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Clinical Study Protocol

Efficacy and safety of an oral complementary medicine combination in people with symptomatic knee osteoarthritis: Protocol for the double-blind, randomized, placebo-controlled ATLAS trial

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ABSTRACT

Objective: To investigate the efficacy and safety of an oral complementary medicine combination formulation relative to placebo, on changes in pain intensity from baseline to week 12, in people with knee osteoarthritis (OA).
Design: A placebo-controlled, double-blind, two-arm, superiority, phase II, Randomized Controlled Trial (RCT) (ACTRN12623000380695). We will recruit 82 participants (~41 per arm), aged ≥40 years, with a clinical diagnosis of symptomatic knee OA and radiographic change on x-ray (Kellgren-Lawrence Grade ≥2). Participants will be randomly allocated to receive either a complementary medicine formulation containing a daily dose of *Boswellia serrata* extract (Boswellin® Super, 250 mg/day), pine bark extract (Fenoprolic™ 70 Organic 100 mg/day), curcumin (500 mg/day), piperine (5 mg/day), and methylsulfonylmethane (MSM, 1500 mg/day), or placebo, for 12-weeks. The primary endpoint will be change from baseline in average knee pain intensity at 12-weeks (visual analogue scale). Secondary endpoints will include change in knee pain from baseline to 12-weeks in the Knee Injury and Osteoarthritis Outcome Score (KOOS), global assessment of disease activity, global rating of change, and health-related quality of life (AQoL-8D).
Ethics and dissemination: This protocol has been approved by the University of Sydney Human Research Ethics Committee (#2021/877). Dissemination will occur through lay summaries, infographics, conference abstracts, oral presentations, theses, and scientific publications.
Conclusion: This RCT will provide credible evidence about the efficacy and safety of this complementary medicine combination and inform updates to international clinical practice standards on the use of complementary medicines in the management of symptomatic knee OA.

1. Introduction

Major advances in the understanding of the pathophysiology of osteoarthritis (OA) have not yet translated into improved treatments [1]. While paracetamol has been prescribed for OA in the past, more recent evidence suggests it provides only minimal improvements in pain and function [2,3], and is thus now recommended against in many clinical practice guidelines [4]. More recent evidence has also raised questions about the longstanding recommendation to prioritize the use of NSAIDs as the "first line" medication option for OA, particularly with respect to

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their limited analgesic effects and potential for cardiovascular and gastrointestinal toxicity [3,5].

A growing field of interest is the management of knee OA with complementary medicines; defined as natural products containing herbal, vitamin and minerals and nutritional compounds. In the management of OA, complementary medicines of interest have included glucosamine, chondroitin sulfate, omega-3 fatty acids, turmeric/curcumin, collagen, and various vitamins and minerals [6,7]. These are often used as adjuncts to conventional treatments for osteoarthritis, aiming to reduce pain, inflammation, and cartilage degradation, as well as to improve joint function and overall quality-of-life [6]. However, there is limited evidence supporting their use in OA, and consequently, the existing clinical guidelines vary across countries in recommending their use [8].

In 2018, our team undertook a systematic review and meta-analysis of complementary medicines for OA and found four lesser-known complementary medicines, including herbal extracts of *Boswellia serrata* extract (BSE), pine bark extract (PBE), curcumin, and the naturally occurring chemical methylsulfonylmethane (MSM), demonstrated the best evidence in improving OA symptoms [9]. We hypothesized that combining these supplements with similar pharmacological properties may offer additive and synergistic effects by acting on different mechanistic pathways [10]. The safety of the trial medicine was tested in an observational pharmacokinetic study that showed the individual ingredients and combination formula did not have a pharmacokinetic interaction and were safe for healthy volunteers [10]. However, in the subsequent randomized clinical trial examining the efficacy and safety of this combination in people with hand OA (RADIANT study), the authors found no evidence that this combination was effective compared to placebo, but it was well tolerated by participants [11]. The authors stressed, however, that due to the heterogeneous nature and distinct phenotypes of OA, this combination may be better suited to other joints [11], particularly for the knee, where most of the prior evidence had been collected.

Therefore, the ATLAS trial aims to investigate the efficacy and safety of an oral complementary medicine combination formulation for treating symptomatic knee OA. The primary objective is to compare the effect of the formulation, relative to placebo, on changes in pain intensity from baseline to week 12. The secondary objectives include comparing the effect of the formulation, relative to placebo, on changes in Knee Injury and Osteoarthritis Outcome Score, global assessment of disease activity, global rating of change, and health-related quality of life (AQoL-8D) from baseline to week 12. We hypothesize that a 12-week treatment regimen with the formulation will be superior to placebo in improving pain intensity in people with symptomatic knee OA. The outcome of this randomized placebo-controlled trial (RCT) will provide reliable evidence for the efficacy and safety of this combination complementary medicine on knee OA symptoms and offer crucial insights to address a significant evidence gap that may contribute to revisions of international clinical practice standards.

