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Non-inferiority of saline versus corticosteroid injections for trapeziometacarpal osteoarthritis: a protocol for a pilot and feasibility randomised controlled trial

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ABSTRACT

Introduction Trapeziometacarpal osteoarthritis (TMO) is among the most prevalent forms of upper extremity osteoarthritis. It is frequently associated with significant levels of pain and disability, particularly among ageing women. The typical care pathway for TMO relies on non-surgical approaches for up to 2 years, before surgery is considered. One of the most common non-surgical approaches is an intra-articular cortisone injection. However, these are not universally recommended due to their safety profile and unclear efficacy compared with saline injections. Recent evidence suggests that saline might be non-inferior to cortisone, but this remains to be clarified. This pilot trial aims to assess the feasibility of a trial examining the non-inferiority of saline compared with cortisone injections for TMO.

Methods and analysis This trial will recruit 40 adults with a diagnosis of TMO and a prescription for a cortisone injection from the Centre hospitalier de l'Université de Montréal (CHUM), Canada. Participants will be randomised to receive either an intra-articular injection of 0.9% sodium chloride (experimental arm, n=20) or triamcinolone acetonide (standard of care, n=20) under fluoroscopic guidance at the Radiology Department or under ultrasound guidance at the Physiatry Clinic. Opaque syringes will be used to blind participants and physicians. Feasibility outcomes, collected at all time points, will include recruitment rates, follow-up completion rates and blinding indices. Preliminary efficacy outcomes, collected at baseline and at 1 day, 1 month, 3 months and 6 months post-injection, will include pain intensity (0–10 scales), hand function (QuickDASH 11-items), cumulative analgesic consumption scores, concurrent interventions, adverse events and number of participants receiving a second injection or an arthroplasty. Descriptive statistics will be used to present feasibility outcomes. Preliminary data on the effectiveness of saline and cortisone injections will inform the design of a large-scale study for formal hypothesis testing.

Ethics and dissemination The trial was approved by the CHUM Human Research Ethics Board (2025-11815). The research output will be presented at conferences and published in a peer-reviewed journal.

Trial registration number NCT06401317.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ One of the first trials to explore the feasibility of examining the non-inferiority of saline as a treatment for trapeziometacarpal osteoarthritis.
⇒ Multidisciplinary team, cross-department collaboration and all in a pragmatic setting.
⇒ The assessment of both patient and physician blinding is a key strength of the current study.
⇒ There is potential for unblinding, both among participants not naive to cortisone injections and skilled physicians who may perceive differences in the fluid viscosity; however, this will be formally assessed using the validated Bang's blinding index.
⇒ Injections being delivered using different imaging guidance methods (fluoroscopy with iodinated contrast vs ultrasound without iodinated contrast) could potentially lead to differences in efficacy and safety. Nonetheless, available data do not suggest that these differences are significant.

INTRODUCTION

The human trapeziometacarpal joint at the thumb is unique in both its anatomy and function, enabling the distinctive movement of opposition.[1] Present only in certain primates, this movement is a critical form of prehension that allows for pinching, grasping and manipulating objects and tools. Consequently, the thumb is essential for daily activities, contributing to approximately half of all hand function.[2] Opposition relies on the trapezium and the first metacarpal being concave and convex, making the trapeziometacarpal joint a specialised saddle

joint.[1] This geometry generates compressive and shear forces that may contribute to trapeziometacarpal joint degeneration or osteoarthritis (TMO).[1]

TMO or thumb base osteoarthritis is among the most painful, disabling and prevalent forms of hand osteoarthritis.[3–5] Its prevalence is higher among women and strongly associated with age,[6 7] with radiographic evidence reported in up to 94% of women over 80 years old.[8] The best available data suggest that around 6% of individuals over 50 and more than one-third of those over 80 have TMO.[7] Pain often worsens during activities involving sustained pinching, thumb abduction or wrist rotation (eg, holding a key, a phone or opening a jar), thereby reducing patients' autonomy.[9 10] Over time, it can impair thumb mobility and hand function, ultimately affecting quality of life and psychological well-being.[3–5 11–14] Globally, the total number of hand osteoarthritis cases, including TMO, is projected to increase by nearly 49% by 2050 compared with 2020, making it a leading cause of disability in adults over 70 years of age.[15]

A range of surgical options is available for TMO.[16] However, these are often a last resort for a smaller proportion of cases in which non-surgical approaches fail.[17 18] The typical care pathway for TMO relies on non-surgical approaches for up to 2 years before surgery is considered.[18] Thus, most patients are managed with oral or injected pharmacological agents and physical interventions such as exercise or orthoses.[19] One of the most common treatments for TMO is an intra-articular cortisone injection.[14 19] The *American College of Rheumatology*[20] recommends its conditional use, as intra-articular cortisone is considered more effective than other injectable agents, such as hyaluronic acid. In contrast, the *European League Against Rheumatism*[17] does not endorse this practice due to the scarcity of high-quality evidence supporting its efficacy.

