CLINICAL STUDY PROTOCOL

Colchicine treatment for patients with hand osteoarthritis: A randomised, placebo-controlled trial.

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2 ABSTRACT

Background: Pharmacological treatment recommendations for hand osteoarthritis (OA) are focused around analgesics that are not targeted at the disease and new treatment strategies are explored continuously. Crystal deposits have been proposed to play a role in the progression of hand OA and may provide an explanation for inflammatory flares. In people with gout and monosodium urate crystal deposits, inflammation and pain can be treated successfully with oral colchicine. This study will assess the effectiveness of oral colchicine for people with hand OA.

Methods: The COLchicine treatment for patients with hand OsteoaRthrithis (COLOR) trial will be a double-blind, randomised, placebo-controlled trial. A total of 100 patients with painful hand OA will be included. Participants will be recruited from a single centre in Denmark. Participants will be randomised 1:1 to achieve oral treatment with colchicine one tablet (0.5 mg) or placebo one tablet bid (twice a day) for 12 weeks. The primary outcome is change in finger joint pain measured on a visual analogue scale spanning from 0 (no pain) to 100 (worst imaginable pain). Secondary outcomes include improvement in function, joint activity measured on physician tender joint count, patient global assessment, hand strength, and health-related quality of life. Inflammation and crystal deposits will be assessed at baseline as exploratory contextual factors measured on ultrasound, dual-energy computed tomography, and cone-beam computed tomography, respectively. Mixed models with repeated measurements, and adjustment for baseline measures will be used to compare changes between groups in the intention-to-treat population after 12 weeks.

Discussion: The COLOR trial is designed to evaluate whether oral colchicine is effective for improving pain in people with painful hand OA. Exploratory analysis will assess if crystal deposition is a predictor of therapeutic response. This study will potentially provide data to support a new treatment option for hand OA that can be managed by both rheumatologist and non-rheumatological doctors in primary and secondary care.

Keywords: Hand Osteoarthritis. Colchicine. Crystal deposition. Double-blind. Placebo-controlled. Randomised.

TABLE OF CONTENT

3 ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse events
ANCOVA	Analysis of covariance
AO	As-observed
AUSCAN	Australian/Canadian hand index score
Bid	Bis in die [two times daily]
CBCT	Cone-beam computed tomography
CI	Confidence interval
CMC	Carpometacarpal
CPP	Calcium pyrophosphate
CPPD	Calcium pyrophosphate deposition
CRF	Case Report Form
CYP3A4	Cytochrome P450 3A4
DECT	Dual-energy computed tomography
DEI	Dual Energy Index
DIP	Distal interphalangeal
EQ-5D	European Quality of Life 5 Dimensions
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HA	Hydroxyapatite
HADS	Hospital Anxiety Depression Scale
HAQ-DI	Health Assessment Questionnaire Disability Index
HOAMRIS	Hand Osteoarthritis Magnetic Resonance Imaging Scoring System
HU	Hounsfield Unit
IAP	Image analysis plan
ICF	Informed consent form
ICMJE	International committee of medical journal editors
IP	Interphalangeal
IPQ	Illness Perception Questionnaire
ITT	Intention-to-treat

KL	Kellgren Lawrence
MCP	Metacarpophalangeal
MSU	Monosodium urate
NSAID	Non-steroid anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PIP	Proximal interphalangeal
PP	Per protocol
PRPs	Patient research partners
PsA	Psoriatic arthritis
Qd	Quaque di [once daily]
PSQI	Pittsburgh Sleep Quality Index
RA	Rheumatoid arthritis
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Standard deviation
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SUSAR	Suspected unexpected serious adverse reaction
US	Ultrasound
VAS	Visual analogue scale

4 TRIAL IDENTIFIER

4.1 Full title of trial

Colchicine treatment for patients with hand osteoarthritis: A randomised, placebo-controlled trial.

4.2 Acronym

COLOR: COLchicine treatment for patients with hand OsteoaRthritis.

4.3 Short title

Colchicine vs placebo for hand OA.

4.4 Health Research Ethics Committee Number

H-20037713

4.5 European clinical trials database (EudraCT number)

2020-002803-20

4.6 Version number and date

Version 2, 24.07.2020

4.7 Revision history

4.7.1 Table 1: Revision history

Version #	Issue date	List of major changes
1.0	04.06.2020	Version for first submission for authority approval
2.0	24.07.2020	At request of the Danish Medicines Agency following changes have been made: Complete list of laboratory samples have been added. Elaborate information and precautions regarding colchicine related reproductive toxicity, including updated guidelines for anti-conceptional therapy in exclusion criteria and timely pregnancy screening of female fertile participants. Procedure for unblinding. Elaborated receiver control of study medication.