2. Materials and methods

2.1. Trial design

ATLAS is a two-arm, placebo-controlled, double-blinded, RCT. The primary endpoint is at 12-weeks. This protocol conforms to the Standard Protocol Items Recommendations for Interventional Trials 2013 Statement [12] and the main results paper will be guided by the Reporting Randomized, Controlled Trials of Herbal Interventions: An Elaborated CONSORT Statement [13].

2.2. Trial setting

ATLAS will be conducted by the Osteoarthritis Clinical Research Group at the Kolling Institute, The University of Sydney (Sponsor), and Royal North Shore Hospital, Sydney, Australia. It will be conducted online, except for eligibility x-rays that will be undertaken at local imaging centers and sample collection and processing for a sub-study, which will occur at Royal North Shore Hospital (Sydney, Australia).

2.3. Participants, recruitment, and eligibility

The trial will recruit 82 participants (~41 per arm) with knee OA from the community. The trial will be promoted through the Osteoarthritis Clinical Research Group's clinical and research networks, paid or free postings on social or traditional media, at community-based events, via local clubs/organizations, health facilities, research institutes, and e-newsletters. We will also accept health professional referrals. If required, the investigators may recruit through clinical trial recruitment companies.

Eligible participants will be aged 40 years or older, with symptomatic knee OA as defined by the American College of Rheumatology criteria [14] and radiographically confirmed in the tibiofemoral (TF) and/or patellofemoral (PF) compartments as Kellgren-Lawrence Grade (KLG) $\geq$2 (Table 1). Participants will be required to have at least moderate average pain intensity of $\geq$40 on a 100-point visual analogue scale (VAS) in at least one knee (index knee) for at least half the days in the previous month.

2.4. Interventions

Participants allocated to the active treatment group will receive an encapsulated formulation, containing a total daily dose of BSE (Boswellin® Super, 250 mg/day), PBE (Fenoprolic ™ 70 Organic, 100 mg/day), curcumin (500 mg/day), piperine (5 mg) and MSM (1500 mg/day). The placebo group will receive an identical encapsulated formulation containing microcrystalline cellulose. The dosage regimen for both arms is four capsules per day, taken as two capsules twice a day, for 12-weeks (Table 2). The specific dosage for this trial was based on the doses reported in previously published studies included in our prior systematic review [15] as well as in more recent studies [16–19], and the availability and cost of the products. Considering the size and number of the supplement combination capsules, we chose a relative low dose with evidence of treatment effect.

Mayne Pharma (Salisbury South, SA, Australia) sourced the produce materials and manufactured the product according to Good Manufacturing Practice as per the International Conference on Harmonization Quality Guideline. One-quarter of the daily dose of the trial products is encapsulated in size 00 (0.95 ml volume) opaque white gelatine capsules. Placebo capsules are identical in weight, shape and color.

2.5. Randomization, treatment allocation and dispensing, and blinding

Eligible participants will be assigned to either the active or placebo group (Fig. 2) using the randomization module of REDCap, with an allocation of 1:1, using random permuted block sizes, and stratified by KLG (KLG 2 & 3 vs KLG 4). The randomization schedule was prepared by a statistician prior to trial commencement.

A designated unblinded researcher will allocate the study kit based on their assigned treatment group. All other members of the research team will remain blinded to the treatment allocation throughout the trial until analysis of the results are completed. A process is in place for unblinding in the event of a medical emergency.

2.6. Permitted, rescue and excluded medications

Participants may use up to 3000 mg daily of acetaminophen/paracetamol as a rescue medication to treat worsening pain. Usage will be captured in a weekly pain survey. Participants will be instructed to abstain from any pain medication for 48-h before the day scheduled for their weekly pain assessments. Participants will be discouraged from taking the following medications and treatments at any time during the trial: corticosteroids (intra-articular or intramuscular); sedative drugs with anesthetic and muscle relaxant properties (e.g., barbiturates, benzodiazepines); other supplements containing one or more of the active ingredients; investigational