A recent systematic review[19] demonstrated that intra-articular saline injections yielded greater reductions in TMO pain and tenderness at the 12-week follow-up compared with triamcinolone acetonide. The effect size was large, with a standardised mean difference of −1.26 (95% CI −1.94 to −0.58). Moreover, multiple adverse effects of cortisone injections have been documented, including subcutaneous atrophy, tendon ruptures and accelerated progression of osteoarthritis.[21–27] Enhanced cartilage thinning and other radiological signs of joint degeneration, ultimately leading to higher rates of joint replacement, occur more often after repeated use of cortisone injections compared with saline injections or no treatment in knee osteoarthritis.[23 24 28] Although the knee and trapeziometacarpal joint differ substantially in anatomy, loading patterns and biomechanics, these findings raise concern that repeated intra-articular cortisone exposure may also adversely affect joint integrity in TMO, thereby providing a rationale for investigating saline as a potentially safer alternative. This is particularly relevant for the trapeziometacarpal joint, which has thinner cartilage.[29]

Cortisone injections have also failed to demonstrate superiority over saline injections for knee[30] and hip[13] osteoarthritis pain. Given the uncertain superior efficacy of cortisone as a therapeutic agent, it becomes imperative to consider alternative options. Several systematic reviews[19 30–32] suggest that neither single nor repeated cortisone injections provide superior symptom relief for knee and TMO compared with other injectables, including saline. Furthermore, intra-articular saline injections into the lumbar facets have shown comparable effects to active substances, including cortisone.[33] These findings suggest that intra-articular saline may exert therapeutic effects across multiple pain conditions, challenging the assumption that it functions solely as a placebo.[34] Previous studies have suggested that the benefits of saline injections may stem from several mechanisms, including dilution of inflammatory mediators through joint lavage,[30 31 33 34] the osmolality effect of slightly hypertonic saline in reducing inflammation and protecting chondrocytes[35] or complex placebo responses potentially amplified by the invasive nature of intra-articular delivery.[31]

Given the lack of robust evidence supporting the superiority of cortisone over saline injections for TMO, saline warrants investigation as a viable, potentially active treatment rather than an inert comparator. However, the non-inferiority of saline injections relative to cortisone—the current standard of care—remains uncertain and largely unexplored. Before a large-scale, fully powered clinical trial can be undertaken, the feasibility of such a non-inferiority design must first be assessed.

Therefore, the overarching aim of this pilot randomised controlled trial is to examine the feasibility of conducting a non-inferiority randomised controlled trial of saline injections for TMO. Specifically, our first aim is to evaluate key feasibility parameters, including recruitment, retention and blinding procedures. In addition, the trial will provide preliminary estimates of treatment effects and variability, which are critical for calculating the sample size required for a future non-inferiority trial.

METHODS

Study design and setting

This will be a pilot, double-blind, pragmatic randomised controlled trial. The study will be conducted in a single clinical setting at the *Centre hospitaller de l'Université de Montréal* (CHUM), following the recommendations of the updated Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[36] and those of the PRECIS-2 (PRagmatic-Explanatory Continuum Indicator Summary 2) guidelines.[37] The PRECIS-2 looks up of nine criteria below (see figure 1): (1) Eligibility criteria (To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?); (2) Recruitment (How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?); (3) Setting (How different are the settings of

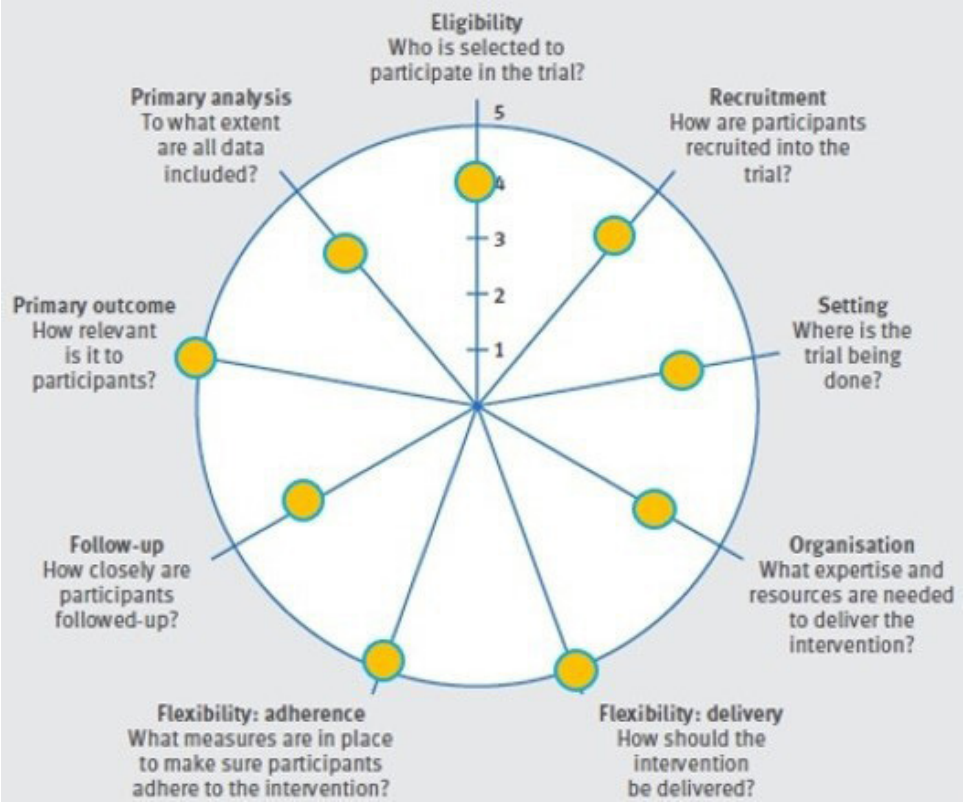

Figure 1 The scorings of this trial using the PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel.[37]

