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Design of a randomised, placebo-controlled, double-blind multicentre study assessing the Effect of ColcHicine on the incidence of knee or hip replacements in symptomatic knee or hip Osteoarthritis: the ECHO trial

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Abstract

Introduction: Osteoarthritis is a multi-factorial disease in which low-grade inflammation is considered to play a pivotal role. Although colchicine is a widely used anti-inflammatory drug in the treatment of gout, its effect in osteoarthritis is still disputed due to inconsistent results of short-term clinical trials. Therefore, we aim to evaluate the effect of long-term colchicine 0.5mg once daily on the incidence of knee or hip replacements in patients with knee or hip osteoarthritis.

Methods and analysis: The ECHO trial is a prospective, multicentre, randomised, double-blind, placebo-controlled, phase III trial in which 1200 participants with knee or hip osteoarthritis tolerant to colchicine during a 30-day run-in period will be 1:1 randomised to colchicine 0.5 mg once daily or matching placebo using concealed allocation. The primary endpoint is the time from randomisation to the first knee or hip replacement assessed up to 4.5 years. Secondary endpoints include course of pain, physical function, joint space width, low-grade inflammation, quality of life, clinical or radiological onset of OA in a new joint group other than the hip or knee, number of participants using pain medication during the study, onset of new cardiovascular events (i.e. myocardial infarction, ischemia-driven coronary revascularization, ischemic stroke, peripheral artery disease or cardiovascular death), and direct and indirect costs related to treatment and disease burden due to osteoarthritis. Harm-related endpoints include the number of (serious) adverse events, the number of withdrawals due to (serious) adverse events, and changes in laboratory data (i.e. serum creatinine, eGFR, and ALAT) throughout the study. The primary analysis will be performed according to the intention-to-treat principle.

Ethics and dissemination: This trial has been approved by the METC East-Netherlands. Findings will be presented at scientific meetings and published in a peer-reviewed scientific journal.

Registration details: CTIS: 2024-511359-16-00. Clinicaltrials.gov: NCT06578182.

Strengths and limitations of this study

- This is the first randomised controlled trial with low-dose, long-term treatment of colchicine in a large number of patients with osteoarthritis
- The trial is designed to facilitate the registration of colchicine as repurposed drug for the indication of knee or hip osteoarthritis
- Participants will be recruited from multiple centres in the Netherlands, improving the generalizability of the results
- Adherence to trial medication may subside over time

Introduction

Osteoarthritis is one of the leading causes of pain and disability, currently affecting more than 500 million people worldwide (1). Towards 2050, it is estimated that the number of osteoarthritis patients will rise by 60 to 100% along with increases in the prevalence of obesity and longevity (2). Without any disease-modifying osteoarthritic drugs (DMOADs) available, a substantial challenge to healthcare systems is posed (3).

The pathophysiology of osteoarthritis is multifactorial and a low-grade chronic inflammation, indicative of an inflammatory phenotype, has been described in the affected joints (4,5). This inflammation is mediated primarily by the innate immune system. A critical component of the innate immune system is the NLRP3 inflammasome, which mediates caspase-1 activation and the secretion of proinflammatory cytokine interleukin 1beta (IL-1β) (6). IL-1β is considered one of the major players implicated in the pathogenesis of osteoarthritis, by both activating innervating nociceptors and promoting joint destruction via catabolic proteins such as matrix metalloproteinases (MMPs) (7). This suggests that therapeutically targeting this pathway in OA may potentially prevent or reduce cartilage destruction and pain, thereby slowing the progression of the disease.

An exploratory analysis in the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) trial involving patients with a history of myocardial infarction has recently supported this hypothesis (8). Inhibiting IL-1β with canakinumab reduced the rates of total knee replacements (TKR) and total hip replacements (THR) during a median follow-up of 3.7 years (hazard ratio, 0.58 [CI, 0.42 to 0.80]) (9). Due to the high cost of canakinumab, however, further exploration of affordable anti-inflammatory therapies with similar properties for the treatment of osteoarthritis is warranted.

Colchicine, an alkaloid extracted from the autumn crocus (*Colchicum autumnale*), is effective in many inflammatory and fibrotic conditions with an acceptable safety profile (10). By binding to tubulins, it prevents microtubules from assemblage and polymerization. This results in disrupted microtubules

function and broad cellular actions including inhibition of the NLRP3 inflammasome and MMP13 (11). Hence, there is reason to assume that colchicine may slow the progression of osteoarthritis.

Up to now, clinical trials evaluating the effect of colchicine in osteoarthritis have shown inconsistent results. Four randomised controlled trials (with follow-ups of less than 6 months) using colchicine 0.5 mg twice daily alone or in combination with nimesulide or piroxicam versus placebo alone or in combination with nimesulide or piroxicam and one randomised controlled trial using colchicine 1.5 mg once daily in combination with paracetamol versus paracetamol alone demonstrated symptomatic benefits regarding pain, function, and global assessment in patients with osteoarthritis (12–16). Moreover, in a non-randomised controlled trial, administration of colchicine 0.5 mg twice daily in combination with paracetamol resulted in stable levels of cartilage oligomeric matrix protein (COMP), suggesting stability of the cartilage (17). When paracetamol was used alone, the levels of serum COMP significantly increased from two months to one year. The results of this study indicate that colchicine might act as a DMOAD by stabilizing cartilage turnover and preventing further degradation.

In contrast, in the COLchicine effectiveness in symptoms and inflammation modification in Knee OsteoArthritis (COLKOA) study, no statistically significant difference in knee osteoarthritis symptoms was seen between colchicine 0.5 mg twice daily and placebo over 16 weeks (18). Nevertheless, COLKOA did find that colchicine reduced systemic inflammation based on high-sensitivity C-reactive protein (hs-CRP) and bone turnover based on Cross-Linked C-Telopeptide Of Type I Collagen (CTXI) which are both biomarkers that are associated with the progression of osteoarthritis. Furthermore, 0.5 mg twice daily colchicine over three months failed to improve symptoms in patients with osteoarthritis in the hands compared with placebo in two randomised controlled trials, but one of these trials may have been underpowered and was likely diluted by non-inflamed osteoarthritis subjects (19–21). Lastly, comparing the efficacy of 1 mg/day colchicine treatment versus 16 weeks of physical therapy in 62 patients with knee osteoarthritis showed that physical therapy was more effective than colchicine in reducing pain and improving physical function (22).

Due to these contradictory results, there is currently not enough evidence to recommend colchicine as a treatment for knee or hand osteoarthritis (12,23). However, it is important to note that each study included no more than 150 patients with follow-up periods not exceeding 1 year. To study the long-term effects of colchicine, a post-hoc analysis of the LoDoCo2 trial was recently performed in which 5522 patients with evidence of coronary disease were randomly assigned to receive colchicine 0.5 mg once daily or matching placebo over a median follow-up of 28.6 months (24). Based on the adverse event data, colchicine 0.5 mg daily was associated with a lower incidence of total knee or hip replacements as compared to placebo (hazard ratio, 0.69 [CI, 0.51 to 0.95]) (25). Long-term safety data from this randomised controlled trial did not show an increase in life-threatening or serious AEs (26). Further investigation of long-term therapy with colchicine to slow disease progression in osteoarthritis is needed as the LoDoCo2 trial was not designed for this purpose.

Therefore, we aim to evaluate the effect of long-term use of colchicine 0.5mg once daily compared to placebo in patients with knee or hip OA on the incidence of knee or hip replacement throughout 3 to 4.5 years.

Methods and analysis

This protocol has been reported following the SPIRIT guidelines (Additional file 1) (27).

Study design

The ECHO trial is designed as a multicentre, randomised, placebo-controlled, double-blind, event-driven superiority trial. After signing informed consent, all eligible patients will use colchicine 1dd0.5mg for 30 days. Patients without adverse events, maintaining adherence, and expressing continued willingness to participate after this open-label run-in period will be randomly allocated in a 1:1 ratio to colchicine or placebo. Depending on the time of inclusion, the trial duration for each patient will range from 3 to 4.5 years as the inclusion period is planned to last 1.5 years and the study end date is approximately the same for all participants. A flowchart is shown in Figure 1.

Study population

To be eligible to participate in this study, participants must meet all of the following criteria: I) clinical diagnosis of knee or hip osteoarthritis; II) aged between 45 and 80 years; and III) at least 2-year history of complaints due to osteoarthritis in the hip and/or knee or documented radiographic changes typical for advanced knee and/or hip osteoarthritis (Kellgren & Lawrence (K&L) score ≥ 2). A potential participant who meets any of the following criteria will be excluded from participation: on a waiting list for primary joint replacement surgery of the hip or knee, irrespective of cause, any absolute contraindication for knee or hip replacement in the future, more than one previous hip or knee replacement, other known medical disease that may affect joints, known generalized pain syndromes such as fibromyalgia, renal impairment as evidenced by serum creatinine >150µmol/l or estimated glomerular filtration rate (eGFR) <50mL/min/1.73m2, liver function impairment as evidenced by serum alanine transferase (ALAT) > 3 ULN (upper limit of normal), blood dyscrasia, high frailty (clinical frailty scale ≥ 7) or predicted life expectancy < 5 years, peripheral neuritis, myositis or marked myo-sensitivity to statins, current use of colchicine for another indication, intolerance to colchicine, use of macrolide antibiotics (i.e. clarithromycin, erythromycin, azithromycin), antimycotics (i.e. ketoconazole, itraconazole and voriconazole), protease inhibitors & anti-retroviral drugs (i.e. ritonavir, lopinavir, tipranavir, atazanavir, darunavir, indinavir, saquinavir, and cobicistat), anti-arrhythmic drugs (i.e. verapamil, diltiazem), or immunosuppressant (i.e. cyclosporine), current enrolment in another trial, incapacitated patients, pregnant or breastfeeding female, fertile female participants not taking sufficient anti-conception, or male participants unwilling to use effective contraception during the study to prevent pregnancy.

Recruitment and screening procedures

Potentially eligible patients visiting the Department of Orthopaedics or Rheumatology from the referral and participating centres in the Netherlands will be informed by their physicians (Additional file 2). In addition, general practitioner practices of the primary care Practice-based Research Network

of Radboudumc Nijmegen, ReumaNederland (a national patient organization and rheumatism research funder), and P-AL (Poly-Artrose Lotgenoten; a national patient organization) will disseminate information on the study and invite people with knee or hip osteoarthritis to show their interest.

Patients who express their interest will be invited to complete an online questionnaire on a secure website (Castor EDC) to assess elementary eligibility criteria and provide their consent to be contacted by a member of the research team. Individuals who had previously expressed their interest before the study's commencement due to national publicity related to our previously published findings of the LoDoCo2 trial will similarly be approached (25). Those deemed potentially eligible will then undergo further screening by phone and will be asked for their consent to contact their treating physician to confirm the diagnosis, send recent X-rays of hip or knee joints if present, and gather additional eligibility information if needed.