3.0	24.11.2020	Stratification was added to the randomisation: age (<75, ≥75), BMI (<30, ≥30), gender (male, female)

4.8 Expected timeline

First patient first visit: September 2020

Last patient first visit: June 2021

Last patient last visit: September 2021

5 INTRODUCTION

5.1 Background

Hand osteoarthritis (OA) is a common disease and the prevalence of symptomatic hand OA has been estimated to 26.2% among women and 13.4% among men (The Framingham Study) [1]. Incidence increases with age and it is more prevalent among women [2]. Pain is the dominant symptom, but swelling and stiffness of the joint also occur [3]. It often affects distal interphalangeal (DIP) joints, thumb base and proximal interphalangeal (PIP) joints, and is bilateral, symmetrical and polyarticular in most cases [4]. Imbalance between on-going repair and destruction leads to characteristic progressive breakdown of articular cartilage and remodelling of the underlying bone [5, 6]. Hand OA affects all components of the joint and periarticular structures [7].

Some patients experience intermittent inflammatory flares [8]. Inflammation is associated with development of erosions in the joint [9]. Erosive hand OA can be difficult to distinguish from rheumatoid arthritis (RA) and psoriatic arthritis (PsA), however autoimmune features are not present in OA [10-12].

Inflammatory reactions in joints with OA could be due to crystal formation [13, 14]. The causal relationship is debated [15, 16]. Calcium-containing crystals have been associated with OA [17], and based on in-vitro studies [13, 14] it is proposed that crystals may be the initiating component for activation of inflammatory pathways [18, 19].

Hand OA treatment aims to reduce symptoms and improve function and quality of life [20]. Management strategies should be patient-centred and multifactorial, embracing non-pharmacological, pharmacological and surgical interventions [20-22]. No therapeutic agent has proven effective in preventing, reversing or halting disease progression.

5.2 Rationale and evidence-based research

Colchicine, a therapeutic agent normally used to treat gout flares, has been trialled for knee OA with divergent results: One study found no symptom reduction when examining oral colchicine as the sole

treatment for an unselected subgroup of patients with knee OA [23]. Even though the study failed to reduce symptoms, a reduction of biomarkers associated with OA severity and progression risk was found. Three trials reported symptom reduction, but examined only women [24] or oral colchicine as an add-on therapy to a cyclooxygenase inhibitor [25] or intra-articular steroid [26]. Oral colchicine is considered safe and well-tolerated, please see section "Risk associated with the intervention" for specifics. To our knowledge no previous or planned trials have tested oral colchicine treatment for patients with hand OA. As efficacy is unknown, we plan to use placebo as comparator control group. If oral colchicine treatment proves effective, further research could consider using other potentially active treatments as comparator.

5.3 Aim

To compare oral colchicine 0.5 mg administered bid (bis in die [two times daily]) for 12 weeks with placebo as a treatment of hand OA symptoms.

5.4 Hypothesis

We hypothesize that oral colchicine is superior to placebo in reducing pain in patients with hand OA.

5.5 Objectives

5.5.1 Primary objective

To compare the effect of oral colchicine 0.5 mg bid, relative to placebo, on changes in finger joint pain of the target hand measured on a visual analogue scale (VAS) from baseline to week 12, in patients with painful hand OA.

5.5.2 Secondary objectives

To compare the effect of oral colchicine 0.5 mg bid, relative to placebo, from baseline to week 12, in patients with painful hand OA on changes in:

- Function of both hands measured on the AUSCAN Hand Index Score
- Thumb base pain of the target hand measured on a VAS scale
- Pain of both hands measured on the Australian/Canadian (AUSCAN) Hand Index Score
- Joint activity of the target hand measured on physician tender joint count
- Patient global assessment measured on a VAS scale
- Quality of life measured on the European Quality of Life 5 Dimensions (EQ-5D)
- Hand strength of the target hand measured on grippit
- Treatment response measured on the Outcome Measures in Rheumatology (OMERACT) and Osteoarthritis Research Society International (OARSI) responder criteria [27] at week 12, in patients with painful hand OA.