the trial from the usual care setting?); (4) Organisation (How different are the resources, provider expertise and the organisation of care delivery in the intervention arm of the trial from those available in usual care?); (5) Flexibility—delivery (How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?); (6) Flexibility—adherence (How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?); (7) Follow-up (How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?); (8) Primary outcomes (To what extent is the trial's primary outcome directly relevant to participants?); and (9) Primary analysis (To what extent are all data included in the analysis of the primary outcome?). The degree of pragmatism for each domain is scored using a 5-point Likert scale: 1. very explanatory, 2. rather explanatory, 3. equally pragmatic and explanatory, 4. rather pragmatic and 5. very pragmatic.

The study protocol has been pre-registered with the clinicaltrials.gov identifier NCT06401317.

A total of 40 patients with a prescription for intra-articular injection will be recruited from two services at the CHUM: 20 from the Plastic Surgery Service and 20 from the Physiatry Clinic. Patients recruited via the Plastic Surgery Service will receive their injection at the Department of Radiology. Patients referred from the Physiatry Clinic will receive their injection on site. The experimental intervention, that is, an intra-articular saline injection, will be compared with the standard of care, an intra-articular cortisone injection. Feasibility and preliminary non-inferiority outcomes will be assessed at 1 day, 1 month, 3 months and 6 months post-intervention (figure 2). The expected duration of participant involvement will range from 6 to 9 months, depending on the waiting time to receive the allocated intervention (estimated to range between 0 and 90 days).

Study population

To be eligible for participation, individuals must meet all of the following inclusion criteria: aged 18 years or older; diagnosed with TMO confirmed by X-ray interpreted by a radiologist; experiencing pain at the base of the thumb; judged by the attending physician to benefit from an intra-articular cortisone injection rather than other treatments (eg, surgery) after failure of conservative management, including paracetamol, non-steroidal anti-inflammatory drugs, and/or orthoses; and able to read, understand and answer either in French or English.

Individuals meeting any of the following criteria will be excluded from participation: having received an intra-articular cortisone injection in the affected thumb within the past 3 months; having undergone surgery on the same thumb; presenting with pain attributable to trauma (eg, fracture or sprain), rheumatoid arthritis or De Quervain's tenosynovitis; being pregnant or breastfeeding; and known allergies to any components of the solutions (triamcinolone acetonide, benzyl alcohol, carboxymethylcellulose sodium, hydrochloric acid, polysorbate, sodium

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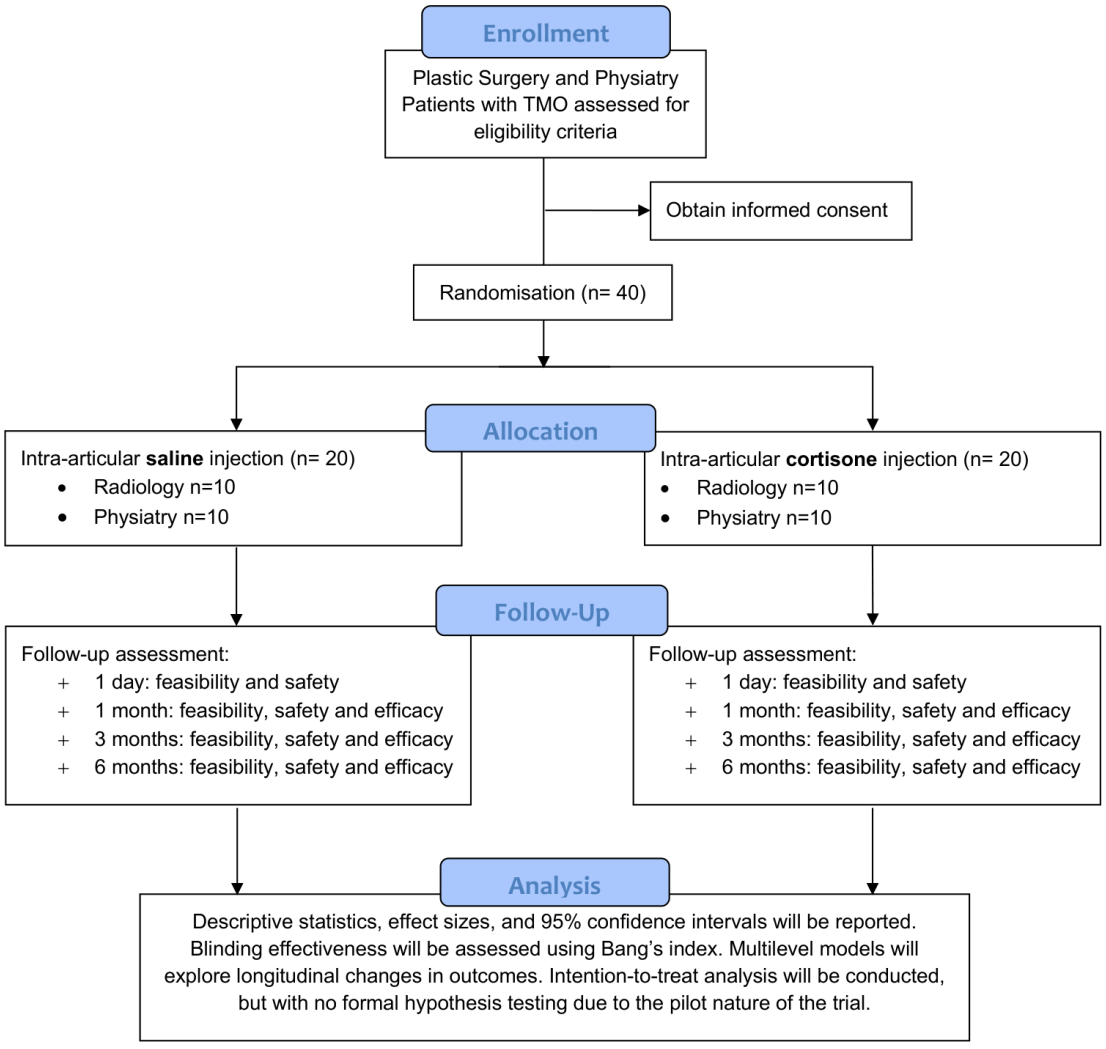