Potentially eligible patients who express their willingness to participate during the phone call will undergo a screening visit at one of the locations of the participating centres in the Netherlands. Following informed consent, blood samples will be collected to assess liver and renal function and all participants will be supplied with open-label colchicine 0.5mg once daily for 30 days (run-in period). Participants will be instructed to commence medication after reviewing laboratory results. If intolerance to colchicine is suspected (e.g. gastro-intestinal upset) patients are instructed to stop therapy immediately and encouraged to re-challenge themselves after five days. If symptoms initially resolve but re-occur when the drug is re-introduced, they will be assumed to be intolerant to colchicine. In addition, if estimated glomerular filtration rate (eGFR) >50mL/min/1.73m2 or serum alanine transferase (ALAT) < 3 ULN (upper limit of normal) at the start of the run-in phase, but <50mL/min/1.73m2 or > 3 at baseline patients will not be randomised.

Patients without adverse events, who maintain adherence, and express a continued willingness to participate after the run-in period will proceed to the baseline visit. Blood samples will be obtained to

assess liver and renal function and an X-ray of the index joint will be taken to assess K&L score and joint space width if not made in the past six months.

Randomisation, blinding and treatment allocation

Eligible patients will be randomised to colchicine 0.5 mg once daily or placebo with an allocation ratio of 1:1. Randomisation will be performed by an independent pharmacist of the Sint Maartenskliniek using block randomisation with variable block sizes of 4, 6, and 8 stratified by centre, K&L score, and index joint. The physician, the participant, and all other staff involved in the trial will be masked to the participant's treatment allocation. Concealed allocation is guaranteed by randomisation software that will assign subjects to treatment groups, matching placebo to colchicine, and strict procedures for blinded and unblinded parties in the drug supply chain. The investigator will unblind the treatment allocation of a subject during the clinical trial only if unblinding is relevant to a subject's safety. In case of unblinding, the investigator can open a physical envelope labelled with the participant's treatment number. This envelope will contain information about the trial medication that was received. Other participants will not be unblinded. To assess the success of blinding, participants will be asked annually to indicate which group they believe they are in.

Intervention

Colchicine Tiofarma 500 microgram tablets will be orally administered with water once a day. If a dose is missed, it should be taken later during the day or skipped if noticed after 12 hours. A matching placebo is the comparator. Trial medication will be (temporarily) discontinued if health issues overrule treatment continuation as determined by the clinical site investigator or if one of the following drugs are prescribed for a given period: macrolide antibiotics (clarithromycin, erythromycin, azithromycin), antimycotics (ketoconazole, itraconazole, and voriconazole), protease inhibitors and anti-retroviral drugs (ritonavir, lopinavir, tipranavir, atazanavir, darunavir, indinavir, saquinavir, and cobicistat), anti-arrhythmic drugs (verapamil, diltiazem), immunosuppressant (cyclosporine).

Study procedures

Patients will be asked to complete online questionnaires using an electronic Data Capture application (Castor EDC) at enrolment, at baseline, and every 3 months after that. Face-to-face contact (either site or home visits) will take place at enrolment, at baseline, and every year during follow-up. The number of visits depends on the moment of inclusion and ranges between a minimum of 5 and a maximum of 7. Participants who discontinue the trial medication or withdraw from the study for any reason will continue to be followed for the primary outcome (knee or hip replacement). The study procedures are shown in Table 1.

Demographics

Data regarding age, sex, ethnicity, education level, profession, employment, index joint, number and type of affected joints, and duration of complaints will be collected at enrolment.

Anthropometrics

Height, weight, and waist circumference will be assessed at baseline. Subsequent measures of weight and waist circumference will be taken during clinical visits. BMI will be calculated using weight and height.

The Older Persons and Informal Caregivers Survey – Short Form (TOPICS-SF)

The TOPICS-SF collects information on morbidity status, functional limitations, emotional well-being, pain experience, cognitive problems, social functioning, and self-perceived health utilizing 22 items and will be assessed at enrolment to calculate a frailty index. Higher scores indicate higher frailty (28).

227 *Table 1.* Study overview.

	Enrolment	Baseline	Follow-up												Close-out
Timepoint in months	-1	0	3	6	9	12	15	18	21	24	27	30	33	…	51	36-54
Eligibility screening	x															
Informed consent	x															
Open label colchicine	←	→														
Allocation		x														
Colchicine or placebo		←	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Sociodemographics																
Age	x															
Sex	x															
Ethnicity	x															
Education level	x															
Employment	x															
Profession	x															
Height	x															
Weight	x					x				x				x		x
Waist circumference	x					x				x				x		x
Disease characteristics																
Index joint	x															
Affected joints	x															
Duration of complaints	x															
Joint replacement		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
New OA diagnosis						x				x				x		x
Comorbidities	x	x				x				x				x		x
Cardiovascular events		x				x				x				x		x
Questionnaires																
Pain medication			x		x		x		x		x		x		x	
MARS-5		x		x		x		x		x		x		x		x
NRS pain		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
WOMAC		x		x		x		x		x		x		x		x
TOPICS-SF	x															
EQ-5D-5L		x		x		x		x		x		x		x		x
iPCQ		x		x		x		x		x		x		x		x
iMCQ		x		x		x		x		x		x		x		x
Pill count		x				x				x				x		x
X-ray*		x														x
Blood sampling	x	x				x										x

Hospital visits are indicated in blue and tele contact moments are indicated in yellow. Since the study end date is approximately the same for all patients and the inclusion period is planned to last 1.5 years, the trial duration for an individual patient ranges between 3 and 4.5 years depending on the time of inclusion.
*If not made in the past 6 months

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Comorbidities

The following comorbid conditions will be documented at each clinical visit: heart disease (for example angina, heart attack, or heart failure); high blood pressure; problems caused by a stroke; leg pain when walking due to poor circulation; lung disease (for example asthma, chronic bronchitis, or emphysema); diabetes mellitus; kidney disease; diseases of the nervous system (for example Parkinson's disease or multiple sclerosis); liver disease; cancer (within the last 5 years); depression; arthritis in your back or other condition affecting your spine; rheumatoid arthritis or another kind of arthritis in addition to osteoarthritis (29).

Joint replacement

Participants will be asked every 3 months about any knee or hip replacement surgery through a multiple-choice question. In case of an event, source documents will be collected for central adjudication.

OA diagnosis

Participants will be asked every 12 months about any new osteoarthritis diagnosis in a joint other than the knee or hip through a yes-no question. In case of an event, source documents will be collected for central adjudication.

Cardiovascular events

Participants will be asked every 12 months about any cardiovascular event defined as myocardial infarction, peripheral artery disease, ischemia-driven coronary revascularization, ischemic stroke, or cardiovascular death through a multiple-choice question. In case of an event, source documents will be collected for central adjudication.

Pain medication

Participants will be asked every 3 months about any concomitant pain medication used, including prescription and over-the-counter medications.

Numeric rating scale (NRS)

The NRS will assess pain levels during rest and during movement at baseline and every 3 months after that. The NRS consists of 11 numbers from 0 to 10, where 0 means no pain and 10 represents the most imaginable pain.

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

The WOMAC is designed to assess pain, stiffness, and physical functioning in patients with knee or hip osteoarthritis utilizing 24 questions and will be assessed at baseline and every 6 months after that (30). Higher scores represent worse outcomes.

European Quality of Life 5-Dimensions 5-Level (EQ-5D-5L)

The EQ-5D-5L measures quality of life at baseline and every 6 months after that using 5 levels of severity in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (31).

iMTA Productivity Cost Questionnaire (iPCQ)

The iPCQ will assess loss of productivity due to OA or joint replacement surgery based on patient-reported absences from paid or unpaid labour at baseline and every 6 months after that (32).

iMTA Medical Consumption Questionnaire (iMCQ)

The iMCQ will assess all relevant healthcare-related costs like outpatient visits to medical specialists, hospitalizations, and paramedic care at baseline and every 6 months after that (33).

Medication Adherence Report Scale (MARS-5)

The MARS-5 questionnaire will be assessed every 6 months to evaluate adherence to trial medication and consists of five self-reported adherence items about forgetting, changing dosage, stopping,

skipping, and taking less medication. Scores range from 5 to 25, with higher scores indicating better medication adherence (34).

Pill count

Adherence to trial medication will be evaluated through pill counts once a year.

Radiography

Radiographic examinations include standard clinical radiographs of the index knee or hip at baseline if not made in the past 6 months and, in a subgroup of 200 patients who have taken at least 80% of the study medication for a minimum of 2 years at the end of the study. Joint space width will be assessed using automated software.

Blood samples

Blood samples will be drawn at enrolment, at baseline, after 1 year, and at the end of the study to assess inflammation (hs-CRP) and safety (kidney function, liver function, creatinine kinase, erythrocytes, leukocytes, thrombocytes, and, if anaemia is present, vitamin B12).

Adverse events

Abnormal CK, eGFR, and ALAT values will be registered throughout the study period. The following adverse events will be systematically assessed once a year: gastrointestinal, infectious, musculoskeletal and connective tissue disorders, cardiac disorders, and neurological disorders.

Study endpoints

The primary endpoint of this study is time to first incident knee or hip replacement from randomisation until the date of first documented knee or hip replacement, date of death, date of loss to follow-up, or study end-date, whichever comes first, assessed up to 4.5 years.

Secondary endpoints include 1) course of pain, 2) course of physical function, 3) course of joint space width, 4) course of low-grade inflammation, 5) course of quality of life, 6) clinical or radiological onset

of OA in a new joint group other than the hip or knee, 7) number of participants using pain medication during the study, 8) onset of new cardiovascular events, including myocardial infarction, ischemia-driven coronary revascularization, ischemic stroke, peripheral artery disease or cardiovascular death, and 9) direct and indirect costs related to treatment and disease burden due to osteoarthritis from randomisation until the date of first documented knee or hip replacement, date of death, date of loss to follow-up, or study end-date, whichever comes first, assessed up to 4.5 years.

Harm-related endpoints include 1) the number of (serious) adverse events, 2) the number of withdrawals due to (serious) adverse events, and 3) changes in laboratory data (i.e. serum creatinine, eGFR and ALAT) throughout the study.

Sample size calculation

This trial is designed to accrue a minimum of 380 primary end-point events for the Cox proportional hazard model to achieve 80% power with an alpha of 0.05 and detect a hazard ratio of 0.75 (based on the exploratory results from the LoDoCo2 trial) (25). To achieve this number of events, the number of required patients varies based on the baseline event rate and the inclusion rate (as with more inclusions at the beginning of the inclusion period, patients will on average have longer follow-up within the planned total study duration of 4.5 years). Therefore, an adaptive design that allows for a blinded re-estimation of the sample size based on the observed number of events and speed of inclusion using the R package BSSRed will be applied (35). The required number of patients and duration of the inclusion period for various scenarios regarding baseline event rate and inclusion rate is shown in Table 2. For all scenarios, the maximum study duration until administrative censoring was set to 4.5 years, with a dropout of 10% at 2 years based on data from the LoDoCo2 trial (26). Scenarios concerning primary event rates were based on a previous study on the proportion of knee or hip replacements after 2 years in a sample of patients consulting an orthopaedic surgeon without indication for replacement (25% event rate) and the estimated proportion of patients consulting their general practitioner receiving hip or knee replacement in 2 years (23% event rate) (36). In addition, we

added a scenario with a conservative estimate (20% event rate). Sample size re-estimation is planned at the end of the planned inclusion period at 18 months and does not require correction for multiplicity as allocation remains blinded and no between-arm comparisons are performed.