5.5.3 Exploratory objectives

To compare the effect of oral colchicine 0.5 mg bid, relative to placebo, from baseline to week 4, in patients with painful hand OA on changes in:

- Finger joint pain of the target hand measured on a VAS scale

To compare the effect of oral colchicine 0.5 mg bid, relative to placebo, from baseline to week 12, in patients with painful hand OA on changes in:

- Stiffness of both hands measured on the AUSCAN Hand Index Score
- Pain, function and stiffness of both hands measured composite on the AUSCAN Hand Index Score
- General physical function measured on the Health Assessment Questionnaire Disability Index (HAQ-DI)
- Physician global assessment measured on a VAS scale
- Joint activity of the target hand measured on physician swollen joint count
- Fatigue measured on a VAS scale
- Anxiety and depression measured on the Hospital Anxiety Depression Scale (HADS)
- Sleep measured on the Pittsburgh Sleep Quality Index (PSQI)
- Illness perception measured on the brief illness perception questionnaire (IPQ)
- Crystal associated serum compounds: serum urate, serum ionized calcium and serum magnesium
- Serum marker for inflammation measured by C-reactive protein
- Inflammation (yes/no) of the target hand as measured on ultrasound (US)

To compare the safety of oral colchicine 0.5 mg bid, relative to placebo, from baseline to week 12, in patients with painful hand OA on changes in:

- Colchicine related adverse events (AE) measured as the number of AE
- Colchicine related serious adverse events (SAE) measured as the number of SAE
- Withdrawals measured on the number of withdrawals in total and the number of withdrawals due to colchicine related AE
- Use of analgesics measured as the use of paracetamol and non-steroid anti-inflammatory drugs (NSAID)

5.5.4 Stratified (subgroup) exploratory objectives

To examine if oral colchicine 0.5 mg bid for 12 weeks treatment response measured on VAS finger joint pain, relative to placebo, differs when stratified by:

  - Presence of active inflammation (yes/no) at baseline as measured on ultrasound

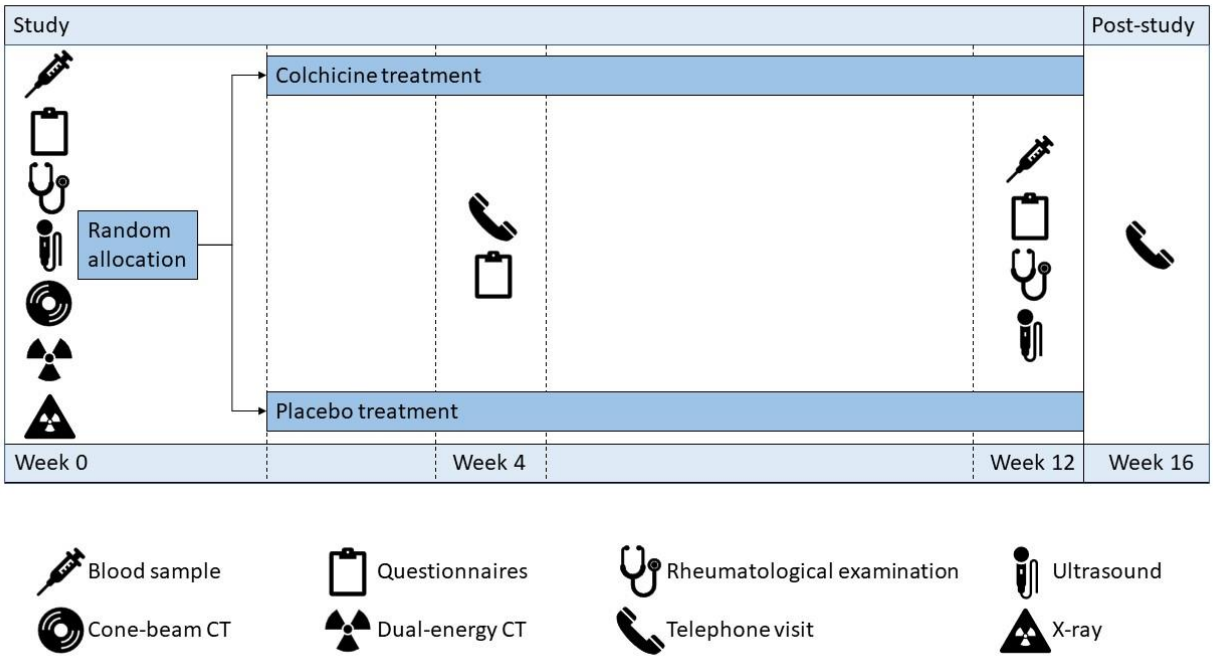
- Presence of joint associated crystal deposits (yes/no) at baseline measured by dual-energy computed tomography (DECT)
- The type of joint associated crystal (Monosodium urate (MSU)/calcium pyrophosphate (CPP)/hydroxyapatite (HA)) at baseline measured by DECT
- The presence of joint associated crystal (yes/no) measured by cone-beam computed tomography (CBCT)
- The type of joint associated crystal (MSU/CPP/HA) measured by CBCT
- Presence of joint associated crystal deposits (yes/no) at baseline measured by ultrasound.
- Body mass index (BMI)
- Degenerative status measured by CBCT
- Degenerative status measured by X-ray