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
Have internet access and an active email account and a fixed address in Australia for the duration of the trial.
Have sufficient English to give informed consent, understand trial protocols, communicate with the research team, and complete online surveys.
Be ≥ 40 years of age
Have pain in the index knee for at least half of the days in the previous month before screening. If both knees are affected by OA, the most symptomatic knee will be the index knee. If both knees are similarly affected, the trial doctor will determine the index knee upon radiographic severity.
Have, on average, moderate knee pain intensity (≥40 on a 100 VAS) in the index knee during the week prior to screening and baseline assessments.
Fulfill the clinical and radiological ACR criteria for knee OA [14] using participant-reported symptoms and/or signs as follows: • Knee pain on most days AND • Osteophytes on X-ray AND • At least one of the following: o ≥ 50 years of age o Morning stiffness <30 min o Crepitus
Confirmed KLG ≥2 in the tibiofemoral (TF) or patellofemoral (PF) compartment based on an X-ray of the index knee [34]. As there is no KLG or OARSI atlas definition of PF OA based on radiographs, the same criteria as TF OA will be used to quantify the severity of radiographic OA in the PF [35].
Willing to maintain a routine (i.e., consistent dosage and frequency) of pharmacological therapies and any other relevant treatments, including physical activity, physical therapy, bracing, or other lifestyle or behavioral treatments for the duration of the trial.
Willing to abstain from protocol-specified prohibited medications for the duration of the trial.
Willing to abstain from any supplements targeting OA for the duration of the trial.
Exclusion criteria
Have known hypersensitivity to the active or placebo components of the trial products (i.e., *Boswellia serrata* extract, curcumin, piperine (black pepper), pine bark extract, MSM, and microcrystalline cellulose USP) or other ingredients of the capsule (Gelatin and Titanium dioxide).
Regularly take centrally acting analgesics (e.g., opioid, duloxetine, pregabalin).
Unwilling to undergo a 48-h washout before the weekly pain assessments.
Unwilling to discontinue products containing the active ingredients: • BSE • PBE • MSM • Curcumin (use of turmeric food spice is allowed) • Piperine (use of black pepper as a food spice is allowed)
Have a history of crystalline diseases (e.g., gout, calcium pyrophosphate deposition disease), autoimmune arthritis (e.g., rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, ankylosing spondylitis), hemochromatosis or fibromyalgia. Exceptions are: • Participants diagnosed with gout are eligible if the condition is being appropriately treated and they have not experienced flare-ups for at least 12-months • Participants diagnosed with hemochromatosis with normal iron levels for at least 12-months
Pregnant or breastfeeding, or of childbearing potential but not willing to use contraceptive methods for the duration of the trial.
Currently taking medications known to have potential pharmacological interaction with one or more of the supplements being tested, including: • Antiplatelet/anticoagulant drugs (e.g., warfarin) • Immunosuppressants (e.g., prednisone) • Antidiabetic medication (e.g., metformin, insulin) • Sulfasalazine, midazolam or norfloxacin • Chemotherapy drugs (e.g., docetaxel, etoposide) • Antiretroviral (anti-HIV) drugs (e.g., saquinavir, indinavir) • Anti-epileptics (e.g., carbamazepine, lamotrigine, vigabatrin, gabapentin, clobazam, clonazepam, ethosuximide, phenytoin, primidone, sodium valproate, topiramate, tiagabine, levetiracetam) • Calcineurin inhibitors (e.g., cyclosporin, tacrolimus) • Other medications metabolized by the enzyme CYP3A4 • Drugs with a very high first-pass metabolism (e.g., buspirone, ergotamine, lovastatin, nimodipine, simvastatin) or high first-pass metabolism (e.g., oestradiol, atorvastatin, felodipine, isradipine, nicardipine and propafenone)
Had previous intra-articular (IA) therapies, including: • IA hyaluronic acid or IA steroid injections in the index knee in the past 6-months or • IA autologous blood product or a stem cell injection in the index knee in the past 12-months
Have any unstable concurrent clinically significant acute, chronic medical conditions or abnormal laboratory findings that would jeopardize the participant's safety, interfere with the protocol's objectives, or affect the participant's compliance.
Have cancer or other tumor-like lesion (except non-melanoma skin cancer) which has been active in the last three years.
Have any condition that could confound the participant's assessment of index knee pain, including, same-side hip pain referred to the knee, diabetic or peripheral neuropathy or knee pain referred from the back.
Have had a knee infection diagnosis within one month of screening.
Have had an acute injury to the index knee within 6 months of screening.
Are participating in another clinical trial or using an investigational drug or device within 30 days of screening.
Anticipate any invasive procedure (or surgery) on the index knee during the trial duration.

VAS: Visual Analog Scale; PASS: Patient Acceptable Symptoms State; ACR: American College of Rheumatology; KLG: Kellgren-Lawrence Grade; TF: Tibiofemoral; PF: Patellofemoral; CPPD: calcium pyrophosphate deposition disease; HIV: Immunodeficiency Virus; IA: Intra-articular.

products from another clinical trial; intra-articular injections of any agents; and any medications known to have potential pharmacological interaction with one or more components of the trial products (Table 1).

2.7. Outcomes and endpoints

Tables 3 and 4 summarize the trial outcomes and data collection points. All outcomes will be self-reported with the 12-week assessment being of primary interest. Participants will nominate their most painful knee (trial index knee). The six mandatory domains recommended by the updated core domain set for hip and knee OA trials will be measured (pain, physical function, quality of life, patient's global assessment of the target joint, adverse events (AE), and mortality) [20]. Outcome measures are validated for OA as recommended by the Osteoarthritis Research Society International [21], the International Consortium for Health Outcomes [22], or have been used previously [11].

Table 2
Trial intervention.

Group	Ingredient and daily dose	Ingredients and dose per capsule	Capsule color	Dosage
Active	- BSE 250 mg - PBE 100 mg - MSM 1500 mg - Curcumin 500 mg - Piperine 5 mg	- BSE 62.5 mg - PBE 25 mg - MSM 375 mg - Curcumin 125 mg - Piperine 1.25 mg	opaque white	Two capsules twice a day
Placebo	Microcrystalline cellulose	Microcrystalline cellulose (matching the weight of the active capsule)	opaque white	Two capsules twice a day

MSM: methylsulfonylmethane.