Figure 2 CONSORT diagram of the proposed pilot randomised controlled trial. CONSORT, Consolidated Standards of Reporting Trials; TMO, trapeziometacarpal osteoarthritis.

chloride or sodium hydroxide) or to iodinated contrast media.

Participants will be recruited directly from the patient population attending the CHUM through posters and pamphlets displayed in the waiting rooms of both services. Patients expressing interest in participating will be pre-screened by their physician to confirm the diagnosis of TMO and determine whether an intra-articular cortisone injection is indicated for each case. Study details will then be provided either by a research assistant on-site or through a subsequent call by the trial coordinator. Patients deemed eligible and agreeing to participate will undergo informed consent via the Research Electronic Data Capture (REDCap) platform (Vanderbilt University, Nashville, Tennessee, USA), or in paper format if preferred.

Randomisation and concealed allocation

Immediately after providing consent, eligible participants will be randomised in a 1:1 ratio to receive either saline or cortisone, stratified by injection site (ie, Radiology or Physiatry). A stratified random allocation sequence with a fixed 1:1 ratio within each injection site will be generated by the study statistician using the secure random number generator function *sample*() in R. This sequence will be used to prepare 20 sealed envelopes per site, each containing a card indicating the allocated substance (saline or cortisone). This will result in four groups: (1) cortisone injection in radiology (n=10); (2) saline injection in radiology (n=10); (3) cortisone injection in physiatry (n=10); and (4) saline injection in physiatry (n=10) (see Consolidated Standards of Reporting Trials (CONSORT) diagram in figure 2).

Only the trial coordinator will have access to the randomisation list and the sequentially numbered allocations sealed within the truly opaque envelopes. Participants and clinicians administering the injections will remain blinded to treatment allocation. The research assistant at the Physiatry site is not involved in randomisation to maintain allocation concealment. This will be ensured by securely storing the sealed envelopes at the Research Centre Pharmacy and the Physiatry Clinic from study initiation and opening them sequentially only after

recording the participant ID and date. For injections in the Department of Radiology, the Research Centre Pharmacy will prepare the allocated solution in a syringe and cover it with opaque tape. The research coordinator will deliver the syringe from the Pharmacy to the designated injection room within the Department of Radiology. The radiologist will then enter and administer the injection. For injections in the Physiatry Clinic, a research assistant will prepare the syringe on site. The physicians involved in follow-up will remain blinded, as they will continue to monitor participants in the context of standard clinical care. Only the research coordinator, the pharmacist, the research assistant and the statistician will not be blinded, as they will also be involved in randomisation, syringe preparation and/or data entry and management. Blinding will be maintained by ensuring that research members who are aware of the syringe contents keep this information confidential throughout the study.

Study interventions

The experimental intervention is an intra-articular injection of 0.25 mL of 0.9% sodium chloride (DIN: 02304341; Hikma Canada Limited) into the trapeziometacarpal joint. The comparator is an intra-articular injection of 0.25 mL of 40 mg/mL triamcinolone acetonide (Kenalog-40, DIN: 01999869; McKesson Canada Corporation), which represents the current standard of care in both services. This active comparator is included because a larger-scale clinical trial will aim to assess the non-inferiority (in terms of efficacy and safety) of the experimental intervention (0.9% sodium chloride). Participants will receive a single injection during the study. Any participant for whom the prescribing physician deems it appropriate to administer a second injection—either with the same solution if pain recurs or with the alternative if the first injection fails to provide relief—or who undergoes arthroplasty during the study period will be considered withdrawn. Data collected up to the last follow-up will be included in the analysis.