Table 2. Estimation of the sample size and length of the inclusion period for varying inclusion rates (1000, 1200, and 1500) per 18 months (the planned inclusion period) and primary event rates (20%, 23%, and 25%) per 2 years.

Inclusion rate per 18 months	**Primary event rate per 2 years**		
	20%	23%	25%
1000	1504 in 27 months	1280 in 23 months	1168 in 21 months
1200	1398 in 20 months	1200 in 18 months	1134 in 17 months
1500	1334 in 16 months	1166 in 14 months	1084 in 13 months

Statistical analysis

Descriptive statistics will be used to describe the study sample. For normally distributed continuous variables, means and standard deviations (SDs) will be calculated. For non-normally distributed continuous variables, medians and interquartile ranges (IQRs) will be reported. Categorical or dichotomous variables will be summarized using absolute numbers and percentages.

The primary analysis will be performed according to the intention-to-treat principle. Kaplan-Meier curves will be used to depict the time to first knee or hip replacement in the two treatment groups. Hazard ratios of treatment with colchicine versus placebo, with corresponding 95% confidence intervals, will be obtained from Cox proportional hazards regression models with stratification by centre, K&L score, and index joint. Sensitivity analyses will be performed by adding covariates for change in body weight over time and cumulative use of pain medication. All randomised patients will be included in the analyses. In addition, a per-protocol analysis of the primary endpoint will be performed in patients who have taken at least 80% of the study medication for a minimum of 2 years.

For the secondary analyses, linear mixed models or generalized estimating equations with repeated measures will be used to estimate mean between-group differences and their 95% CIs for continuous and binary secondary outcomes. Participants will be included as random effect and treatment allocation as fixed effect factors. Missing data will be handled by the mixed model.

A cost-effectiveness analysis will be carried out alongside the trial comparing colchicine to placebo from a societal perspective. First, the EQ-5D-5L will assess the impact of both strategies on the quality of life, and the utility will be used to derive a QALY estimate for each patient according to the trapezium rule. Second, volumes of OA-related care will be measured at the patient level using the iMCQ, and loss of productivity due to OA or joint replacement surgery will be estimated based on patient-reported absences from paid (or unpaid) labour measured with the iPCQ. To determine the cost prices for each volume of consumption, the standard cost prices from the 'Dutch Guidelines for Cost Analyses' and www.medicijnkosten.nl will be used. For units of care where no standard prices are available real cost prices will be determined based on full cost pricing. Productivity losses will be valued through the friction cost method. Finally, the incremental cost-effectiveness ratio will be calculated by dividing the difference in costs (medical and societal) by the difference in QALYs between the groups. The ICER, indicating the additional cost required to gain one QALY, can be compared to the willingness to pay value. Uncertainty in the ICER will be non-parametrically determined using bootstrap techniques (1000 replications).

No formal statistical testing will be conducted for the harm-related endpoints. AEs and SAEs will be presented as numbers and percentages per intervention arm. The relationship between AEs and SAEs with the trial treatment will be evaluated and numbers and percentages of treatment-related AEs and SAEs will be presented per treatment arm. Deaths, AEs, and SAEs resulting in treatment discontinuation will be reported.

Harm-related considerations

Except for planned hospitalisations because of knee or hip replacements, the investigator will record all AEs and SAEs including the date of occurrence, a description of the event and its severity, duration, and the actions taken. All AEs and SAEs will be followed until they have abated or a stable situation has been reached. Due to the size and duration of the trial, an independent Data and Safety Monitoring Committee consisting of one rheumatologist, one clinical epidemiologist, and one pharmacist from the

Sint Maartenskliniek will blindly review the trial's progress including updated figures on recruitment and safety data biannually and will advise on optimal execution. No interim analysis will be done.

Data management

Data will be collected and processed following the General Data Protection Regulation (EU) 2016/679. Data will be entered in Castor EDC, recorded on eCRF forms, and stored on a department server with automatic back-ups. Paper-based data will be stored in locked cabinets at each site. Data will be kept for 25 years.

Subjects will be identified by a study-specific subject number and/or code in the database. Names and other identifying details will not be included in any study data electronic file. The key to the code is safeguarded by principle investigators.

Data quality will be promoted by data checks. If missing, questionable, or out-of-range values are identified, these will be queried and corrected if possible. If this is not possible, questionable or out-of-range values will be excluded from analyses.

Monitoring and quality assurance will be established according to the advice of the NFU (Dutch Federation of University Medical Centres (NFU)). A qualified monitor of the Department of Research of the Sint Maartenskliniek will visit all participating centres before trial commencement and annually thereafter to check trial procedures, including data recording, verification of source data, and safety assessments.

Patient and public involvement

From the pre-application of the grant for this project, 2 patient representatives of the STAP panel (Key To Active Participation; a hospital-based patient panel of around 50 patient research partners with rheumatic diseases to support orthopedic and rheumatology research (both clinical and preclinical) at Radboudumc and Sint Maartenskliniek) actively engaged in this project. During this phase, the relevance and feasibility of this project were assessed. Suggestions were provided about participant

retention, medication adherence, and the assessment of adverse effects. This resulted in insights about the order of questionnaires and the amount and type of contact with researchers. Information about adverse effects and interaction with other drugs has been added to the patient information form (PIF). Their request to investigate differences between men and women has been incorporated in the statistical analysis.

After grant approval, 2 additional patient representatives agreed to actively participate in this project: 1 member of the national patient organization P-AL and 1 member of the STAP panel. They provided feedback on the PIF and evaluated the feasibility for patients by testing study procedures. During later research phases, patient representatives will be involved by drafting a questionnaire to assess elementary eligibility criteria if patients express their interest to participate following disseminated study information from national publicity related to our previously published finding of the LoDoCo2 trial, ReumaNederland or P-AL and promoting participant retention. In addition, patient representatives will give input about the wording of results from a patient perspective, write lay summaries, and can co-author scientific publications.

Ethics and dissemination

The proposed trial has been registered with the EU Clinical Trials Register (2024-511359-16-00) and on clinicaltrials.gov (NCT06578182). The protocol has been approved by METC East-Netherlands. Written informed consent will be obtained from all participants by the treating or research physician (Additional file 3). A separate question in the ICF will ask for permission to store and reuse personal data and samples for further research. Findings will be presented at scientific meetings and published with the full trial protocol in a peer-reviewed scientific journal. Pseudonymized data will be made available on reasonable request.

Authors' contributions.

Conception and design: MH, CE, JC, BB, and CP. Design of the statistical analysis plan: MH, CE, and WK. Drafting of the present manuscript: MH. Critical revision: CE, JC, JS, HS, WK, SK, BB, and CP. Final approval: MH, CE, JC, JS, HS, WK, SK, BB, CP. Funding acquisition: MH, CE, JC, JS, HS, WK, SK, BB, and CP.

Funding statement

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Competing interests statement

JC received consulting fees from Amgen and Novo Nordisk, participated on a Data Safety Monitoring Board or Advisory Board in the EDIT-CAS study and BioNTech malaria vaccine program, and has a leadership or fiduciary role in the executive committee LIBREXIA AF and Chair Event Adjudication committee REDEFINE/REIMAGINE. JS received consulting fees from Smith & Nephew consultancy. SK has a leadership or fiduciary role in the Board Dutch Knee Society, President Commission on Quality Royal Dutch Orthopaedic Society, and is chairman of Department Orthopaedic Surgery CWZ.

Full references

1. Long H, Liu Q, Yin H, et al. Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019. Arthritis and Rheumatology. 2022 Jul 1;74(7):1172–83.
2. Steinmetz JD, Culbreth GT, Haile LM, et al. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Rheumatol. 2023 Sep 1;5(9):e508–22.
3. Osteoarthritis: A serious disease [Internet]. Osteoarthritis Research Society International. 2016 [cited 2022 Aug 18]. Available from: https://oarsi.org/education/oarsi-resources/oarsi-white-paper-oa-serious-disease

4. Kapoor M, Martel-Pelletier J, Lajeunesse D, et al. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol. 2011;7:33–42.

5. Zhu R, Fang H, Wang J, et al. Inflammation as a therapeutic target for osteoarthritis: A literature review of clinical trials. Clinical Rheumatology. Springer Science and Business Media Deutschland GmbH; 2024.

6. Robinson WH, Lepus CM, Wang Q, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016;12:580–92.

7. Conaghan PG, Cook AD, Hamilton JA, et al. Therapeutic options for targeting inflammatory osteoarthritis pain. Nat Rev Rheumatol. 2019;15:355–63.

8. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. New England Journal of Medicine. 2017 Sep 21;377(12):1119–31.

9. Schieker M, Conaghan PG, Mindeholm L, et al. Effects of interleukin-1β inhibition on incident hip and knee replacement: Exploratory analyses from a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2020;173(7):509–15.

10. Leung YY, Yao Hui LL, Kraus VB. Colchicine-Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. 2015;45:341–50.

11. Takeuchi K, Ogawa H, Kuramitsu N, et al. Colchicine protects against cartilage degeneration by inhibiting MMP13 expression via PLC-γ1 phosphorylation. Osteoarthritis Cartilage. 2021;29:1564–74.

12. Singh A, Molina-Garcia P, Hussain S, et al. Efficacy and safety of colchicine for the treatment of osteoarthritis: a systematic review and meta-analysis of intervention trials. Clin Rheumatol. 2022;Epub ahead of print.

13. Das SK, Mishra K, Ramakrishnan S, et al. A randomized controlled trial to evaluate the slow-acting symptom modifying effects of a regimen containing colchicine in a subset of patients with osteoarthritis of the knee. Osteoarthritis Cartilage. 2002;10(4):247–52.

14. Das SK, Ramakrishnan S, Mishra K, et al. A randomized controlled trial to evaluate the slow-acting symptom-modifying effects of colchicine in osteoarthritis of the knee: A preliminary report. Arthritis Care Res (Hoboken). 2002;47(3):280–4.

15. Aran S, Malekzadeh S, Seifirad S. A double-blind randomised controlled trial appraising the symptom-modifying effects of colchicine on osteoarthritis of the knee. Clin Exp Rheumatol. 2011;29:513–8.

16. Erden M, Ediz L, Hız Ö, et al. Effect of Colchicine on Total Antioxidant Capacity, Antioxidant Enzymes and Oxidative Stress Markers in Patients with Knee Osteoarthritis. Int J Clin Med. 2012;3:377–82.

17. Srivastava R, Das SK, Goel G, et al. Does long term colchicine prevent degradation of collagen fiber network in osteoarthritis? Int J Rheum Dis. 2017;21:114–7.

18. Leung YY, Haaland B, Huebner JL, et al. Colchicine lack of effectiveness in symptom and inflammation modification in knee osteoarthritis (COLKOA): a randomized controlled trial. Osteoarthritis Cartilage. 2018;26(5):631–40.

19. Davis CR, Ruediger CD, Dyer KA, et al. Colchicine is not effective for reducing osteoarthritic hand pain compared to placebo: a randomised, placebo-controlled trial (COLAH). Osteoarthritis Cartilage. 2021;29(2):208–14.