2.7.1. Primary outcome

Index knee pain intensity, will be collected from baseline to week 12, assessed using a 0–100 point VAS, in response to the question "How much pain in your LEFT/RIGHT knee did you experience on average over the past week" (0–100 = worst pain possible)?" [23]. The primary endpoint, based on the change from baseline, will be the between-group difference after 12-weeks, estimated from the least square means and adjusted for baseline levels to reduce random variation.

2.7.2. Secondary outcomes, other outcomes and endpoints

Details of the secondary outcomes and other data collected are provided in Tables 3 and 4.

2.8. Patient and public involvement

The trial intervention, methods, and materials were evaluated in four people with knee OA during a two-week pilot study (March–April 2024). Participants provided feedback on the trial procedures, intervention burden, and time commitment. Participants also provided feedback on all participant-related documents. The protocol was amended to reflect participant feedback. Pilot data will not be analyzed in the main trial.

2.9. Trial procedures

The trial procedures and sequence of events are shown in Fig. 1, Fig. 2, and Table 3. All online surveys will be completed by participants on their own devices using the Research Electronic Data Capture system [24].

Table 3
Secondary outcomes and additional outcomes collected from study participants.

No #	Outcome	Details
Secondary outcomes		
1	*Change in participant-reported knee pain intensity*	Calculated from baseline to weeks 1 through to 11 on a 100-point VAS (0 = no pain to 100 = worst pain possible).
1	*Change in knee pain*	Collected at weeks 2, 6 and 12. Change in other knee symptoms calculated from baseline to weeks 2, 6 and 12. Derived from the relevant (pain) sub-scale of the KOOS questionnaire. The KOOS is a knee-specific instrument developed to assess participants symptoms and functional limitations related to knee OA, with 42 questions across five separately scored subscales [36]. Each question is measured using Likert responses (0–4), and questions pertain to the previous seven days. The KOOS is a widely used disease-specific instrument whose reliability, validity and responsiveness have been demonstrated [37].
2	*Change in other knee symptoms*	Collected at weeks 2, 6 and 12. Change in other knee symptoms calculated from baseline to weeks 2, 6 and 12. Derived from the KOOS other symptoms subscale.
3	*Change in knee function in daily living*	Collected at weeks 2, 6 and 12. Change in other knee symptoms calculated from baseline to weeks 2, 6 and 12. Derived from the KOOS function in daily living (ADL) subscale.
4	*Change in knee function with sport and recreation*	Collected at weeks 2, 6 and 12. Change in other knee symptoms calculated from baseline to weeks 2, 6 and 12. Derived from the KOOS function with sport and recreation subscale.
5	*Change in knee-related quality of life*	Collected at weeks 2, 6 and 12. Change in other knee symptoms calculated from baseline to weeks 2, 6 and 12. Derived from the KOOS knee-related Quality of Life subscale.
6	*Change in Patient Global Assessment (PGA) of disease activity*	Collected at weeks 2, 6 and 12. Change calculated from baseline to week 12 in response to the question, "Considering all the ways your knee osteoarthritis affects you, how have you been during the past week?". The single question is scored on a 100-point VAS (0 = very well to 100 = very poor) [38].
7	*Change in the health-related quality of life*	Collected at weeks 2, 6 and 12. Change calculated from baseline to weeks 2, 6 and 12 from the Assessment of Quality-of-Life measure (AQoL-8D) [39]. The AQoL is a health-related multi-attribute utility QoL instrument with 35 questions across 8 separately scored dimensions [39]. Higher scores indicate better quality of life.
8	Treatment response	Fulfilment of Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria at week 12.
Other outcomes collected from participants		
1	*Treatment satisfaction*	Will be assessed at weeks 6 and 12 by the *Patient Acceptable Symptom State* [40] (PASS, yes/no) question: "Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current symptom state is satisfactory?". If "no", the follow-up question "Would you consider your current symptom state as being so unsatisfactory that you think the treatment has failed?" will determine treatment failure.
2	*Perceived improvement in the index knee*	Will be assessed at weeks 6 and 12 by the Global Rating of Change (GRC) question: "Which option best represents the change in PAIN in your RIGHT/LEFT knee since you began the study?". Participants will score this question using a 5-point Likert scale (1 = much better to 5 = much worse).
3	*Participant safety*	Assessed through weekly self-reported adverse events monitoring from baseline through to week 12.
4	*Use of rescue pain medication*	Self-reported in weekly surveys.
5	*Treatment adherence*	Measured by self-reported intake of the number of capsules taken in the morning and night for each day in the past week and confirmed by self-reported capsule count at the end of the study (week 12).
6	*Psychological traits and states, contextual, and social factors*	Assessed by the MPsQ (Cognivia questionnaire associated with the placebo response) and administered via the Placebell® technology. Items are self-reported by participants on a 5-point scale (1 = strongly disagree to 5 = strongly agree).
7	*Participants' technology self-efficacy*	Will be measured at baseline only using a modified Computer self-efficacy scale [41].
8	*OA knee flare occurrence*	Assessed at baseline, week 6 and week 12 using a self-report Flare-OA 16 questionnaire [42,43]. This questionnaire has been developed to investigate and characterize a knee or hip osteoarthritis flare occurrence in the past 4 weeks, from the participant's perspective. It comprises items in five dimensions: pain, swelling, stiffness, psychological aspects, and impact of symptoms, with answers on a numerical rating scale (0–10).