The Research Centre Pharmacy will prepare and distribute the trial interventions to the Department of Radiology per the randomisation list provided by the trial coordinator. For the Physiatry Clinic, the on-site research assistant will prepare the trial interventions rather than the Pharmacy, since both are on separate CHUM sites. Syringes will contain 0.25 mL of either 0.9% sodium chloride injection United States Pharmacopeia (USP) or 40 mg/mL triamcinolone acetonide injectable suspension USP. At the Department of Radiology, intra-articular injections will be performed by a radiologist under fluoroscopic guidance, using a dorsolateral approach without local anaesthesia, as per standard practice. First, a 25-gauge, 1-inch or 1.5-inch needle will be inserted into the trapeziometacarpal (TM) joint. An extension tubulure connected to a syringe prefilled with iodinated contrast (Omnipaque 240 (iohexol 240 mg I/mL), DIN: 02172739, GE Healthcare Canada) will then be attached to the needle, and a volume of 0.1–0.2 mL of the contrast will be injected into the TM joint to confirm intra-articular placement. Subsequently, a 1 mL syringe containing 0.25 mL of either 0.9% sodium chloride injection USP or triamcinolone acetonide 40 mg/mL (10 mg), covered with opaque tape by a pharmacist, will be attached to the extension tubulure. The agent will then be injected into the TM joint. At the Physiatry Clinic, physiatrists typically administer 0.25 mL of cortisone injections with 0.25 mL of lidocaine under ultrasound guidance, using the same dorsolateral approach and needle specifications as the radiologist. However, to avoid the confounding variable, that is, lidocaine, the local anaesthesia will be replaced with saline solution. Therefore, syringes will contain either 0.5 mL of 0.9% sodium chloride injection USP or 0.25 mL of 40 mg/mL triamcinolone acetonide (10 mg) and 0.25 mL of 0.9% sodium chloride. Before administration, the syringe will be shaken to ensure a uniform suspension. Aseptic technique will be used throughout to minimise infection risk, and the suspension will be inspected for aggregation before withdrawal. Both agents will be stored at room temperature.[27 38]

Outcomes

Feasibility outcomes

The primary aim of this study is to assess the feasibility of conducting a larger clinical trial. Accordingly, the primary outcomes will focus on key feasibility parameters, including recruitment rate, follow-up completion rate (proportion of participants who complete follow-up assessment at a time-point (1, 3 or 6 months), attrition rates and the success of blinding procedures.

The weekly recruitment rate (ie, number of participants enrolled per week) will be estimated from administrative data collected during the active enrolment period. The proportion of enrolled participants relative to the number of participants screened and deemed eligible will also be reported to inform the projected recruitment timeline and resource needs for a fully powered trial.[39] Follow-up completion will be monitored on an ongoing basis by measuring the proportion of participants completing each follow-up relative to the total number randomised. Attrition will be determined as the proportion of participants lost to follow-up at each time point. Reasons for discontinuation or withdrawal from the study will be documented and reported. See table 1 for a representation of the study and participants' timeline according to the SPIRIT recommendations.

Finally, evaluating the effectiveness of blinding procedures is crucial in determining whether double blinding is feasible. Patient blinding will be investigated using a single survey item asking participants which treatment they believe they received.[40] The three response categories provided will be: 'cortisone injection', 'saline injection' or 'I don't know'. This question will be administered via REDCap at 1 day and at 1 month, 3 months and 6 months post-injection. For those without access to REDCap, a phone-based survey alternative will be offered. The effectiveness of physician blinding will be ascertained immediately after the injection, using a similar survey item in

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Table 1 Participant timeline: schedule of enrolment, interventions and assessments.

	Trial period					
	Enrollment		Post-randomisation			Close-out
TIMEPOINT	−90 days to 0	0	+1 day	+30 days	+90 days	+180 days
Enrollment:						
Eligibility screen	X					
Informed consent	X					
Randomisation		X				
Intervention/comparator:						
Intra-articular injection: 0.9% sodium chloride		X				
Intra-articular injection: triamcinolone acetonide		X				
Assessments:						
Weekly recruitment rate	X	X				
Proportion of enrolled participants	X	X				
Follow-up completion rate			X	X	X	X
Attrition rate			X	X	X	X
TMO pain		X		X	X	X
Hand function (QuickDASH)		X		X	X	X
Hospital Anxiety and Depression scores		X				
Cumulative Analgesic Consumption		X	X	X	X	X
Concurrent intervention		X	X	X	X	X
Adverse events			X	X	X	X
Physician blinding			X			
Participant blinding			X	X	X	X
Participants receiving a second injection				X	X	X
Participants undergoing arthroplasty				X	X	X

AEs, adverse events; Fxn, function; HAD, Hospital Anxiety and Depression Scale; TMO, trapeziometacarpal osteoarthritis.

REDCap. Physicians will be asked which treatment they believed they administered using three response categories: 'cortisone injection', 'saline injection' or 'I don't know'.[40]

Preliminary efficacy outcomes

The secondary aim of the study is to collect preliminary data on the potential non-inferiority of saline injections compared with cortisone injections as the standard of care. Non-inferiority will be assessed through efficacy and safety outcomes at four time points after intervention: day 1 (to evaluate adverse events (AEs) only) and at 1, 3 and 6 months for efficacy outcomes (see figure 3 and table 1).