5.6 Trial design

This study is designed as a randomised, placebo-controlled, double-blind trial with two parallel groups and a primary endpoint of changes in hand OA pain after 12 weeks measured on VAS finger joint pain. The study will include 100 participants. Treatment duration was based on previous studies [23-26]. Participants will receive treatment with either oral colchicine 0.5 mg bid or identically appearing placebo bid. The dose is the same as in standard gout treatment and previous studies.

Participants will be seen by a medical doctor (or his/her delegate) at baseline and at week 12. A target hand will be selected, corresponding to the hand with most severe OA. When appropriate and possible, baseline and outcome measures will be target hand specific. Participants will be contacted by telephone by a medical doctor (or his/her delegate) after 4 weeks of treatment to assess AE and treatment adherence. The target hand of all participant will be examined using X-ray and will be scanned by US, DECT and CBCT at baseline. Only the US imaging modality will be repeated at week 12. Participants will be asked to fill out questionnaires at baseline, week 4 and week 12. Laboratory monitoring will be performed at baseline and week 12. A post-study telephone visit at week 16 will assess AE, SAE, study drug withdrawal symptoms (i.e. symptoms that occur upon abrupt discontinuation of study drug) and general hand OA symptoms. Post-study treatment will consist of conventional hand OA treatment, which can be assigned by any medical doctor (e.g. the participants general practitioner), including the study investigator or his/her delegate. The trial design will examine superiority of oral colchicine vs. placebo. Trial design overview is presented in **figure 1**.

5.6.1 Figure 1: Trial design



The figure presents the trial design. CT: Computed tomography. Study's primary endpoint is at 12 weeks.

6 METHOD

The study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline [28, 29]. The study will be conducted in agreement with the described protocol. Any protocol deviation, violation, amendment or alteration will be described in the Statistical Analysis Plan (SAP) and final study report.

6.1 Study setting

The study and radiological examinations will take place at Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark.

6.1.1 Eligibility criteria

Study participants will have a diagnosis of hand OA. Diagnosis will be confirmed by a medical doctor at baseline and participants must fulfil the American College of Rheumatology (ACR) criteria for hand OA [3]:

- Hand pain, aching or stiffness on most days the previous 4 weeks

And at least 3 of the following features:

- Hard tissue enlargement of ≥2 of the 10 selected joints*
- Hard tissue enlargement of ≥2 of the 10 DIP joints
- Fewer than 3 swollen metacarpophalangeal (MCP) joints
- Deformity of at least 1 of 10 selected joints*

*The 10 selected joints are the second and third DIP, the second and third PIP, and the first carpometacarpal joints of both hands.

6.1.2 Inclusion criteria

An individual will be eligible for study participation if he/she meets the following criteria:

1. Age ≥18 years.
2. Hand OA according to the ACR criteria above.
3. Hand OA finger pain: Pain at rest ≥40 mm on VAS (0 to 100 mm range).

6.1.3 Exclusion criteria

A participant will be excluded from the study if he/she meets any of the following criteria listed below. Some exclusion criteria require a blood sample, please see section "Visit 2: Screening visit". A complete list of blood samples throughout the trial is available in **Appendix 1**. Known diseases will be based on diagnosis registered in the participants health journal. If an exclusion diagnose is suspected necessary diagnostics will be performed before inclusion in the study.

Comorbidities

1. Other known medical disease that may affect joints, e.g. RA, gout, PsA
2. Positive anti-cyclic citrullinated peptide (>10 kU/L)
3. Known cutaneous deposition diseases (e.g. amyloidosis or porphyria).
4. Known blood dyscrasias and coagulation disorders
5. Known malignancy (except successfully treated squamous or basal cell skin carcinoma)
6. Elevated alanine transaminase (>45 U/L females, >70 U/L for males)
7. Creatinine clearance ≤60 ml/min
8. Elevated creatine kinase (>210 U/L females, >280 U/L for males)
9. Known allergies towards the interventions
10. Drug or alcohol abuse in the last year
11. Generalised pain syndromes such as fibromyalgia
12. Current reflux
13. Current or recurrent diarrhoeal illnesses

14. Current abdominal pain
15. Known peripheral neuropathies
16. Any other condition or impairment that, in the opinion of the investigator, makes a potential participant unsuitable for participation or which obstruct participation, such as e.g. psychiatric disorders.