20. Døssing A, Henriksen M, Ellegaard K, et al. Colchicine twice a day for hand osteoarthritis (COLOR): a double-blind, randomised, placebo-controlled trial. Lancet Rheumatol [Internet]. 2023 Apr; Available from: https://linkinghub.elsevier.com/retrieve/pii/S2665991323000656

21. Plotz B, Pillinger M, Samuels J. Colchicine and clinical trials for hand osteoarthritis. Vol. 30, Osteoarthritis and Cartilage. W.B. Saunders Ltd; 2022. p. 172–3.

22. Cioroianu GO, Florescu A, Mușetescu AE, et al. Colchicine versus Physical Therapy in Knee Osteoarthritis. Life. 2022 Sep 1;12(9).

23. Liu W, Wang HC, Su C, et al. The Evaluation of the Efficacy and Safety of Oral Colchicine in the Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trails. Biomed Res Int. 2022;2022:2381828.

24. Nidorf SM, Fiolet ATL, Eikelboom JW, et al. The effect of low-dose colchicine in patients with stable coronary artery disease: The LoDoCo2 trial rationale, design, and baseline characteristics. Am Heart J. 2019;218:46–56.

25. Heijman MWJ, Fiolet ATL, Mosterd A, et al. Association of Low-Dose Colchicine With Incidence of Knee and Hip Replacements : Exploratory Analyses From a Randomized, Controlled, Double-Blind Trial. Ann Intern Med [Internet]. 2023 May 30; Available from: http://www.ncbi.nlm.nih.gov/pubmed/37247416

26. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. New England Journal of Medicine. 2020;383(19):1838–47.

27. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials DEVELOPMENT OF THE SPIRIT 2013 STATEMENT [Internet]. Vol. 158, Ann Intern Med. 2013. Available from: www.annals.org

28. Santoso AMM, Lutomski JE, Hofman CS, et al. Development of a Patient-Reported Outcome Measure for Geriatric Care: The Older Persons and Informal Caregivers Survey Short Form. Value in Health. 2018 Oct 1;21(10):1198–204.

29. Rolfson O, Wissig S, van Maasakkers L, et al. Defining an International Standard Set of Outcome Measures for Patients With Hip or Knee Osteoarthritis: Consensus of the International Consortium for Health Outcomes Measurement Hip and Knee Osteoarthritis Working Group. Arthritis Care Res (Hoboken). 2016 Nov 1;68(11):1631–9.

30. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833–40.

31. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011;20:1727–36.

32. Bouwmans C, Krol M, Severens H, et al. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. Value in Health. 2015 Sep 1;18(6):753–8.

33. iMTA Productivity and Health Research Group. Manual iMTA Medical Cost Questionnaire (iMCQ). Rotterdam; 2018.

34. Chan AHY, Horne R, Hankins M, et al. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol. 2020 Jul 1;86(7):1281–8.

35. Friede T, Pohlmann H, Schmidli H. Blinded sample size reestimation in event-driven clinical trials: Methods and an application in multiple sclerosis. Pharm Stat. 2019 May 1;18(3):351–65.

36. Mahler EAM, den Broeder AA, den Broeder N, et al. Short-term clinical worsening is a clear predictor for worsening at 2 years in established knee and hip osteoarthritis. Clin Exp Rheumatol. 2019;37(3):414–21.

538 **Figure 1. Flowchart of the study.**

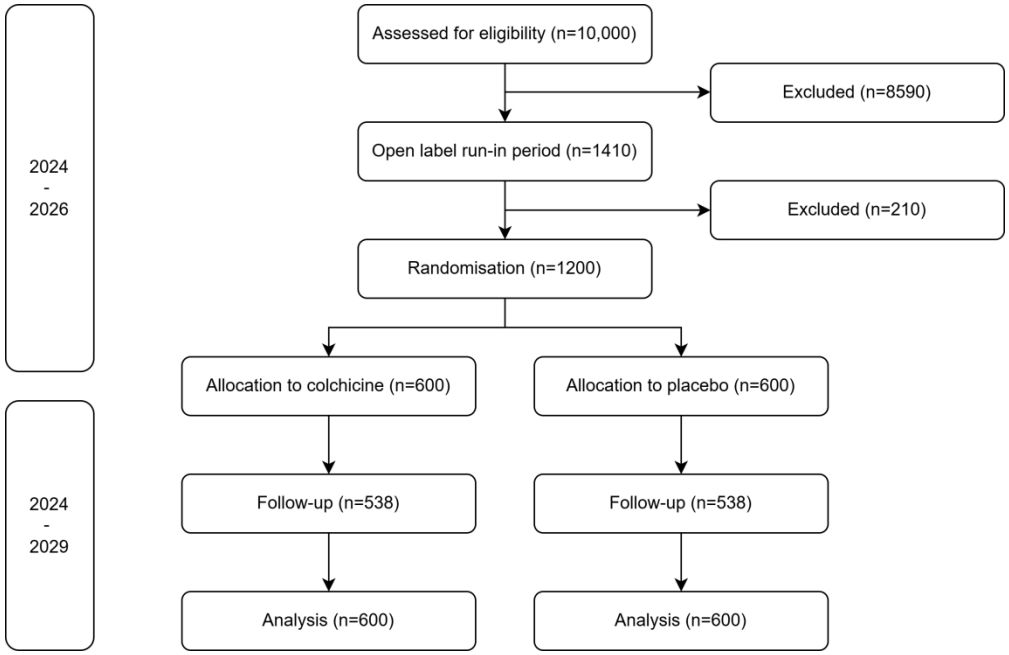

Figure 1. Flowchart of the study

440x285mm (157 x 157 DPI)

SPIRIT-Outcomes 2022 Checklist (for combined completion of SPIRIT 2013 and SPIRIT-Outcomes 2022 items)[a]

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	-	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	-	Abstract
	2b	All items from the World Health Organization Trial Registration Data Set	-	clinicaltrials.gov
Protocol version	3	Date and version identifier	-	clinicaltrials.gov
Funding	4	Sources and types of financial, material, and other support	-	Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	-	Title page and au
	5b	Name and contact information for the trial sponsor	-	Title page
	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	-	Funding
	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)	-	NA
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	-	Introduction
	6b	Explanation for choice of comparators	-	Introduction
Objectives	7	Specific objectives or hypotheses	-	Introduction

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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)	-	Study design
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	-	Recruitment and screening procedures
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)	-	Study population
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (for specific guidance see TIDieR checklist and guide)	-	Intervention
	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)	-	Intervention
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-	Study procedures
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-	Intervention
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	-	Study procedures and study endpoints

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	12.1		Provide a rationale for the selection of the domain for the trial's primary outcome	Study endpoints
	12.2		If the analysis metric for the primary outcome represents within-participant change, define and justify the minimal important change in individuals	NA
	12.3		If the outcome data collected are continuous but will be analyzed as categorical (method of aggregation), specify the cutoff values to be used	NA
	12.4		If outcome assessments will be performed at several time points after randomization, state the time points that will be used for analysis	Study endpoints
	12.5		If a composite outcome is used, define all individual components of the composite outcome	NA
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)	-	Study procedures
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	-	Sample size calculation
	14.1		Define and justify the target difference between treatment groups (eg, the minimal important difference)	NA
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-	Recruitment and screening procedures
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	-	Randomisation, blinding and treatment allocation

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	Randomisation, blinding and treatment allocation
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-	Randomisation, blinding and treatment allocation
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-	Randomisation, blinding and treatment allocation
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-	Randomisation, blinding and treatment allocation
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	-	Study procedures
	18a.1		Describe what is known about the responsiveness of the study instruments in a population similar to the study sample	Study procedures
	18a.2		Describe who will assess the outcome (eg, nurse, parent)	Study procedures
	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	-	Study procedures

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	Data management
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	-	Statistical analysis
	20a.1		Describe any planned methods to account for multiplicity in the analysis or interpretation of the primary and secondary outcomes (eg, coprimary outcomes, same outcome assessed at multiple time points, or subgroup analyses of an outcome)	Statistical analysis
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-	Statistical analysis
	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)	-	Statistical analysis
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	-	Harm-related considerations
	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	-	NA
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	-	Harm-related considerations

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-	NA
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-	Ethics and dissemination
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)	-	Ethics and dissemination
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	-	Ethics and dissemination
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-	Ethics and dissemination
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	-	Ethics and dissemination
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	-	Competing interests statement
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	-	Ethics and dissemination
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	-	NA
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	-	Ethics and dissemination
	31b	Authorship eligibility guidelines and any intended use of professional writers	-	NA

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-	Ethics and dissemination
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-	Additional file 3
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	-	Study procedures

[a]It is strongly recommended that this checklist be read in conjunction with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement paper 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 and is reproduced with permission.

[b]Indicates page numbers and/or manuscript location: to be completed by authors.

	University hospital	Peripheral hospital	Tertiary hospital
Participating centres		CWZ Gelderse Vallei Ede* Noordwest Ziekenhuisgroep Alkmaar* Rijnstate Ziekenhuis Arnhem*	Sint Maartenskliniek Reade*
Referral centres	Radboudumc	Bernhoven Uden	

*expressed their willingness to participate but are not yet officially registered as centre

Bijlage E: toestemmingsformulier proefpersoon

Behorende bij Het effect van colchicine op het aantal knie- of heupprotheses (ECHO)

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts en/of specialist te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om informatie op te vragen bij mijn huisarts en/of specialist(en) die mij behandelt voor artrose.
- Ik geef de onderzoeker toestemming om mijn huisarts of specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoekers toestemming om mijn gegevens en lichaamsmateriaal te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden. En om het middel te laten registreren.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik weet dat ik niet zwanger mag worden/mijn partner niet zwanger mag maken tijdens het onderzoek en tot 6 na het stoppen met de studiemedicatie.
- De onderzoeker heeft met mij besproken hoe ik het beste voorkom dat ik zwanger word/dat mijn partner zwanger wordt.
- Wilt u in de tabel hieronder ja of nee aankruisen?

Ik geef toestemming om mijn gegevens te bewaren om dit te gebruiken voor ander onderzoek, zoals in de informatiebrief staat.	Ja ☐	Nee☐
Ik geef toestemming om mijn (overgebleven) lichaamsmateriaal te bewaren om dit te gebruiken voor ander onderzoek, zoals in de informatiebrief staat. Het lichaamsmateriaal wordt daarvoor nog 10 jaar bewaard.	Ja ☐	Nee☐
Ik geef toestemming om mij eventueel na dit onderzoek te vragen of ik wil meedoen met een vervolgonderzoek.	Ja ☐	Nee☐
Ik geef de onderzoekers toestemming om na het onderzoek te laten weten welke behandeling ik heb gehad/ in welke groep ik zat.	Ja ☐	Nee☐

- Ik wil meedoen aan dit onderzoek.

Mijn naam is (proefpersoon): …….

Handtekening: …… Datum : __ / __ / __

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):…….
Handtekening:…… Datum: __ / __ / __

De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.

