself sitting with a stress ball held in your hand. Practice squeezing the ball until it is about half compressed.
Repeat 10 times.

Week 3 to 6

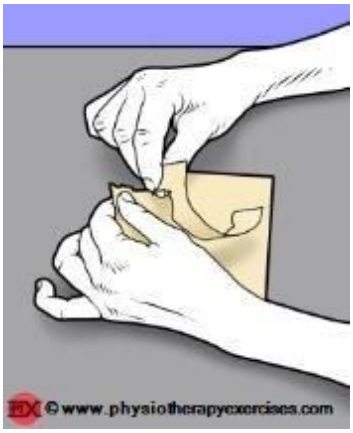
Perform the following exercises as taught by your therapist three days a week. Exercises should not aggravate the pain. You should stop short of aggravating pain.

1. Thumb Opposition



Position yourself with your hand resting in front of you. Practice touching the tip of your thumb to the tip of your index finger, then to the tip of your middle finger and then to the tip of your ring finger. If pain free, you can aim to touch the tip of your thumb to the tip of your little finger.
Repeat this movement 15 times.

2. Tearing paper



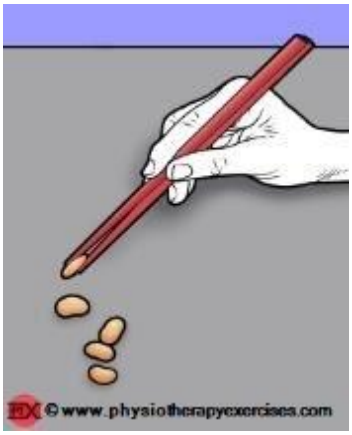
Position yourself with a piece of paper in front of you. Fold the paper into quarters. Tear the paper.

Repeat 10 times.

3. Tracing line on ball

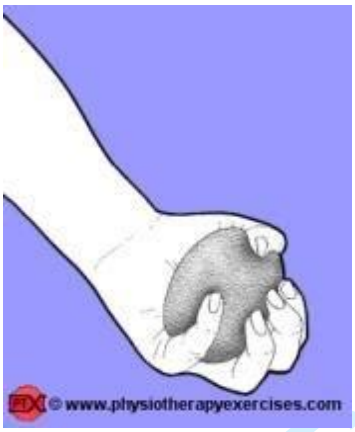
Position yourself with your hand resting on the ball in front of you. Slide your thumb along the line of the ball, while moving the ball with your finger tips.
Trace the line on the ball 15 times.

4. Using chopsticks



Position yourself with the chopsticks in your hand. Use the chopsticks to pick up a bean and place into the container.
Repeat 15 times.

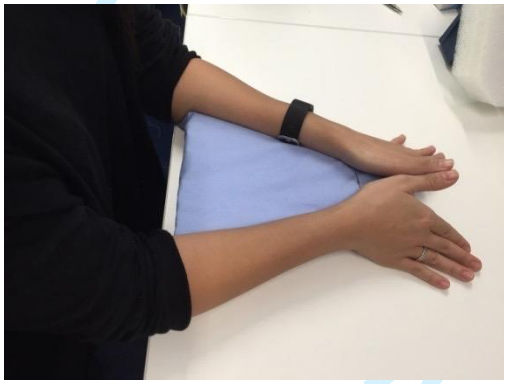
5. Squeezing ball



Position yourself sitting with a stress ball held in your hand. Practice squeezing the ball until it is about three-quarters compressed. Repeat 10 times.

Appendix 3. Technique for the acquisition of the Eaton stress view radiograph.

The radiographs will be obtained in the PA projection with the hand and stress view of the trapeziometacarpal joint placed over an X-ray cassette (the volar aspect of the hand touching the cassette), with the forearms held about 10 cm apart and pronated approximately 45° in neutral deviation. The participants will be instructed to place the thumbs parallel (nails symmetric without tilt) and to actively press them together (inwards and down) with the metacarpophalangeal (MCP) and interphalangeal (IP) joints touching. The wrists are held in neutral alignment and the elbows flexed to 90° bilaterally with the subject seated. The top of the foam piece is placed under both thumbs and the rest of the foam is used to keep the forearms apart as shown in the images provided in this Appendix. The study coordinator will provide this protocol to the radiographer and assure that the technique is being correctly executed.



Appendix 4. Ultrasound scanning protocol.

Lateral longitudinal scans on both the radio-dorsal and radio-palmar side of the first CMC joint will be used to assess inflammatory and structural ultrasonographic findings (i.e. synovitis, Power Doppler signal, osteophytes, articular cartilage damage, joint space narrowing, and bone erosion). Dichotomous grading scales will be used to score all features, in addition to semi-quantitative grading scales for synovitis, Power Doppler signal, and osteophytes. The OMERACT US group has shown the reliability of these scales [1, 2]. In addition, joint space narrowing will be assessed using a quantitative scale, measured in mm, as the distance from the edge of trapezium to the edge of first metacarpal.

In addition, we will examine the ability of high-resolution ultrasonography to delineate morphological characteristics of anterior oblique ligament and radio-dorsal ligaments, the main stabilizing ligaments of this joint.

Subluxation of the first CMC joint is not an uncommon finding in OA due to specific ligament instability, as the anterior oblique ligament plays an important role in preventing volar metacarpal subluxation. The role of dynamic ultrasonographic stress test in detecting the instability of first CMC joint will be assessed. To replicate a clinical test used to detect anterior oblique ligament insufficiency [3], the joint will be held in palmar abduction position, and maximal volarly directed stress will be applied to the base of the first metacarpal, as the methods described to test the stability of this ligament in normal healthy joints [4].

REFERENCES

1. Alcalde, M., et al., A systematic literature review of US definitions, scoring systems and validity according to the OMERACT filter for tendon lesion in RA and other inflammatory joint diseases. Rheumatology, 2012. 51(7): p. 1246-1260.

2. Iagnocco, A., et al., The reliability of musculoskeletal ultrasound in the detection of cartilage abnormalities at the metacarpo-phalangeal joints. Osteoarthritis and Cartilage, 2012. 20(10): p. 1142-1146.

3. Takwale VJ, Stanley JK, Shahane SA. Post-traumatic instability of the trapeziometacarpal joint

of the thumb: diagnosis and the results of reconstruction of the beak ligament. J Bone Joint Surg Br 2004; 86:541–545.

4. Chiavaras, M.M., et al., Sonography of the anterior oblique ligament of the trapeziometacarpal joint: a study of cadavers and asymptomatic volunteers. AJR Am J Roentgenol, 2010. 195(6): p. W428-34.

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

Section/item	Item No	Description	Addressed on page number
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	____yes_____
Protocol version	3	Date and version identifier	____N/A_____
Funding	4	Sources and types of financial, material, and other support	____17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1_____
	5b	Name and contact information for the trial sponsor	____N/A_____
	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	____17_____
	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	3,4
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	4
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)	4
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	5
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)	5,6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8,9
	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)	14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10,11
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	9,10
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 Figure)	11,12

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	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6,7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	9,10,12
	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	14

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	16
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	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15,16
	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)	15
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	13,14
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	16
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)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	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	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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	16
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	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16,17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	yes
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.