Efficacy will be explored through TMO pain intensity and upper limb function, both considered core outcomes for osteoarthritis clinical trials by the international consensus group OMERACT (*Outcome measures in Rheumatology*)[41 42] and for pain trials based on the IMMPACT (*Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials*) recommendations.[43]

Participants will rate their current, average and worst pain intensity over the past 7 days using a 0–10 numerical rating scale (0=no pain and 10=worst pain possible).[44]

Upper limb function will be assessed with the QuickDASH,[45 46] a short version of the widely used 30-item *Disabilities of the Arm, Shoulder and Hand* questionnaire. The 11-item QuickDASH assesses the level of physical function and symptoms among patients with musculoskeletal conditions affecting the upper limb and has been adapted for TMO.[14] The total score ranges from 0 (no disability) to 100 (maximum disability).[46]

Measuring concomitant analgesic use has also been proposed as a core outcome for pain trials by IMMPACT.[43] Therefore, it will be captured using the Cumulative Analgesic Consumption Score (CACS).[47] This tool combines a qualitative assessment based on the WHO analgesic ladder[48 49] with a quantitative evaluation based on a score computed from the number of analgesics taken from each of three different categories: acetaminophen/nonsteroidal anti-inflammatory drug (NSAIDs), weak opioids and strong opioids.[47]

Safety, a critical component in estimating non-inferiority, will be assessed through both spontaneous participant reports[50] and active surveillance via follow-up questionnaires. All AEs occurring from the time of study

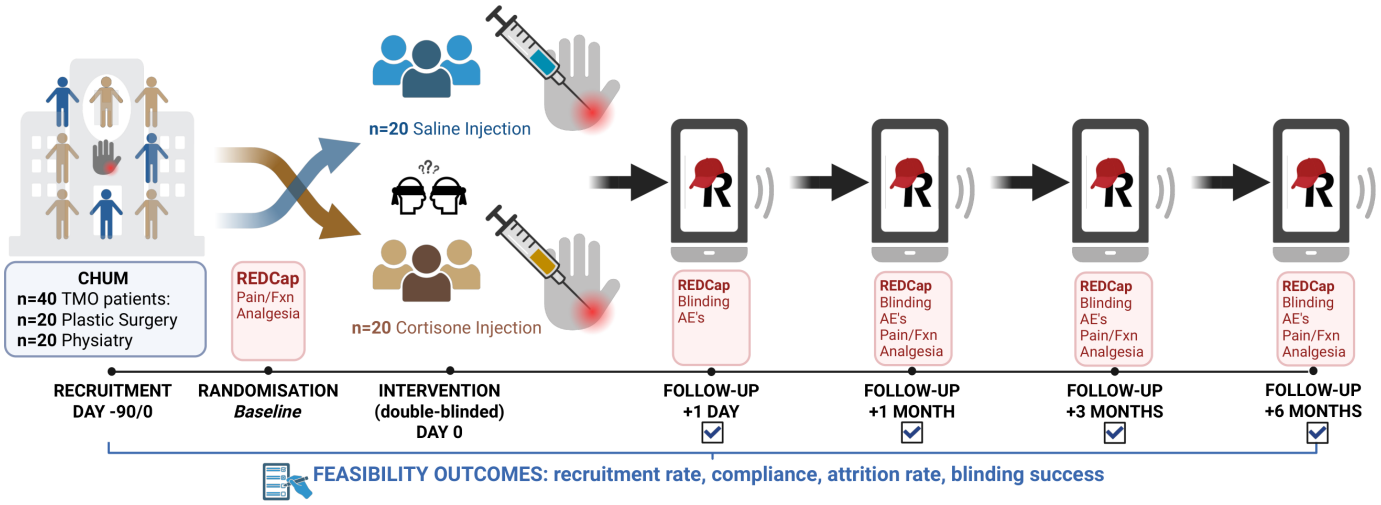

Figure 3 Overview of the pilot trial timeline and study design. Participants with trapeziometacarpal osteoarthritis (TMO) will be recruited from the Centre hospitalier de l'Université de Montreal's (CHUM) Plastic Surgery and Physiatry clinics (total n=40) and randomised 1:1 to receive a single intra-articular injection of either saline or cortisone. Follow-up assessments will be conducted via REDCap or in paper format at 1 day and at 1 month, 3 months and 6 months post-injection. Primary feasibility outcomes include recruitment rate, follow-up completion, attrition rate and blinding success. AE, adverse event;

intervention through 6 months post-injection will be recorded, regardless of attribution. The information collected will include the event description, date of onset, symptom duration (in days), resolution/stabilisation of the event and any medical assistance received. All reported AEs will be reviewed by a qualified physician who is part of the study team and will be responsible for assessing the severity of an AE (mild, moderate, severe, serious or fatal)[51 52] and the relationship to the study intervention (certainly related, probable, possible, improbable, not assessable and unrelated).

The number of participants requesting a second injection with a different solution due to a perceived lack of efficacy will be compared between groups (saline vs cortisone). Similarly, the number of participants requesting a second injection with the same solution due to pain relapse will be compared between groups. Finally, the number of participants undergoing arthroplasty during the study period will also be compared between groups.

Study procedures

After providing informed consent, recruited participants will be randomised prior to receiving their allocated intervention. Due to its pragmatic nature, there could be a delay of up to 3 months before receiving the injection. Once the injection date is confirmed, an opaque syringe containing the allocated solution will be prepared by the Research Centre Pharmacy for the Department of Radiology or by the on-site research assistant of the Physiatry Clinic. Three days before the injection, participants will be contacted to remind them to complete the baseline questionnaire, either online via REDCap or in paper format. This questionnaire will include sociodemographic and medical history items, TMO pain ratings,[14 44] hand function (QuickDASH),[14 46] concurrent pain medication[47] and interventions (eg, orthosis), as well as depressive symptoms, measured using the Hospital Anxiety and Depression Scale (0–21 for each subscale,[53] a known covariate of TMO pain and hand function.[14]

Participants will receive monetary compensation to offset potential costs associated with study participation. The amount will be proportional to the number of completed questionnaire responses, up to a maximum of $C50. Participants will continue to receive medical follow-up as part of their routine clinical care. Participants will receive only one injection in this trial. However, to respect the pragmatic nature of the design, participants who request and are prescribed a second injection (with the same or a different agent) will be allowed to do so, although they will be considered withdrawn from the study.