BMJ Open

Design of a randomised, placebo-controlled, double-blind multicentre study assessing the Effect of ColcHicine on the incidence of knee or hip replacements in symptomatic knee or hip Osteoarthritis: the ECHO trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-098096.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Feb-2025
Complete List of Authors:	Heijman, Michelle; Sint Maartenskliniek, Department of Research; Radboud University Medical Center, Department of Rheumatology van den Ende, Cornelia; Sint Maartenskliniek, Department of Research; Radboud University Medical Center, Department of Rheumatology Cornel, Jan; Radboud University Medical Center, Department of Cardiology; Noordwest Ziekenhuisgroep, Department of Cardiology; Dutch Network for Cardiovascular Research (WCN) Smolders, José; Sint Maartenskliniek, Department of Orthopedics Schers, Henk; Radboud University Medical Center, Department of Primary and Community Care Kievit, Wietske; Radboud University Medical Center, Department of Health Evidence Koeter, Sander; Canisius Wilhelmina Hospital, Department of Orthopedics van den Bemt, Bart; Sint Maartenskliniek, Department of Pharmacy; Radboud University Medical Center, Department of Pharmacy Popa, Calin; Sint Maartenskliniek, Department of Rheumatology; Radboud University Medical Center, Department of Rheumatology
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	RHEUMATOLOGY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Drug Therapy, Randomized Controlled Trial, Inflammation

Design of a randomised, placebo-controlled, double-blind multicentre study assessing the Effect of ColcHicine on the incidence of knee or hip replacements in symptomatic knee or hip Osteoarthritis: the ECHO trial

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Abstract

Introduction: Osteoarthritis is a multi-factorial disease in which low-grade inflammation is considered to play a pivotal role. Although colchicine is a widely used anti-inflammatory drug in the treatment of gout, its effect in osteoarthritis is still disputed due to inconsistent results of short-term clinical trials. Therefore, we aim to evaluate the effect of long-term colchicine 0.5mg once daily on the incidence of knee or hip replacements in patients with knee or hip osteoarthritis.

Methods and analysis: The ECHO trial is a prospective, multicentre, randomised, double-blind, placebo-controlled, phase III trial in which 1200 participants with knee or hip osteoarthritis tolerant to colchicine during a 30-day run-in period will be 1:1 randomised to colchicine 0.5 mg once daily or matching placebo using concealed allocation. The primary endpoint is the time from randomisation to the first knee or hip replacement assessed up to 4.5 years. Secondary endpoints include course of pain, physical function, joint space narrowing, low-grade inflammation, quality of life, clinical or radiological onset of OA in a new joint group other than present at baseline, number of participants using pain medication during the study, onset of new cardiovascular events (i.e. myocardial infarction, ischemia-driven coronary revascularization, ischemic stroke, peripheral artery disease or cardiovascular death), and direct and indirect costs related to treatment and disease burden due to osteoarthritis. Harm-related endpoints include the number of (serious) adverse events, the number of withdrawals due to (serious) adverse events, and changes in laboratory data (i.e. serum creatinine, eGFR, and ALAT) throughout the study. The primary analysis will be performed according to the intention-to-treat principle.

Ethics and dissemination: This trial has been approved by the METC East-Netherlands. Findings will be presented at scientific meetings and published in a peer-reviewed scientific journal.

Registration details: CTIS: 2024-511359-16-00. Clinicaltrials.gov: NCT06578182.

Strengths and limitations of this study

- This is the first randomised controlled trial with low-dose, long-term treatment of colchicine in a large number of patients with osteoarthritis recruited from multiple centres in the Netherlands
- The primary endpoint is the time from randomisation until the date of first documented knee or hip replacement, date of death, date of loss to follow-up, or study end-date, whichever comes first assessed up to 4.5 years
- The adaptive design of this event-driven trial allows for a blinded re-estimation of the sample size
- Adherence to trial medication may subside over time

Introduction

Osteoarthritis is one of the leading causes of pain and disability, currently affecting more than 500 million people worldwide [1]. Towards 2050, it is estimated that the number of osteoarthritis patients will globally rise by 60 to 100% along with increases in the prevalence of obesity and longevity [2]. Without any disease-modifying osteoarthritic drugs (DMOADs) available, a substantial challenge to healthcare systems is posed [3].

The pathophysiology of osteoarthritis is multifactorial and a low-grade chronic inflammation, indicative of an inflammatory phenotype, has been described in the affected joints [4,5]. This inflammation is mediated primarily by the innate immune system. A critical component of the innate immune system is the NLRP3 inflammasome, which mediates caspase-1 activation and the secretion of proinflammatory cytokine interleukin 1beta (IL-1β) [6]. IL-1β is considered one of the major players implicated in the pathogenesis of osteoarthritis, by both activating innervating nociceptors and promoting joint destruction via catabolic proteins such as matrix metalloproteinases (MMPs) [7]. This suggests that therapeutically targeting this pathway in OA may potentially prevent or reduce cartilage destruction and pain, thereby slowing the progression of the disease.

An exploratory analysis in the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) trial involving patients with a history of myocardial infarction has recently supported this hypothesis [8]. Inhibiting IL-1β with canakinumab reduced the rates of total knee replacements (TKR) and total hip replacements (THR) during a median follow-up of 3.7 years (hazard ratio, 0.58 [CI, 0.42 to 0.80]) [9]. Due to the high cost of canakinumab, however, further exploration of affordable anti-inflammatory therapies with similar properties for the treatment of osteoarthritis is warranted.

Colchicine, an alkaloid extracted from the autumn crocus (*Colchicum autumnale*), has been widely used in acute crystal-induced inflammation and gout flare prophylaxis [10]. By binding to tubulins, it prevents microtubules from assemblage and polymerization. This results in disrupted microtubules

function and broad cellular actions including inhibition of the NLRP3 inflammasome and MMP13 [11]. Hence, there is also reason to assume that colchicine may slow the progression of osteoarthritis.

Up to now, three randomised controlled trials with follow-ups of less than 6 months using colchicine 0.5 mg twice daily alone or in combination with nimesulide or piroxicam versus placebo alone or in combination with nimesulide or piroxicam demonstrated symptomatic benefits regarding pain, function, and global assessment in patients with osteoarthritis [12–15]. These results were confirmed by another randomised controlled trial using colchicine 1.5 mg once daily in combination with paracetamol versus paracetamol alone [16]. Moreover, in a non-randomised controlled trial, administration of colchicine 0.5 mg twice daily in combination with paracetamol resulted in stable levels of cartilage oligomeric matrix protein (COMP), suggesting stability of the cartilage [17]. When paracetamol was used alone, the levels of serum COMP significantly increased from two months to one year. The results of this study indicate that colchicine might act as a DMOAD by stabilizing cartilage turnover and preventing further degradation.

In contrast, in the COLchicine effectiveness in symptoms and inflammation modification in Knee OsteoArthritis (COLKOA) study, no statistically significant difference in knee osteoarthritis symptoms was seen between colchicine 0.5 mg twice daily and placebo over 16 weeks [18]. Nevertheless, COLKOA did find that colchicine reduced systemic inflammation based on high-sensitivity C-reactive protein (hs-CRP) and bone turnover based on Cross-Linked C-Telopeptide Of Type I Collagen (CTXI) which are both biomarkers that are associated with the progression of osteoarthritis. Furthermore, 0.5 mg twice daily colchicine over three months failed to improve symptoms in patients with osteoarthritis in the hands compared with placebo in two randomised controlled trials, but one of these trials may have been underpowered and was likely diluted by non-inflamed osteoarthritis subjects [19–21]. Lastly, comparing the efficacy of 1 mg/day colchicine treatment versus 16 weeks of physical therapy in 62 patients with knee osteoarthritis showed that physical therapy was more effective than colchicine in reducing pain and improving physical function [22].

Due to these contradictory results, there is currently not enough evidence to recommend colchicine as a treatment for knee or hand osteoarthritis [12,23]. However, it is important to note that each study included no more than 150 patients with follow-up periods not exceeding 1 year. To study the long-term effects of colchicine, a post-hoc analysis of the LoDoCo2 trial was recently performed in which 5522 patients with evidence of coronary disease were randomly assigned to receive colchicine 0.5 mg once daily or matching placebo over a median follow-up of 28.6 months [24]. Based on the adverse event data, colchicine 0.5 mg daily was associated with a lower incidence of total knee or hip replacements as compared to placebo (hazard ratio, 0.69 [CI, 0.51 to 0.95]) [25]. Long-term safety data from this randomised controlled trial did not show an increase in life-threatening or serious AEs [26]. Further investigation of long-term therapy with colchicine to slow disease progression in osteoarthritis is needed as the LoDoCo2 trial was not designed for this purpose.

Therefore, we aim to evaluate the effect of long-term use of colchicine 0.5mg once daily compared to placebo in patients with knee or hip OA on the incidence of knee or hip replacement throughout 3 to 4.5 years.

Methods and analysis

This protocol has been reported following the SPIRIT guidelines (Additional file 1) [27].

Study design

The ECHO trial is designed as a multicentre, randomised, placebo-controlled, double-blind, event-driven superiority trial. After signing informed consent, all eligible patients will use colchicine 0.5mg once daily for 30 days. Patients without adverse events, maintaining adherence, and expressing continued willingness to participate after this open-label run-in period will be randomly allocated in a 1:1 ratio to colchicine or placebo. Depending on the time of inclusion (planned between January 2025 and July 2026), the trial duration for each patient will range from 3 to 4.5 years, as the study end date

is approximately the same for all participants (estimated at April 2029). A flowchart is shown in Figure 1.

Study population

To be eligible to participate in this study, participants must meet all of the following criteria: I) clinical diagnosis of knee or hip osteoarthritis; II) aged between 45 and 80 years; and III) at least 2-year history of complaints due to osteoarthritis in the hip and/or knee or documented radiographic changes typical for advanced knee and/or hip osteoarthritis (Kellgren & Lawrence (K&L) score ≥ 2). A potential participant who meets any of the following criteria will be excluded from participation: on a waiting list for primary joint replacement surgery of the hip or knee, irrespective of cause, any absolute contraindication for knee or hip replacement in the future, more than one previous hip or knee replacement, other known medical disease that may affect joints, known generalized pain syndromes such as fibromyalgia, renal impairment as evidenced by serum creatinine >150µmol/l or estimated glomerular filtration rate (eGFR) <50mL/min/1.73m2, liver function impairment as evidenced by serum alanine transferase (ALAT) > 3 ULN (upper limit of normal), blood dyscrasia, high frailty (clinical frailty scale ≥ 7) or predicted life expectancy < 5 years, peripheral neuritis, myositis or marked myo-sensitivity to statins, current use of colchicine for another indication, intolerance to colchicine, use of macrolide antibiotics (i.e. clarithromycin, erythromycin, azithromycin), antimycotics (i.e. ketoconazole, itraconazole and voriconazole), protease inhibitors & anti-retroviral drugs (i.e. ritonavir, lopinavir, tipranavir, atazanavir, darunavir, indinavir, saquinavir, and cobicistat), anti-arrhythmic drugs (i.e. verapamil, diltiazem), or immunosuppressant (i.e. cyclosporine), current enrolment in another trial, incapacitated patients, pregnant or breastfeeding female, fertile female participants not taking sufficient anti-conception, or male participants unwilling to use effective contraception during the study to prevent pregnancy.

Recruitment and screening procedures

Potentially eligible patients visiting the Department of Orthopaedics or Rheumatology from the referral and participating centres in the Netherlands will be informed by their physicians (Additional file 2). In addition, general practitioner practices of the primary care Practice-based Research Network of Radboudumc Nijmegen, ReumaNederland (a national patient organization and rheumatism research funder), and P-AL (Poly-Artrose Lotgenoten; a national patient organization) will disseminate information on the study and invite people with knee or hip osteoarthritis to show their interest.