Medical history

17. History of hand surgery within 12 months prior enrolment.
18. History of arthroplasty or arthrodesis in the hand

Management strategies

19. Treatment with P-glycoprotein inhibitors and/or cytochrome P450 3A4 (CYP3A4) inhibitors, see section "Colchicine safety in drug-drug interactions" and **table 7**. If potential participants have been treated with these pharmaceuticals previously, treatment must be terminated 5 half-lifes before initiation of study drug.
20. Use of systemic corticosteroids equivalent of ≥ 7.5 mg prednisolone daily within 3 months.
21. Participation in experimental device or experimental drug study 3 months prior to enrolment.
22. Intra-articular treatments or aspirations of any kind of any joint in the hands 3 months before inclusion
23. Intra-articular corticosteroids into any joint 1 months before inclusion
24. Current use of synthetic or non-synthetic opioids
25. Scheduled surgery during study participation
26. Planning to start other treatment for hand OA in the study participation period.

Reproductive system

27. Pregnancy.
28. Planned pregnancy within the study period, 3 months after end of study treatment for female fertile participant and 6 months after end of study treatment for male participant.
29. Insufficient anti-conception therapy for female fertile participants within the study period and 3 months after end of study treatment. Sufficient anti-conception therapy consists of intra-uterine device (coil),hormonal anti-conception (birth control pills, implant, intra-uterine system, dermal patch, vaginal ring, or injections) or sexual abstinence Female participants are considered infertile if they are postmenopausal or if they have undergone surgical sterilisation (bilateral salpingectomy, hysterectomy or bilateral oophorectomy). Postmenopausal state is defined as no menses for 12 months without alternative medical cause before inclusion in the study. Menopause state will be confirmed by measurement of follicle stimulating hormone.

30. Insufficient anti-conception therapy for male participants within the study period and 6 months after end of study treatment. Sufficient anti-conception therapy consists of condom or sexual abstinence. Male participants are considered sterile if they have undergone surgical sterilisation (vasectomy).
31. Breast-feeding

6.1.4 Selection of target hand

A target hand will be selected for outcome assessment. Selection of the target hand will adhere to the following, with advancement to next step if unable to choose target hand based on the given criteria.

1. The hand with most overall pain, assessed by VAS finger joint pain.
2. The hand with most overall reduced function, assessed by AUSCAN function subscale.
3. The hand with most overall stiffness, assessed by AUSCAN stiffness subscale.
4. The hand with most swollen joints, assessed by physician joint count.
5. The hand with most tender joints, assessed by physician joint count.
6. The hand with highest summed radiographic score, assessed by radiographic scoring of conventional X-ray.
7. If unable to select target hand based on the above criteria, a target hand will be randomly assigned.

Target hand will be registered in the Case Report Form (CRF).