All outcomes are collected via participant self-report. KOOS: Knee Injury and Osteoarthritis Outcome Score; VAS: Visual Analog Scale; PGA: Patient global assessment; AQoL-8D: Assessment of Quality of Life; GRC: Global Rating of Change; e-PCF: Electronic Participant Consent Form; PASS: Patient Acceptable Symptoms State; MPsQ Cognivia questionnaire associated with placebo response subscales; VAS: Visual Analogue Scale.

Table 4
Outline of trial procedures and data collection timepoints.

Timepoints	Screening	Baseline		Follow-up period											
	≤ 8 weeks prior to randomization	*≤ 1 week prior to randomization*	*Between baseline and treatment start*	*Wk 1*	*Wk 2*	*Wk 3*	*Wk 4*	*Wk5*	*Wk6*	*Wk7*	*Wk8*	*Wk9*	*Wk 10*	*Wk 11*	*Wk 12*
Online Screening	X														
e-PCF	X														
X-ray assessment	X														
Demographics		X													
Medical history		X													
Comorbidity assessment		X													
Computer self-efficacy		X													
BAS-MPsQ		X													
HBB-MPsQ		X													
VAS pain	X	X		X	X	X	X	X	X	X	X	X	X	X	X
PASS									X						X
KOOS		X			X				X						X
PGA		X			X				X						X
GRC									X						X
AQoL-8D		X			X				X						X
Flare-OA		X							X						X
PDS-MPsQ			X												
STT-MPsQ			X												
Treatment allocation			X												
E-prescription			X												
Dispensing			X												
Shipment			X												
Blood collection (Optional)			X		X										X
Treatment compliance				X	X	X	X	X	X	X	X	X	X	X	X
Adverse events				X	X	X	X	X	X	X	X	X	X	X	X
Pain medication usage				X	X	X	X	X	X	X	X	X	X	X	X

wk1-12: weeks 1–12; KOOS: Knee Injury and Osteoarthritis Outcome Score; VAS: Visual Analog Scale; PGA: Patient global assessment; AQoL-8D: Assessment of Quality of Life; GRC: Global Rating of Change; e-PCF: Electronic Participant Consent Form; PASS: Patient Acceptable Symptoms State; MPsQ Cognivia questionnaire associated with placebo response subscales.

2.9.1. Online screening

People interested in participating will complete an online screening survey based on the main eligibility criteria (Table 1). Participants may be contacted by the research team if further information is required to determine eligibility.

2.9.2. e-Participant Consent

A consenting video will inform eligible participants of the trial aim, procedures, time commitment, and potential risks and benefits. After the opportunity to reflect and ask questions, participants will be invited to sign an electronic Participant Consent Form (e-PCF).

2.9.3. X-ray screening

A recent (within last 12-months) x-ray including a weight-bearing posteroanterior (PA) view of both knees and a skyline view of the index knee will be reviewed by the trial doctor for eligibility confirmation, including a radiographic assessment according to the Altman Atlas and Atlas of Standard Radiographs of Arthritis [25,26].

2.9.4. Medication Washout

A 48-h washout prior to baseline survey completion will be required for analgesics (e.g., paracetamol), oral or topical NSAIDs, centrally acting analgesics, or any dietary supplements for OA that do not contain any of the trial product components. A two-month washout prior to baseline survey completion will be required for participants taking supplements or supplement combinations containing any of the trial product ingredients (i.e., curcumin, BSE, PBE, MSM).

2.9.5. Enrolment

Eligible consenting participants will provide demographic data, medical history, and the baseline primary, secondary and other outcome measures (Table 4). Knee pain intensity will be reassessed to confirm eligibility.

2.9.6. Treatment start

After receiving their trial products, the participant's treatment start date will be scheduled by the study team. Treatment adherence will be monitored by online surveys. Treatment may be discontinued prior to 12-weeks in case of an unacceptable adverse event or at the participant's or Principal Investigator's discretion. No dose reductions will be permitted.

2.9.7. Follow-up surveys

Follow-up surveys will be automatically scheduled via Research Electronic Data Capture from Day 1 (Table 3, Fig. 1). Pain intensity will be assessed weekly, along with treatment adherence, AE, and pain medication use. Other secondary outcomes will be assessed at weeks 2, 6, and 12. The Patient Acceptable Symptoms State, Global Rating of Change, and Flare questions will only be assessed at weeks 6 and 12.