Sample size justification

Since the correlation between baseline TMO pain and 1-month post-injection TMO pain has not been reported in the literature, the mean and SD of pain intensity reductions 1 month after saline and cortisone injections were estimated[54] using the median, IQR and group sizes reported by Meenagh *et al*.[55] For these estimates, different values of correlation were considered (see online supplemental table 1). Based on these data and assuming a conservative correlation coefficient of 0.10 between baseline and 1-month post-injection measures (not reported in the literature), a target sample size of 102 participants was calculated, increasing to 120 to account for a 15% attrition rate. The correlation coefficient and attrition rate estimated from this pilot trial will subsequently be used to refine the sample size calculation for the full-scale trial. This sample size was derived using a superiority margin of 1 point on a 0–10 scale for minimal clinically important difference and 2 points for clinical significance, based on IMMPACT recommendations.[56]

An analysis of covariance (ANCOVA) model adjusted for baseline pain with a two-sided significance level of 0.05 and 80% power was used for this calculation.[57] This target sample size would also be adequate for a linear mixed model as it meets the recommendations of Austin and Steyerberg for at least two observations per independent variable for model parameter and SE estimations.[58] For the current pilot trial, we aim to recruit 40 participants, which would suffice to show small to medium effect sizes[59] and represents over 9% of the full trial sample size, as recommended for a pilot study.[60] This pilot sample size will also allow us to estimate key feasibility proportions (eg, recruitment, attrition) with sufficient precision (ie, ±15 percentage points at the 95% confidence level), even in conservative scenarios (ie, proportions around 50%).

Statistical analysis

All analyses will be conducted based on the intention-to-treat principle. Missing data will be handled through multilevel modelling (MLM) under the assumption of missing at random. Given the pilot nature of the trial, no formal hypothesis testing will be performed. Instead, the trial will report descriptive statistics, effect size and variance estimates, along with 95% CIs to inform sample size calculations and outcome selection for a fully powered trial.

Feasibility outcomes will be presented using descriptive statistics, with stratification by injection site (Radiology vs Physiatry) to account for potential heterogeneity. These include the weekly recruitment rate, the proportion of participants enrolled relative to those screened and eligible, follow-up completion rates and attrition rates at each follow-up. To analyse the effectiveness of blinding procedures for both patients and physicians, Bang's blinding index will be computed.[40 61] The blinding index ranges from −1 to 1, where 0 signifies perfect blinding, a value of 1 indicates a complete lack of blinding (ie, perfect guesses) and −1 suggests systematic incorrect guesses. Blinding indices will be calculated at four time points for patients and a single time point for physicians.

MLM will be used to explore changes in pain intensity, hand function and analgesic medication use over time. MLM is considered appropriate for longitudinal data analysis,[62 63] as it accounts for repeated measures and nested data structures. Models will be built parsimoniously to include time, intervention group (saline vs cortisone), injection site (radiology vs physiatry), and the appropriate interaction terms as covariates or predictors. These models will serve to estimate between- and within-subject variability, informing the design and sample size of larger trials. For all models, the assumptions of normality, linearity and homoscedasticity will be assessed using residual plots and other diagnostic tools. To determine the non-inferiority of saline injection vs cortisone injection, the CIs of the interaction terms estimated at each time point after the intervention will be calculated and compared with the minimum clinically important difference,[64 65] which is >10% pain reduction on a scale of 10 for pain intensity[66] and 15.9 points for hand function as measured by QuickDASH.[67] A decrease in CACS will also be considered as additional evidence of non-inferiority.

The type, onset date, duration and necessity of medical assistance for AEs will be summarised descriptively by intervention group (saline injection *vs* cortisone injection), and the frequency of AEs will be compared between groups. The number of participants who receive a second injection with a different or the same solution, as well as those who undergo arthroplasty, will also be summarised descriptively and compared qualitatively between groups.

Study monitoring

Monitoring of the trial will be performed to verify that the rights and well-being of participants are protected, the reported trial data are accurate, complete and verifiable from source documents, and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), *International Council on Harmonisation (ICH) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6(R2)* and local regulations and requirements. VF will assume the medical/clinical part of study monitoring, while TH and CG-M will assume the scientific aspect. They will meet every 3 months to assess the safety and efficacy data on each arm of the study.

Data management

All data will be collected at the CHUM Research Centre and entered into REDCap, a secure, web-based application housed on CHUM servers. Patients will be identified only by a unique study ID; no names or identifying information will appear in reports or paper records. Research data for analysis and reporting will be transmitted to and stored in the secure eREG system at CHUM, without contact or identifying information. Study management systems will be password-protected. Paper copies will be kept in a locked filing cabinet at the CHUM under the responsibility of the principal investigator and accessible only to authorised personnel or those mandated by the CHUM Research Ethics Committee or Health Canada. They will be destroyed 15 years after the study concludes. At the study end, databases will be de-identified and archived at eREG. The principal investigator will retain source documents, consent forms, Case Report Form (CRFs) and patient identification records in a secure location for at least 15 years to allow for audits.