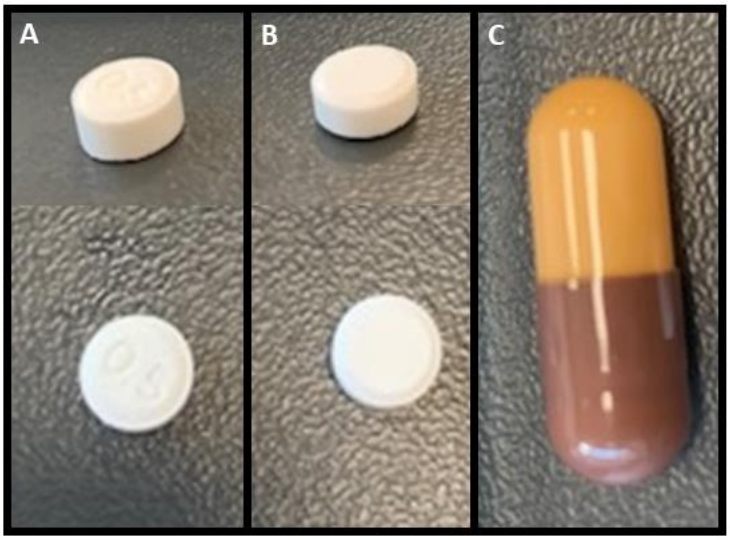
6.2 Study treatments

6.2.1 Intervention and placebo

Participants in the intervention group will receive 0.5 mg tablets of colchicine. Participants in the placebo group will receive placebo tablet. As it was not possible to ensure identical tablets, tablets are packed in identical capsules, ensuring blinding, see **figure 2**. The capsules are made from bovine gelatine and are halal. Capsules are to be administered orally bid: morning and evening, no specific time-slots are advised. The intervention tablets are commercially available Colchicine “Tiofarma”. The Colchicine “Tiofarma” tablet is round, flat, off-white, diameter 6 mm, height 3 mm, and the text “0,5” is printed on one side. The placebo tablet consists of lactose monohydrate 50 mg, potato starch 45 mg, magnesium stearate 0.5 mg, and talc 4.5 mg, it is round, flat, off-white, diameter 6 mm, height approximately 2 mm, and no text printed on it. Medication including packing will be provided by the central pharmacy of the capital region. The etiquette on the study medication container will contain a treatment number which the participant will be assigned upon randomisation, see **figure 3**. Each package will contain 56 tablets, and each participant will

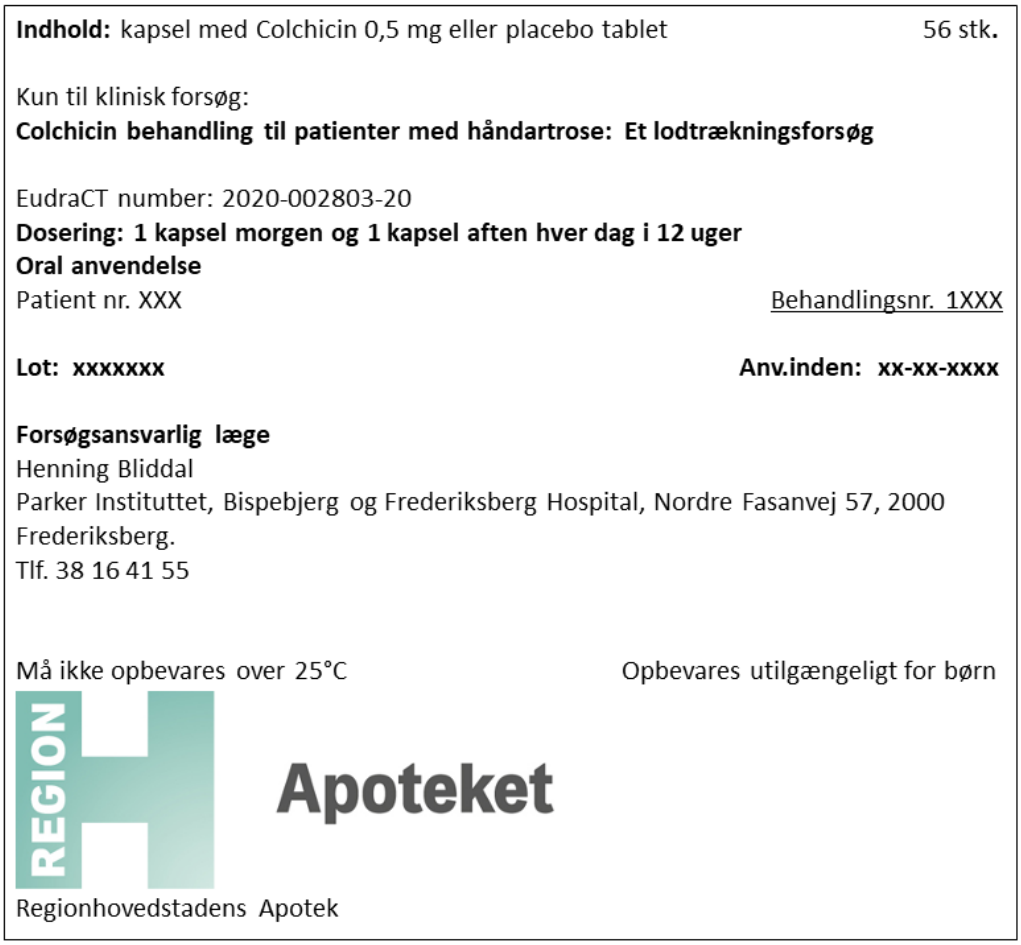
be provided with 3 packages corresponding to 168 tablets in total. Medication will be sent from the Central Pharmacy of the capital region to the Parker Institute by transportation following the standard for shipment of medication from the Central Pharmacy of the capital region to the hospitals. Standard shipment from the Central Pharmacy follows a validated supply chain and is therefore not temperature logged during transportation. Medication will be received by GCP-trained personal at the Parker Institute. Receiver control will contain following assessment: Date [dd.mm.yyyy], is the received medication in agreement with the ordered (yes/no), are the packing intact (yes/no), is there any sign of damage (yes/no), batch no., name of receiving personal, signature of receiving personal. The assessment sheet will be stored for documentation.Medicine will be stored in a locked room destined for medicine. Study medication will be placed separately from other medicine. Storing will adhere to recommended storing condition at the etiquette i.e. at room temperature not exceeding 25°C. The participant will receive treatment for the entire study period upon randomisation, distribution of medicine to participants will be documented. At week 12 participants will be requested to return unused medication, which also will be documented. Returned medication will be stored at the Parker Institute in a locked room, separately from unused medication. Once the last participant has attended his/her week 12 visit the returned study medication will be sent with courier to the central pharmacy of the capital region where it will be destroyed in agreement the pharmacy's standard procedure. The central pharmacy of the capital region provides receipt for both receiving and sending medication, which will be kept for documentation.