2.10. Sub-study for future biomarker analysis

A parallel sub-study will be conducted to collect and store serum at baseline, week 2 and week 12 for future biomarker analysis (Fig. 1) to investigate the change of serum C-terminal crosslinked telopeptide type

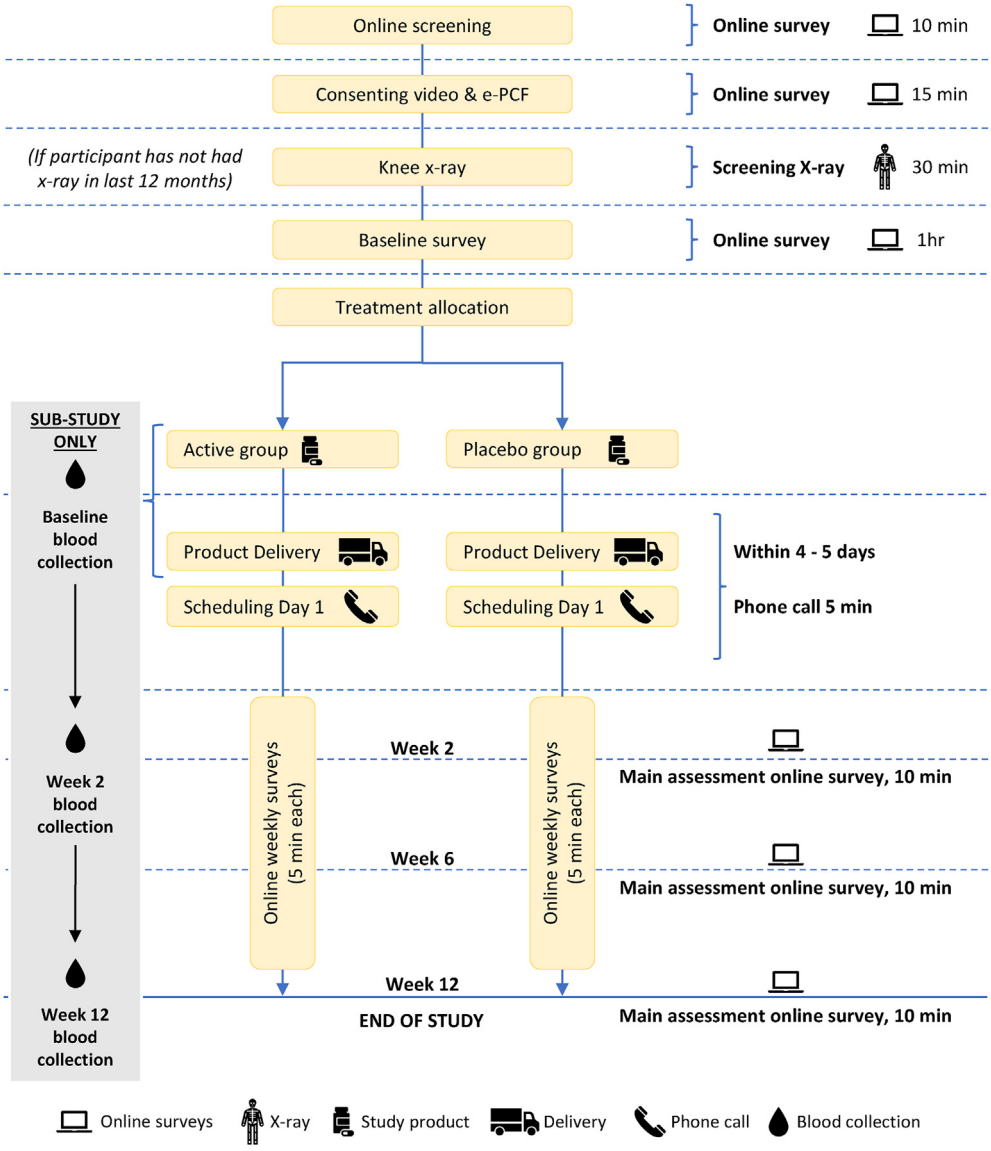

Fig. 1. Trial flow chart.

II collagen (sCTXII), serum hyaluronan, and serum N-telopeptide of type I collagen (sNTX-I) after the treatment. Participation in the sub-study will be optional. Serum will be stored at −80 °C until analysis.

2.11. Statistical methods

2.11.1. Sample size estimation, power and justification

An 18 point difference on the VAS was considered to represent the minimal clinically important difference between groups [27]. To detect an 18 point between-group difference in VAS pain (100-scale) at 12 weeks (primary outcome assessment), assuming a standard deviation of 24 points for change from baseline and a two-sided α-level of 0.05 [28], a total of 58 participants (~29 per group) would be needed to achieve 80% statistical power. To account for potential withdrawals and missing data, and to achieve a more robust power of 90%, a total sample size of 78 participants (~39 per group) should be targeted in the intention-to-treat (ITT) population. Ultimately, in agreement with the sponsors, the decision was made to target the enrolment of 82 participants in total (~41 patients per group), allowing for up to 30% loss to follow-up while still maintaining adequate statistical power (1-β = 80%).

2.11.2. Statistical methods

The statistical analysis will be performed by a blinded statistician. Descriptive statistics of baseline characteristics will be provided for each group to provide an understanding of the trial population and the initial data distribution before inferential statistical analyses are conducted.