Patients who express their interest will be invited to complete an online questionnaire on a secure website (Castor EDC) to assess elementary eligibility criteria and provide their consent to be contacted by a member of the research team. Individuals who had previously expressed their interest before the study's commencement due to national publicity related to our previously published findings of the LoDoCo2 trial will similarly be approached [25]. Those deemed potentially eligible will then undergo further screening by phone and will be asked for their consent to contact their treating physician to confirm the diagnosis, send recent X-rays of hip or knee joints if present, and gather additional eligibility information if needed.

Potentially eligible patients who express their willingness to participate during the phone call will undergo a screening visit at one of the locations of the participating centres in the Netherlands. Following informed consent, blood samples will be collected to assess liver and renal function and all participants will be supplied with open-label colchicine 0.5mg once daily for 30 days (run-in period). Participants will be instructed to commence medication after reviewing laboratory results. If intolerance to colchicine is suspected (e.g. gastro-intestinal upset) patients are instructed to stop therapy immediately and encouraged to re-challenge themselves after five days. If symptoms initially resolve but re-occur when the drug is re-introduced, they will be assumed to be intolerant to colchicine. In addition, if estimated glomerular filtration rate (eGFR) >50mL/min/1.73m2 or serum alanine transferase (ALAT) < 3 ULN (upper limit of normal) at the start of the run-in phase, but <50mL/min/1.73m2 or > 3 at baseline patients will not be randomised.

Patients without adverse events, who maintain adherence, and express a continued willingness to participate after the run-in period will proceed to the baseline visit. Blood samples will be obtained to assess liver and renal function and an X-ray of the index joint will be taken to assess K&L score and joint space narrowing if not made in the past six months.

Randomisation, blinding and treatment allocation

Eligible patients will be randomised to colchicine 0.5 mg once daily or placebo with an allocation ratio of 1:1. Randomisation will be performed by an independent pharmacist of the Sint Maartenskliniek using block randomisation with variable block sizes of 4 and 6 stratified by centre, K&L score, and index joint. The physician, the participant, and all other staff involved in the trial will be masked to the participant's treatment allocation. Concealed allocation is guaranteed by randomisation software that will assign subjects to treatment groups, matching placebo to colchicine, and strict procedures for blinded and unblinded parties in the drug supply chain. The investigator will unblind the treatment allocation of a subject during the clinical trial only if unblinding is relevant to a subject's safety. In case of unblinding, the investigator can open a physical envelope labelled with the participant's treatment number. This envelope will contain information about the trial medication that was received. Other participants will not be unblinded. To assess the success of blinding, participants will be asked annually to indicate which group they believe they are in.

Intervention

Colchicine Tiofarma 500 microgram tablets will be orally administered with water once a day. If a dose is missed, it should be taken later during the day or skipped if noticed after 12 hours. A matching placebo is the comparator. Trial medication will be (temporarily) discontinued if health issues overrule treatment continuation as determined by the clinical site investigator or if one of the following drugs are prescribed for a given period: macrolide antibiotics (clarithromycin, erythromycin, azithromycin), antimycotics (ketoconazole, itraconazole, and voriconazole), protease inhibitors and anti-retroviral

drugs (ritonavir, lopinavir, tipranavir, atazanavir, darunavir, indinavir, saquinavir, and cobicistat), anti-arrhythmic drugs (verapamil, diltiazem), immunosuppressant (cyclosporine).

Study procedures

Patients will be asked to complete online questionnaires using an electronic Data Capture application (Castor EDC) at enrolment, at baseline, and every 3 months after that. Face-to-face contact will take place at enrolment, at baseline, and every year during follow-up. The number of visits depends on the moment of inclusion and ranges between a minimum of 5 and a maximum of 7. Participants who discontinue the trial medication or withdraw from the study for any reason will continue to be followed for the primary outcome (knee or hip replacement). The study procedures are shown in Additional file 3.

Demographics

Data regarding age, sex, ethnicity, education level, profession, employment, smoking, alcohol, index joint, number and type of affected joints, and duration of complaints will be collected at enrolment.

Anthropometrics

Height, weight, and waist circumference will be assessed at baseline. Subsequent measures of weight and waist circumference will be taken during clinical visits. BMI will be calculated using weight and height.

Comorbidities

The following comorbid conditions will be documented at each clinical visit: heart disease (for example angina, heart attack, or heart failure); high blood pressure; problems caused by a stroke; leg pain when walking due to poor circulation; lung disease (for example asthma, chronic bronchitis, or emphysema); diabetes mellitus; kidney disease; diseases of the nervous system (for example Parkinson's disease or multiple sclerosis); liver disease; cancer (within the last 5 years); depression; arthritis in your back or

other condition affecting your spine; rheumatoid arthritis or another kind of arthritis in addition to osteoarthritis [28].

Joint replacement

Participants will be asked every 3 months about any knee or hip replacement surgery through a multiple-choice question. In case of an event, source documents will be collected for central adjudication.

OA diagnosis

Participants will be asked every 12 months about any new osteoarthritis diagnosis in a joint other than the knee or hip through a yes-no question. In case of an event, source documents will be collected for central adjudication.

Cardiovascular events

Participants will be asked every 12 months about any cardiovascular event defined as myocardial infarction, peripheral artery disease, ischemia-driven coronary revascularization, ischemic stroke, or cardiovascular death through a multiple-choice question. In case of an event, source documents will be collected for central adjudication.

Pain medication

Participants will be asked every 3 months about any concomitant pain medication used, including prescription and over-the-counter medications.

Numeric rating scale (NRS)

The NRS will assess pain levels during rest and during movement at baseline and every 3 months after that. The NRS consists of 11 numbers from 0 to 10, where 0 means no pain and 10 represents the most imaginable pain.

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

The WOMAC is designed to assess pain, stiffness, and physical functioning in patients with knee or hip osteoarthritis utilizing 24 questions and will be assessed at baseline and every 6 months after that [29]. Higher scores represent worse outcomes.

European Quality of Life 5-Dimensions 5-Level (EQ-5D-5L)

The EQ-5D-5L measures quality of life at baseline and every 6 months after that using 5 levels of severity in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [30].

iMTA Productivity Cost Questionnaire (iPCQ)

The iPCQ will assess loss of productivity due to OA or joint replacement surgery based on patient-reported absences from paid or unpaid labour at baseline and every 6 months after that [31].

iMTA Medical Consumption Questionnaire (iMCQ)

The iMCQ will assess all relevant healthcare-related costs like outpatient visits to medical specialists, hospitalizations, and paramedic care at baseline and every 6 months after that [32].

Medication Adherence Report Scale (MARS-5)

The MARS-5 questionnaire will be assessed every 6 months to evaluate adherence to trial medication and consists of five self-reported adherence items about forgetting, changing dosage, stopping, skipping, and taking less medication. Scores range from 5 to 25, with higher scores indicating better medication adherence [33].

Pill count

Adherence to trial medication will be evaluated through pill counts once a year.

Radiography

Radiographic examinations include standard clinical radiographs of the index knee or hip at baseline if not made in the past 6 months and, in a subgroup of 200 patients who have taken at least 80% of the

study medication for a minimum of 2 years at the end of the study. Joint space narrowing will be assessed using automated software.

Blood samples

Blood samples will be drawn at enrolment, at baseline, after 1 year, and at the end of the study to assess inflammation (hs-CRP) and safety (kidney function, liver function, creatinine kinase, erythrocytes, leukocytes, thrombocytes, and, if anaemia is present, vitamin B12).

Adverse events

Abnormal CK, eGFR, and ALAT values will be registered throughout the study period. The following adverse events will be systematically assessed once a year: gastrointestinal, infectious, musculoskeletal and connective tissue disorders, cardiac disorders, and neurological disorders.

Study endpoints

The primary endpoint of this study is time from randomisation until the date of first documented knee or hip replacement, date of death, date of loss to follow-up, or study end-date, whichever comes first, assessed up to 4.5 years.

Secondary endpoints include 1) course of pain, 2) course of physical function, 3) course of joint space narrowing, 4) course of low-grade inflammation, 5) course of quality of life, 6) number of participants with and time to clinical or radiological onset of OA in a new joint group other than present at baseline, 7) number of participants using pain medication during the study, 8) onset of new cardiovascular events, including myocardial infarction, ischemia-driven coronary revascularization, ischemic stroke, peripheral artery disease or cardiovascular death, and 9) direct and indirect costs related to treatment and disease burden due to osteoarthritis from randomisation until the date of first documented knee or hip replacement, date of death, date of loss to follow-up, or study end-date, whichever comes first, assessed up to 4.5 years.

Harm-related endpoints include 1) the number of (serious) adverse events, 2) the number of withdrawals due to (serious) adverse events, and 3) changes in laboratory data (i.e. serum creatinine, eGFR and ALAT) throughout the study.

Sample size calculation

This trial is designed to accrue a minimum of 380 primary end-point events for the Cox proportional hazard model to achieve 80% power with an alpha of 0.05 and detect a hazard ratio of 0.75 (based on the exploratory results from the LoDoCo2 trial) [25]. To achieve this number of events, the number of required patients varies based on the baseline event rate and the inclusion rate (as with more inclusions at the beginning of the inclusion period, patients will on average have longer follow-up within the planned total study duration of 4.5 years). Therefore, an adaptive design that allows for a blinded re-estimation of the sample size based on the observed number of events and speed of inclusion using the R package BSSRed will be applied [34]. The required number of patients and duration of the inclusion period for various scenarios regarding baseline event rate and inclusion rate is shown in Table 1. For all scenarios, the maximum study duration until administrative censoring was set to 4.5 years, with a dropout of 10% at 2 years based on data from the LoDoCo2 trial [26]. Scenarios concerning primary event rates were based on a previous study on the proportion of knee or hip replacements after 2 years in a sample of patients consulting an orthopaedic surgeon without indication for replacement (25% event rate) and the estimated proportion of patients consulting their general practitioner receiving hip or knee replacement in 2 years (23% event rate) [35]. In addition, we added a scenario with a conservative estimate (20% event rate). Based on these assumptions, 1410 patients will enter the run-in phase and 1200 patients will be randomised. Sample size re-estimation is planned at the end of the planned inclusion period at 18 months and does not require correction for multiplicity as allocation remains blinded and no between-arm comparisons are performed.

Table 1. Estimation of the sample size and length of the inclusion period for varying inclusion rates (1000, 1200, and 1500) per 18 months (the planned inclusion period) and primary event rates (20%, 23%, and 25%) per 2 years.

Inclusion rate per 18 months	**Primary event rate per 2 years**		
	20%	23%	25%
1000	1504 in 27 months	1280 in 23 months	1168 in 21 months
1200	1398 in 20 months	1200 in 18 months	1134 in 17 months
1500	1334 in 16 months	1166 in 14 months	1084 in 13 months

Statistical analysis

Descriptive statistics will be used to describe the study sample. For normally distributed continuous variables, means and standard deviations (SDs) will be calculated. For non-normally distributed continuous variables, medians and interquartile ranges (IQRs) will be reported. Categorical or dichotomous variables will be summarized using absolute numbers and percentages.