6.2.1.1 Figure 2: Study treatment



A: Commercial colchicine tablet [Colchicin "Tiofarma"]. B: Placebo tablet. C: Capsule in which all study medication is packed.

6.2.1.2 Figure 3: Study treatment etiquette



6.2.2 Concomitant therapies

Non-pharmacological interventions are allowed if use is stable for the 3 months prior to enrolment and will remain stable until the week 12 visit. Participants are not allowed to start a new non-pharmacological intervention aimed at the upper extremities and cervical spine until the week 12 visit has been reached.

The following therapies will be allowed as concomitant OA therapies during the trial, if a stable dosage has been used for 3 months prior to enrolment, and a stable dosage will continue until the week 12 visit:

- Chondroitin sulphate (oral administration)
- Glucosamine (oral administration)
- Bisphosphonate (oral administration)
- Capsaicin (topical administration)

Concomitant therapies will be recorded at baseline.

Participants are permitted to remain on their baseline paracetamol (oral administration) and non-steroid anti-inflammatory drugs (NSAID) (oral or topical administration) if a stable dose has been used 14 days prior enrolment. We will request participants to pause paracetamol and NSAID 24 hours before study visits 3, 4 and 6. Participants are not allowed to initiate other medical treatment for OA pain, e.g. opioids, immunomodulating therapy, joint arthrocentesis, or injections. Surgical treatments of the hands are not allowed during study participation.

6.2.3 Treatment adherence

Adherence will be registered in the CRF. Participants will be asked about treatment adherence at week 4 and week 12.

- Participant reported adherence: Study drug used bid, study drug used between bid and qd (quaque di [once daily]), study drug used qd, study drug used less than qd, study drug not used.

Participants will be requested to return excess medication and tablets will be counted at week 12. The number of tablets returned will be registered.

6.3 Outcomes

6.3.1 Primary outcome

Change from baseline in VAS finger joint pain of the target hand at week 12

6.3.2 Secondary outcomes

Secondary outcomes are change from baseline to week 12 in:

- Physical function of both hands assessed by AUSCAN physical function subscale
- VAS thumb base pain of the target hand
- Pain of both hands assessed by AUSCAN hand pain subscale
- Joint activity of the target hand assessed by physician tender joint count in the target hand
- VAS patient global assessment
- Quality of life assessed by the EQ-5D
- Hand strength of the target hand assessed by grippit
- Fulfilment of OMERACT-OARSI responder criteria [27]

6.3.3 Exploratory outcomes

Change from baseline in

- VAS finger joint pain of the target hand at week 4
- Stiffness of both hands assessed by AUSCAN stiffness subscale at week 12

- Hand OA symptoms of both hands assessed by the total AUSCAN score at week 12
- Physical function of both hands assessed by the HAQ-DI at week 12
- VAS physician global assessment at week 12
- Physician swollen joint count of the target hand at week 12
- VAS fatigue at week 12
- Risk of anxiety and depression assessed by HADS at week 12
- Sleep quality assessed by PSQI at week 12
- Illness perception assessed by the brief IPQ at week 12
- Serum urate level at week 12
- Serum ionized calcium level at week 12
- Serum magnesium level at week 12
- C-reactive protein level at week 12

All safety outcomes are considered as exploratory outcomes

- Occurrence of colchicine related AE at week 12
- Occurrence of colchicine related SAEs at week 12
- Withdrawals from the study (regardless of reason) at week 12
- Withdrawals due to colchicine related AEs at week 12
- Use of oral paracetamol and NSAID will be recorded from baseline to week 12 daily by a participant diary, see **appendix 2**.