2.11.2.1. Descriptive statistics. Continuous variables will be summarized by means and standard deviation where appropriate or median (range), and categorical variables will be presented as frequency (percentage).

2.11.2.2. Inferential statistics. Our main analyses will estimate between-group differences in continuous outcomes at 12-weeks for both primary and secondary outcomes, using the ITT population. We will analyze continuous outcomes as change from baseline using repeated measures mixed linear models including participants as random effects, with fixed effect factors for randomization group, week, and the corresponding interaction (group × week), while adjusting for baseline values and the stratification factors (KLG with 2 levels). Data from all available 13 time points will be utilized (Table 4). Results will be presented as least square means with standard errors, and differences between least square means

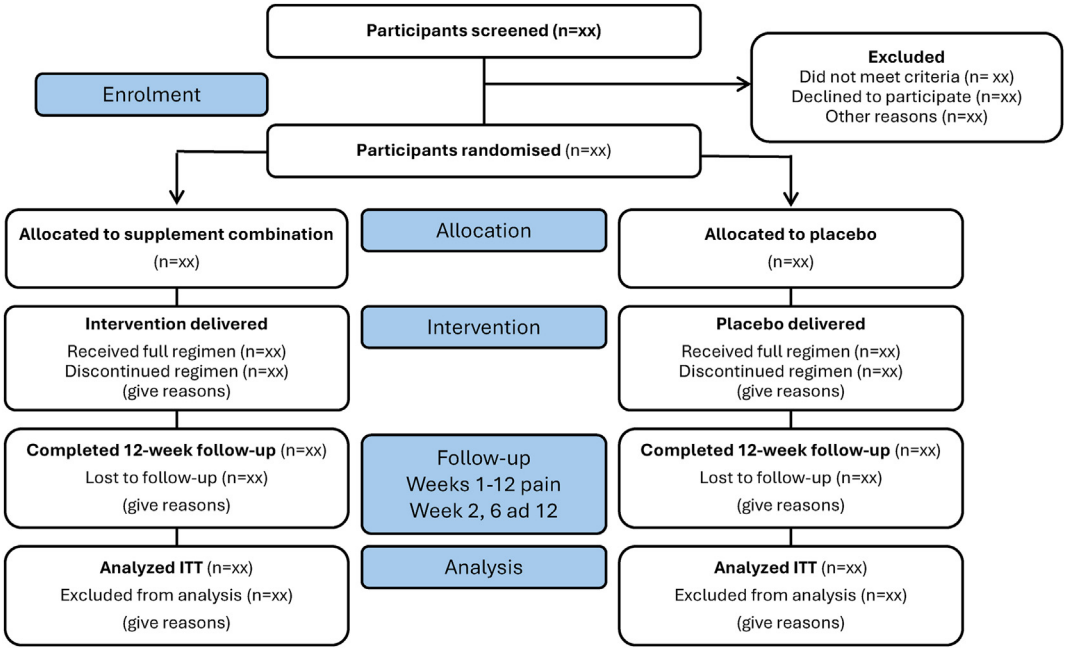

Fig. 2. Consort diagram.

will be reported with two-sided 95% CIs [29]. The between-group difference in the primary outcome will be assessed by a two-sided test with an α level of 0.05. Superiority will be defined when the 95% CI for the primary endpoint excludes the null. No explicit adjustments for multiplicity will be applied; rather, secondary outcomes will be analyzed and interpreted in a predefined prioritized order (gatekeeping). Missing data for the continuous outcomes will be handled implicitly by the mixed linear model [30]. Dichotomous responder analyses will be presented as categorical data, and groups will be compared and reported using odds ratios; missing data for the categorial responder indices will be handled using a conservative 'non-responder imputation'.

2.11.2.3. Exploratory Analysis 1. Placebell©™ covariates will be calculated for each participant to characterize the subjects' placebo response. The correlation between the Placebell©™ covariates and the primary endpoint will be assessed using Pearson's correlation. Adjusted comparisons between groups will also be performed while considering both the baseline values of the primary endpoints and the Placebell©™ Covariate. Cognivia will use data from placebo-treated subjects to calibrate new Placebell©™ models. If the calibration is successful, the new model will be available for covariate production in future studies.

2.11.2.4. Exploratory Analysis 2. We will perform subgroup analysis for: i) tibiofemoral vs patellofemoral OA; ii) KLG $\leq$3 vs 4; and iii) Technology self-efficacy: not confident [<80] vs confident [$\geq$80]. We will also explore participant response to treatment between the two groups using the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria [31]. Responder analysis will include the proportion of participants who achieved at least 20% and 50% improvement in pain VAS and patient global assessment using chi-squared tests. We will use logistic regression models adjusted for age, sex, and body mass index to compare responses between treatment groups. A per-protocol analysis will also be performed, including only participants who achieved a minimum of 80% treatment adherence. No interim analyses will be conducted.

2.11.2.5. Exploratory analysis 3 (moderator and mediator analyses). Exploratory analyses will be conducted to investigate potential moderators and mediators that could influence response to treatment at 12-weeks. Preidentified potential moderator factors include OA phenotypes, KLG grade, technology self-efficacy, and weight-bearing. Potential mediator factors include use of pain medications, treatment adherence, and participants satisfaction with allocated treatment.