The primary analysis will be performed according to the intention-to-treat principle. Kaplan-Meier curves will be used to depict the time to first knee or hip replacement in the two treatment groups. Hazard ratios of treatment with colchicine versus placebo, with corresponding 95% confidence intervals, will be obtained from Cox proportional hazards regression models with stratification by centre, K&L score, and index joint. Sensitivity analyses will be performed by adding covariates for change in body weight over time and cumulative use of pain medication. All randomised patients will be included in the analyses. In addition, a per-protocol analysis of the primary endpoint will be performed in patients who have taken at least 80% of the study medication for a minimum of 2 years.

For the secondary analyses, linear mixed models or generalized estimating equations with repeated measures will be used to estimate mean between-group differences and their 95% CIs for continuous and binary secondary outcomes. Participants will be included as random effect and treatment allocation as fixed effect factors. Missing data will be handled by the mixed model.

A cost-effectiveness analysis will be carried out alongside the trial comparing colchicine to placebo from a societal perspective. First, the EQ-5D-5L will assess the impact of both strategies on the quality of life, and the utility will be used to derive a QALY estimate for each patient according to the trapezium

rule. Second, volumes of OA-related care will be measured at the patient level using the iMCQ, and loss of productivity due to OA or joint replacement surgery will be estimated based on patient-reported absences from paid (or unpaid) labour measured with the iPCQ. To determine the cost prices for each volume of consumption, the standard cost prices from the 'Dutch Guidelines for Cost Analyses' and www.medicijnkosten.nl will be used. For units of care where no standard prices are available real cost prices will be determined based on full cost pricing. Productivity losses will be valued through the friction cost method. Finally, the incremental cost-effectiveness ratio will be calculated by dividing the difference in costs (medical and societal) by the difference in QALYs between the groups. The ICER, indicating the additional cost required to gain one QALY, can be compared to the willingness to pay value. Uncertainty in the ICER will be non-parametrically determined using bootstrap techniques (1000 replications).

No formal statistical testing will be conducted for the harm-related endpoints. AEs and SAEs will be presented as numbers and percentages per intervention arm. The relationship between AEs and SAEs with the trial treatment will be evaluated and numbers and percentages of treatment-related AEs and SAEs will be presented per treatment arm. Deaths, AEs, and SAEs resulting in treatment discontinuation will be reported.

Harm-related considerations

Except for planned hospitalisations because of knee or hip replacements, the investigator will record all AEs and SAEs including the date of occurrence, a description of the event and its severity, duration, and the actions taken. All AEs and SAEs will be followed until they have abated or a stable situation has been reached. Due to the size and duration of the trial, an independent Data and Safety Monitoring Committee consisting of one rheumatologist, one clinical epidemiologist, and one pharmacist from the Sint Maartenskliniek will blindly review the trial's progress including updated figures on recruitment and safety data biannually and will advise on optimal execution. No interim analysis will be done.

Data management

Data will be collected and processed following the General Data Protection Regulation (EU) 2016/679. Data will be entered in Castor EDC, recorded on eCRF forms, and stored on a department server with automatic back-ups. Paper-based data will be stored in locked cabinets at each site. Data will be kept for 25 years.

Subjects will be identified by a study-specific subject number and/or code in the database. Names and other identifying details will not be included in any study data electronic file. The key to the code is safeguarded by principle investigators.

Data quality will be promoted by data checks. If missing, questionable, or out-of-range values are identified, these will be queried and corrected if possible. If this is not possible, questionable or out-of-range values will be excluded from analyses.

Monitoring and quality assurance will be established according to the advice of the NFU (Dutch Federation of University Medical Centres (NFU)). A qualified monitor of the Department of Research of the Sint Maartenskliniek will visit all participating centres before trial commencement and annually thereafter to check trial procedures, including data recording, verification of source data, and safety assessments.

Patient and public involvement

From the pre-application of the grant for this project, 2 patient representatives of the STAP panel (Key To Active Participation; a hospital-based patient panel of around 50 patient research partners with rheumatic diseases to support orthopedic and rheumatology research (both clinical and preclinical) at Radboudumc and Sint Maartenskliniek) actively engaged in this project. During this phase, the relevance and feasibility of this project were assessed. Suggestions were provided about participant retention, medication adherence, and the assessment of adverse effects. This resulted in insights about the order of questionnaires and the amount and type of contact with researchers. Information about adverse effects and interaction with other drugs has been added to the patient information form

(PIF). Their request to investigate differences between men and women has been incorporated in the statistical analysis.

After grant approval, 2 additional patient representatives agreed to actively participate in this project: 1 member of the national patient organization P-AL and 1 member of the STAP panel. They provided feedback on the PIF and evaluated the feasibility for patients by testing study procedures. During later research phases, patient representatives will be involved by drafting a questionnaire to assess elementary eligibility criteria if patients express their interest to participate following disseminated study information from national publicity related to our previously published finding of the LoDoCo2 trial, ReumaNederland or P-AL and promoting participant retention. In addition, patient representatives will give input about the wording of results from a patient perspective, write lay summaries, and can co-author scientific publications.

Ethics and dissemination

The proposed trial has been registered with the EU Clinical Trials Register (2024-511359-16-00) and on clinicaltrials.gov (NCT06578182). The protocol has been approved by METC East-Netherlands. Written informed consent will be obtained from all participants by the treating or research physician (Additional file 4). A separate question in the ICF will ask for permission to store and reuse personal data and samples for further research. Findings will be presented at scientific meetings and published with the full trial protocol in a peer-reviewed scientific journal. Pseudonymized data will be made available on reasonable request.

Authors' contributions.

Conception and design: MH, CE, JC, BB, and CP. Design of the statistical analysis plan: MH, CE, and WK. Drafting of the present manuscript: MH. Critical revision: CE, JC, JS, HS, WK, SK, BB, and CP. Final approval: MH, CE, JC, JS, HS, WK, SK, BB, CP. Funding acquisition: MH, CE, JC, JS, HS, WK, SK, BB, and CP. Guarantor: CP.

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Competing interests statement

JC received consulting fees from Amgen and Novo Nordisk, participated on a Data Safety Monitoring Board or Advisory Board in the EDIT-CAS study and BioNTech malaria vaccine program, and has a leadership or fiduciary role in the executive committee LIBREXIA AF and Chair Event Adjudication committee REDEFINE/REIMAGINE. JS received consulting fees from Smith & Nephew consultancy. SK has a leadership or fiduciary role in the Board Dutch Knee Society, President Commission on Quality Royal Dutch Orthopaedic Society, and is chairman of Department Orthopaedic Surgery CWZ. All other authors have no competing interest to declare.

Full references

1. Long H, Liu Q, Yin H, et al. Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019. Arthritis and Rheumatology. 2022;74:1172–83.
2. Steinmetz JD, Culbreth GT, Haile LM, et al. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Rheumatol. 2023;5:e508–22.
3. Osteoarthritis: A serious disease [Internet]. Osteoarthritis Research Society International. 2016 [cited 2022 Aug 18]. Available from: https://oarsi.org/education/oarsi-resources/oarsi-white-paper-oa-serious-disease
4. Kapoor M, Martel-Pelletier J, Lajeunesse D, et al. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol. 2011;7:33–42.
5. Zhu R, Fang H, Wang J, et al. Inflammation as a therapeutic target for osteoarthritis: A literature review of clinical trials. Clinical Rheumatology. Springer Science and Business Media Deutschland GmbH; 2024.

6. Robinson WH, Lepus CM, Wang Q, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016;12:580–92.

7. Conaghan PG, Cook AD, Hamilton JA, et al. Therapeutic options for targeting inflammatory osteoarthritis pain. Nat Rev Rheumatol. 2019;15:355–63.

8. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. New England Journal of Medicine. 2017;377:1119–31.

9. Schieker M, Conaghan PG, Mindeholm L, et al. Effects of interleukin-1β inhibition on incident hip and knee replacement: Exploratory analyses from a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2020;173:509–15.

10. Leung YY, Yao Hui LL, Kraus VB. Colchicine-Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. 2015;45:341–50.

11. Takeuchi K, Ogawa H, Kuramitsu N, et al. Colchicine protects against cartilage degeneration by inhibiting MMP13 expression via PLC-γ1 phosphorylation. Osteoarthritis Cartilage. 2021;29:1564–74.

12. Singh A, Molina-Garcia P, Hussain S, et al. Efficacy and safety of colchicine for the treatment of osteoarthritis: a systematic review and meta-analysis of intervention trials. Clin Rheumatol. 2022;Epub ahead of print.

13. Das SK, Mishra K, Ramakrishnan S, et al. A randomized controlled trial to evaluate the slow-acting symptom modifying effects of a regimen containing colchicine in a subset of patients with osteoarthritis of the knee. Osteoarthritis Cartilage. 2002;10:247–52.

14. Das SK, Ramakrishnan S, Mishra K, et al. A randomized controlled trial to evaluate the slow-acting symptom-modifying effects of colchicine in osteoarthritis of the knee: A preliminary report. Arthritis Care Res (Hoboken). 2002;47:280–4.

15. Aran S, Malekzadeh S, Seifirad S. A double-blind randomised controlled trial appraising the symptom-modifying effects of colchicine on osteoarthritis of the knee. Clin Exp Rheumatol. 2011;29:513–8.

16. Erden M, Ediz L, Hız Ö, et al. Effect of Colchicine on Total Antioxidant Capacity, Antioxidant Enzymes and Oxidative Stress Markers in Patients with Knee Osteoarthritis. Int J Clin Med. 2012;3:377–82.

17. Srivastava R, Das SK, Goel G, et al. Does long term colchicine prevent degradation of collagen fiber network in osteoarthritis? Int J Rheum Dis. 2017;21:114–7.

18. Leung YY, Haaland B, Huebner JL, et al. Colchicine lack of effectiveness in symptom and inflammation modification in knee osteoarthritis (COLKOA): a randomized controlled trial. Osteoarthritis Cartilage. 2018;26:631–40.

19. Davis CR, Ruediger CD, Dyer KA, et al. Colchicine is not effective for reducing osteoarthritic hand pain compared to placebo: a randomised, placebo-controlled trial (COLAH). Osteoarthritis Cartilage. 2021;29:208–14.

20. Døssing A, Henriksen M, Ellegaard K, et al. Colchicine twice a day for hand osteoarthritis (COLOR): a double-blind, randomised, placebo-controlled trial. Lancet Rheumatol [Internet]. 2023 Apr; Available from: https://linkinghub.elsevier.com/retrieve/pii/S2665991323000656

21. Plotz B, Pillinger M, Samuels J. Colchicine and clinical trials for hand osteoarthritis. Vol. 30, Osteoarthritis and Cartilage. W.B. Saunders Ltd; 2022. p. 172–3.

22. Cioroianu GO, Florescu A, Mușetescu AE, et al. Colchicine versus Physical Therapy in Knee Osteoarthritis. Life. 2022;12.

23. Liu W, Wang HC, Su C, et al. The Evaluation of the Efficacy and Safety of Oral Colchicine in the Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trails. Biomed Res Int. 2022;2022:2381828.