Patient and public involvement

No patient partner or association has been involved with this project at this stage.

Ethics and dissemination

This trial was approved by the CHUM human research ethics board (2025-11815). The protocol and the off-label use of intra-articular 0.9% sodium chloride received a No Objection Letter from Health Canada on 30 May 2025.

The results of this study will be submitted for presentation at scientific conferences locally (CHUM Research Centre), provincially (Quebec Pain Research Network)

and nationally (Canadian Pain Society). In addition, the trial will be submitted for publication in a scientific journal in the field.

DISCUSSION

In the years to come, the burden of osteoarthritis is expected to rise as the global population ages.[15] Given the essential role of thumb mechanics in hand function,[2] TMO is likely to be particularly detrimental to manual occupational activities, including those in the rapidly growing field of information technologies and related sectors. Far from being an ideal standard of care for the management of TMO, cortisone injections have prompted serious concerns about their efficacy.[17] Evidence has failed to demonstrate the superiority of cortisone over seemingly inert saline for multiple osteoarthritis conditions, including TMO.[19 30–32] Moreover, the safety profile of cortisone injections is also a reason for concern, particularly when repeated injections are administered. In some cases, the treatment may fare worse than the natural course of the disease, paradoxically accelerating the progression of osteoarthritis.[21–28] Notwithstanding, cortisone remains among the most commonly used interventions for these patients.[14 19]

An alternative explanation for this phenomenon is that intra-articular saline, the most common comparator in cortisone trials, may exert therapeutic effects through specific biological mechanisms. The proposed pilot trial will provide preliminary data to determine whether examining sodium chloride as an active agent, rather than an inert placebo, is indeed feasible. Achieving this would represent a critical first step toward potentially reshaping osteoarthritis pain management. However, to further support the hypothesis that saline has genuine therapeutic potential, successful blinding needs to be achieved and maintained throughout the trial. This is essential to determine whether saline acts through specific mechanisms independent of contextual or ritual factors. Indeed, observing a statistical effect of saline would not suffice to establish a causal link; a plausible biological mechanism is also required.[68] Previous investigations have speculated that joint rinsing may dilute inflammatory mediators,[30 31 33 34] or that slightly hypertonic saline might induce an osmolality effect to reduce joint inflammation and preserve chondrocytes.[35] Alternatively, others have posited that benefits from saline could be explained by complex placebo effects, potentially enhanced by its invasive route of delivery.[31] If non-inferiority can indeed be evaluated under appropriate blinding conditions, this may open the door to investigating these mechanisms, among others, among putative mechanisms of intra-articular saline injections and to considering their use as part of routine clinical care.

Strengths and limitations

To the best of our knowledge, this will be the first trial to explore the feasibility of examining the non-inferiority of saline as a treatment for TMO. This is timely, given emerging trials exploring alternatives to cortisone injections for various forms of osteoarthritis, including the use of lower doses previously considered to be below the effectiveness threshold.[69 70] The proposed trial will benefit from a large, multidisciplinary team with broad expertise covering all aspects required for its successful implementation. Collaboration across multiple departments involved in the care of patients with TMO is a vital asset for the trial's pragmatic nature. It will also allow determining whether differences exist in terms of recruitment rate, patient profile, treatment delivery and blinding. The CHUM offers modern and efficient infrastructure that will facilitate all trial procedures, including blinding strategies, which are already being tested in a concurrent clinical trial. In particular, the assessment of both patient and physician blinding is a key strength of the current study that has been rarely conducted in previous trials.

While cross-department collaboration is certainly a strength, it also implies that participants recruited at different CHUM locations will not receive identical care. Injections will be delivered using different imaging guidance methods, with or without iodinated contrast, and with triamcinolone either diluted in saline or undiluted, which could potentially result in differences in efficacy and safety. Nonetheless, available data do not suggest that these differences are significant.[71 72] Other potential limitations include a relatively short follow-up period, justified by the pragmatic nature of the study: most patients who do not significantly improve at 6 months consider a second injection or alternatives, including surgery,[16–18] and longer-term safety outcomes (eg, radiographic progression) would not be captured. For the same reasons, participants will be allowed to use concurrent interventions, which may introduce confounders. To mitigate the risk, the use of concurrent pain medication and other interventions (eg, orthosis) will be documented using a validated metric.[47] There is also potential for unblinding, both among participants who are not naïve to cortisone injections and among skilled physicians, who may perceive differences in the fluid viscosity. Nonetheless, this remains a relatively unexplored area that will be formally assessed using the validated Bang's blinding index.[40] Since this is a pilot study designed to determine feasibility with a small sample size of 40, the results may suggest non-inferiority of saline injections compared with cortisone injections, particularly in cases where a false negative is due to insufficient power to detect an actual difference between the interventions. This remains a significant limitation in interpreting the findings. Therefore, a fully powered trial should follow this pilot study. Furthermore, no patient partners have been involved at this stage, but we plan to involve patients in designing the full trial. Finally, although the trial focuses on feasibility outcomes, the exploration of efficacy could be enriched by imaging-based measures, which have provided critical safety data for cortisone injections but

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remain unexplored in TMO. If feasible, future fully powered trials may incorporate these measures alongside clinical outcomes.

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