2.12. Safety management and adverse events

Self-reported AE data will be collected weekly throughout trial treatment. Reported AEs will be assessed by the trial doctor and AEs related (possibly, probably, definitely) to the trial intervention will be followed until resolution. Knee OA flare-ups will not be considered reportable AEs.

Expected adverse reactions to the trial intervention may include diarrhea, bloating, abdominal pain, nausea, gastro-esophageal reflux, dizziness, hypotension, headache, fatigue, insomnia, increased risk of bleeding and bruising, itching, or worsening of allergy symptoms, and possible decrease in blood sugar level. A summary of AEs will be reported to the Data Safety and Monitoring Board every six months.

2.13. Data collection and management

All data will be collected in REDCap, and hosted on the University of Sydney server [24]. Data will be cleaned using self-monitoring of data entry and a risk-based data verification plan will be implemented. An independent Data Safety and Monitoring Board will meet 6-monthly to monitor participant safety.

2.14. Ethics

This protocol was designed in accordance with the Declaration of Helsinki, and trial conduct will follow the International Conference on Harmonization - Good Clinical Practice guidelines. The trial has been approved by the University of Sydney Human Research Ethics Committee (2021/877, version 8, dated June 19, 2024). Participants will provide informed e-Participant consent before being enrolled and undergoing any trial procedure. The trial has been prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12623000380695, April 14, 2023).

2.15. Dissemination plans

We will publish the main trial in a peer-reviewed journal. Authors will comply with the International Committee of Medical Journal Editors authorship criteria. We will disseminate the results, with pooled or deidentified participant information, in lay summaries, infographics, conference abstracts, oral presentations, reports, theses, and scientific publications.

2.16. Timelines

Recruitment will commenced in June 2024, and is expected to be completed by February 2025 (8 months). Follow-up data collection is expected to be completed in May 2025.

3. Discussion

There is international interest in using complementary medicines to manage chronic conditions such as knee OA. Given the lack of evidence for the efficacy and safety of many commonly used formulations, further trials are needed to fill this evidence gap. We have chosen to test a combination formulation containing ingredients that are generally regarded as safe including BSE, PBE, curcumin and MSM. This is based on the view that a synergistic interaction will occur resulting in a greater therapeutic effect than any one single ingredient. As such, any favourable effects found will only be attributable to the combination, and not extrapolated to the efficacy of individual ingredients. Further, despite the favourable safety profile shown for these complementary medicines [32,33], including in our previous trial of the same combination [11], there is still potential for harms, including side effects such as nausea or headache to BSE and PBE, or hypotension with the use of Curcumin. There may also be a potential interaction between the formulation and medications participants are taking. We will monitor and document potential drug-herb interactions during this trial. If the ATLAS intervention is shown to be effective and safe, we anticipate the results will have a significant impact through informing clinical practice guidelines regarding an evidence-based complementary medicines for the management of knee OA."

Author contributions

DJH and XL conceived the project and secured funding. XL and SR developed the initial trial protocol, which received additional contributions from all authors. KB and SC have written the trial procedures manuals, and DJH, JLB and XL will oversee the running of the trial. The Kolling Institute's biostatistician performed the sample size calculations and designed the statistical analyses. AS and JLB wrote the first and final draft of the manuscript. All authors participated in the trial design, provided feedback on drafts of this protocol paper and read and approved the final manuscript.

Funding, vendors and collaborators

The conduct of the trial has been funded by an Australian National Health and Medical Research Council Investigator Fellowship (#1194737). Mayne Pharma (Salisbury South, SA, Australia) are responsible for material sourcing, manufacturing, labelling, packaging and storing the trial products. Cognivia (Belgium) have developed a placebo response questionnaire and will be responsible for analyzing the placebo response. Cognivia is a company that aims to predict participant response and behavior in clinical trials and healthcare by combining patient psychology and AI/machine learning. The funder and vendors have no role in the design of this trial, its conduct, analysis, data interpretation, manuscript writing, and dissemination of the results.

Declaration of competing interest

JLB is supported by an unrestricted Fellowship grant from Haleon Australia and is employed by the University of Sydney. DJH is the editor of the osteoarthritis section for UpToDate and co-editor in Chief of Osteoarthritis and Cartilage. DJH provides consulting advice on scientific advisory boards for Haleon, Pfizer, Lilly, TLCBio, Novartis, Tissuegene, and Biobone. JHar has received payments, travel and/or accommodation for providing expert advice about traditional, complementary and integrative medicine to industry, government bodies and non-government organizations. They have spoken at conferences and/or provided consultations for which honoraria, registration, travel and/or accommodation have been paid for by the organizers. LD and SR receive royalties from UpToDate. AJM has provided educational services for Bayer and served on a clinical advisory board for Viatris. The Sydney Pharmacy School receives research funding for a postgraduate scholarship from GlaxoSmithKline for a PhD scholar under the supervision of AJM.

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