24. Nidorf SM, Fiolet ATL, Eikelboom JW, et al. The effect of low-dose colchicine in patients with stable coronary artery disease: The LoDoCo2 trial rationale, design, and baseline characteristics. Am Heart J. 2019;218:46–56.

25. Heijman MWJ, Fiolet ATL, Mosterd A, et al. Association of Low-Dose Colchicine With Incidence of Knee and Hip Replacements : Exploratory Analyses From a Randomized, Controlled, Double-Blind Trial. Ann Intern Med [Internet]. 2023 May 30; Available from: http://www.ncbi.nlm.nih.gov/pubmed/37247416

26. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. New England Journal of Medicine. 2020;383:1838–47.

27. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials DEVELOPMENT OF THE SPIRIT 2013 STATEMENT [Internet]. Vol. 158, Ann Intern Med. 2013. Available from: www.annals.org

28. Rolfson O, Wissig S, van Maasakkers L, et al. Defining an International Standard Set of Outcome Measures for Patients With Hip or Knee Osteoarthritis: Consensus of the International Consortium for Health Outcomes Measurement Hip and Knee Osteoarthritis Working Group. Arthritis Care Res (Hoboken). 2016;68:1631–9.

29. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833–40.

30. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011;20:1727–36.

31. Bouwmans C, Krol M, Severens H, et al. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. Value in Health. 2015;18:753–8.

32. iMTA Productivity and Health Research Group. Manual iMTA Medical Cost Questionnaire (iMCQ). Rotterdam; 2018.

33. Chan AHY, Horne R, Hankins M, et al. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol. 2020;86:1281–8.

34. Friede T, Pohlmann H, Schmidli H. Blinded sample size reestimation in event-driven clinical trials: Methods and an application in multiple sclerosis. Pharm Stat. 2019;18:351–65.

35. Mahler EAM, den Broeder AA, den Broeder N, et al. Short-term clinical worsening is a clear predictor for worsening at 2 years in established knee and hip osteoarthritis. Clin Exp Rheumatol. 2019;37:414–21.

534 **Figure 1. Flowchart of the study.**

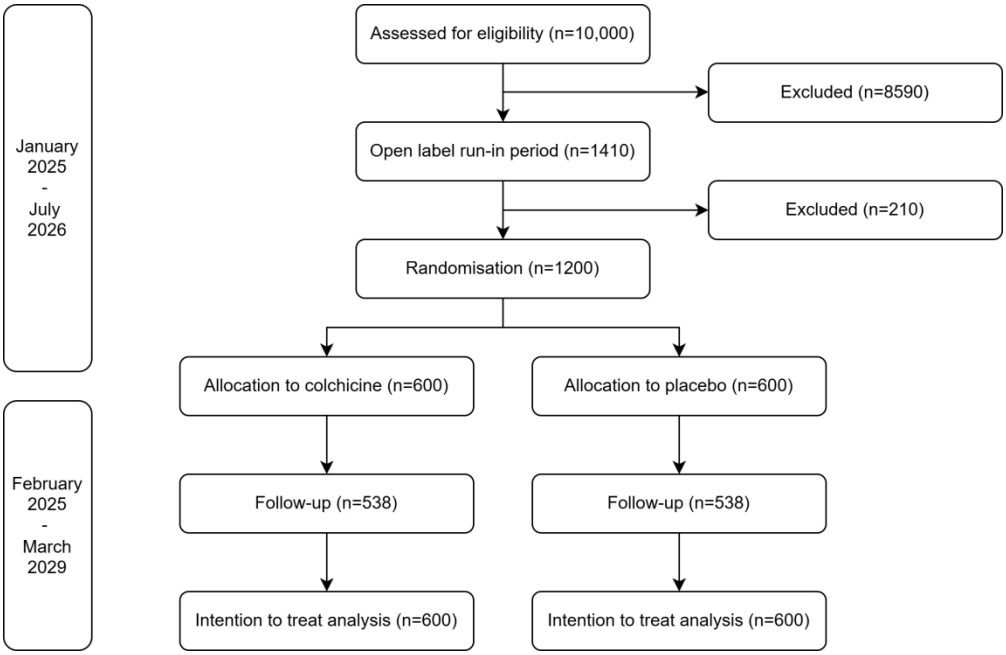

Figure 1. Flowchart of the study

439x284mm (118 x 118 DPI)

SPIRIT-Outcomes 2022 Checklist (for combined completion of SPIRIT 2013 and SPIRIT-Outcomes 2022 items)[a]

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	-	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	-	Abstract
	2b	All items from the World Health Organization Trial Registration Data Set	-	clinicaltrials.gov
Protocol version	3	Date and version identifier	-	clinicaltrials.gov
Funding	4	Sources and types of financial, material, and other support	-	Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	-	Title page and au
	5b	Name and contact information for the trial sponsor	-	Title page
	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	-	Funding
	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)	-	NA
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	-	Introduction
	6b	Explanation for choice of comparators	-	Introduction
Objectives	7	Specific objectives or hypotheses	-	Introduction

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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)	-	Study design
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	-	Recruitment and screening procedures
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)	-	Study population
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (for specific guidance see TIDieR checklist and guide)	-	Intervention
	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)	-	Intervention
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-	Study procedures
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-	Intervention
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	-	Study procedures and study endpoints

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	12.1		Provide a rationale for the selection of the domain for the trial's primary outcome	Study endpoints
	12.2		If the analysis metric for the primary outcome represents within-participant change, define and justify the minimal important change in individuals	NA
	12.3		If the outcome data collected are continuous but will be analyzed as categorical (method of aggregation), specify the cutoff values to be used	NA
	12.4		If outcome assessments will be performed at several time points after randomization, state the time points that will be used for analysis	Study endpoints
	12.5		If a composite outcome is used, define all individual components of the composite outcome	NA
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)	-	Study procedures
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	-	Sample size calculation
	14.1		Define and justify the target difference between treatment groups (eg, the minimal important difference)	NA
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-	Recruitment and screening procedures
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	-	Randomisation, blinding and treatment allocation

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	Randomisation, blinding and treatment allocation
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-	Randomisation, blinding and treatment allocation
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-	Randomisation, blinding and treatment allocation
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-	Randomisation, blinding and treatment allocation
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	-	Study procedures
	18a.1		Describe what is known about the responsiveness of the study instruments in a population similar to the study sample	Study procedures
	18a.2		Describe who will assess the outcome (eg, nurse, parent)	Study procedures
	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	-	Study procedures

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	Data management
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	-	Statistical analysis
	20a.1		Describe any planned methods to account for multiplicity in the analysis or interpretation of the primary and secondary outcomes (eg, coprimary outcomes, same outcome assessed at multiple time points, or subgroup analyses of an outcome)	Statistical analysis
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-	Statistical analysis
	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)	-	Statistical analysis
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	-	Harm-related considerations
	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	-	NA
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	-	Harm-related considerations

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-	NA
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-	Ethics and dissemination
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)	-	Ethics and dissemination
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	-	Ethics and dissemination
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-	Ethics and dissemination
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	-	Ethics and dissemination
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	-	Competing interests statement
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	-	Ethics and dissemination
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	-	NA
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	-	Ethics and dissemination
	31b	Authorship eligibility guidelines and any intended use of professional writers	-	NA

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-	Ethics and dissemination
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-	Additional file 3
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	-	Study procedures

[a]It is strongly recommended that this checklist be read in conjunction with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement paper 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 and is reproduced with permission.

[b]Indicates page numbers and/or manuscript location: to be completed by authors.

	University hospital	Peripheral hospital	Tertiary hospital
Participating centres		Canisius Wilhelmina Hospital Gelderse Vallei* Noordwest Hospital Group Alkmaar* Rijnstate* Reinier Haga Medical Diagnostic Centre*	Sint Maartenskliniek Reade*
Referral centres	Radboudumc	Bernhoven	

*expressed their willingness to participate but are not yet officially registered as centre

	Enrolment	Baseline	Follow-up													Close-out
Timepoint in months	-1	0	3	6	9	12	15	18	21	24	27	30	33	...	51	36-54
Eligibility screening	x															
Informed consent	x															
Open label colchicine	←	→														
Allocation		x														
Colchicine or placebo		←	→													
Sociodemographics																
Age	x															
Sex	x															
Ethnicity	x															
Education level	x															
Employment	x															
Profession	x															
Smoking	x															
Alcohol	x															
Height	x															
Weight	x					x				x				x		x
Waist circumference	x					x				x				x		x
Disease characteristics																
Index joint	x															
Affected joints	x															
Duration of complaints	x															
Joint replacement			x	x	x	x	x	x	x	x	x	x	x	x	x	x
New OA diagnosis						x				x				x		x
Comorbidities	x	x				x				x				x		x
Cardiovascular events		x				x				x				x		x
Questionnaires																
Pain medication			x		x		x		x		x		x		x	
MARS-5		x		x		x		x		x		x		x		x
NRS pain	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
WOMAC		x		x		x		x		x		x		x		x
EQ-5D-5L		x		x		x		x		x		x		x		x
iPCQ		x		x		x		x		x		x		x		x
iMCQ		x		x		x		x		x		x		x		x
Pill count		x				x				x				x		x
X-ray*		x														x
Blood sampling	x	x				x										x

Hospital visits are indicated in blue and tele contact moments are indicated in yellow. Since the study end date is approximately the same for all patients and the inclusion period is planned to last 1.5 years, the trial duration for an individual patient ranges between 3 and 4.5 years depending on the time of inclusion. *If not made in the past 6 months

Appendix E: Informed consent form – subject

Belonging to The effect of colchicine on the number of knee- and hip prostheses (ECHO)

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I wanted to take part.
- I know that taking part is voluntary. I also know that at any time I can decide not to take part in the study. Or to stop taking part. I do not have to explain why.
- I give the investigator consent to inform my doctor and/or specialist who treats me that I am taking part in this study.
- I give consent to request information from my doctor and/or specialist treating me about osteoarthritis.
- I give consent to give my doctor or specialist information about accidental discoveries made during the study that are important for my health.
- I give consent to collect and use my data and/or body material. The investigators only do this to answer the question of this study. And to register the medicinal product.
- I know that some people will be able to see all of my data to review the study. These people are mentioned in this information sheet. I give consent to let them see my data for this review.
- I know that I cannot get pregnant/cannot get my partner pregnant during the study and until 6 months after stopping the trial medication.
- The investigator discussed with me how I can best prevent becoming pregnant/my partner from becoming pregnant.
- Please tick yes or no in the table below.

I give consent to store my data to use for other research, as stated in the information sheet.	Yes ☐	No☐
I give consent to have my (remaining) body material stored for use in other research, as stated in the information sheet. The body material is stored for this purpose for another 10 years.	Yes ☐	No☐
I give consent to ask me after this study if I want to participate in a follow-up study.	Yes ☐	No☐
I give consent to let me know after the study which treatment I received/in which group I was.	Yes ☐	No☐

- I want to take part in this study.

My name is (subject): ……..

Signature: …… Date : __/__/__

Subject Information

I declare that I have fully informed this subject about the study mentioned.

If any information becomes known during the study that could influence the subject's consent, I will let this subject know in good time.

Investigator name (or their representative): .....

Signature:…… Date: __/__/__

The study subject will receive a complete information sheet, together with a signed version of the consent form.