6.3.4 Stratified (subgroup) exploratory outcomes

- Change from baseline in inflammations as evaluated by US synovitis score at week 12
- MSU, CPP and HA (yes/no) detected by US at baseline
- MSU, CPP and HA (yes/no) detected by DECT at baseline
- MSU, CPP and HA (yes/no) detected by CBCT at baseline
- Height and weight at baseline
- Degenerative status detected by CBCT
- Degenerative status detected by X-ray

6.4 Measures for descriptive statistics

For descriptive statistics we will collect medical and surgical history, comorbidities, concomitant therapy and co-medication (i.e. current treatments with indications other than OA). Information will be collected primarily by interviewing the patient. Electronic health journal and electronic medicinal chart will be assessed for additional information by using the participants unique personal identity number (CPR-number).

We will collect the following information:

- Age [years]
- Sex (male/female)
- Dominant hand (left/right/ambidextrous)
- OA specific
    - Hand OA symptom duration [year]
    - Joint pain at other sites (yes/no), if yes specify location: neck, shoulder, elbow, wrist, upper back, lower back, hip, knee, ankle, feet, other.
    - Known OA at other sites identified from medical records (yes/no), if yes: knee OA, hip OA, other OA (specify in text).
- Medical and surgical history, both current and previous: Diagnosis, debut [dd.mm.yyyy], ended [dd.mm.yyyy], ongoing (yes/no).
- Menopausal state (pre-menopause/menopause/post-menopause/not relevant)
- Medication: Name, form (e.g. tablet or mixture), route of administration, dose, frequency, indication (diagnose), treatment start [dd.mm.yyyy], treatment terminated [dd.mm.yyyy], ongoing (yes/no).

Information will be registered in the CRF. For descriptive statistics hand photos of both hands will be taken. For the hand photo hands will be positioned on a horizontal surface, palms down, relaxed, fingers apart. Hands will be positioned side-by-side.

6.5 Description of efficacy outcome measures

All questionnaires and scoring sheets are available in **appendix 3**. At baseline (visit 3) and 12 week (visit 6) data will be collected via touchscreens in the clinic using Cirkeline, see section “Case Report Forms.” Questionnaires at the telephone visit (week 4) will be collected using RedCap, see section “Visit 4: Week 4 telephone visit”.

6.5.1.1 VAS

VAS will be used for scoring of pain, fatigue, physician global assessment and patient global assessment. The scale spans from 0 to 100, where 0 equals no symptoms and 100 equals worst imaginable symptoms. Recall period is 1 week, thus participants will be asked to score average symptoms within the last week. Pain will be assessed separately for finger joints and thumb base. For finger joint pain participants will be asked to score the average pain in the 2nd to 5th finger joints. For thumb base pain participants will be asked to score the average pain in at the thumb base. Participant will be asked to score both finger joint and thumb base pain in the target hand and the non-target hand. The remainder of the VAS scores are not hand specific but aimed at overall measures. For fatigue participants will be asked to score average fatigue. For patient global assessment, participant will be asked to score average general health. Physician global assessment does not have a recall period, but is based on experience of health in general, physicians will be asked to score general health.

6.5.1.2 AUSCAN

The Australian/Canadian hand OA index AUSCAN, is a validated questionnaire with 3 subscales assessing pain, hand stiffness and hand function during the last 48 hours [30, 31]. The AUSCAN questionnaire is not a target hand specific measures but addresses both hands. Validation is limited by focus on right hand dominant individuals [32]. It will be available as an appendix for application to Health Research Ethics Committee, but not for publication as it is copyrighted, for further information go to www.womac.com. AUSCAN comes in both Likert and a visual analogue scale format, and this study uses the visual analogue scaled format.

6.5.1.3 HAQ-DI

HAQ-DI assesses the difficulty associated with performing everyday activities, recall period is 1 week. Questions are rated on a scale of 0-3. A validated Danish translation is available [33]. HAQ-DI is not a hand specific measure.

6.5.1.4 Quality of life

EQ-5D is a standardised patient-reported instrument for use as a measure of health outcome and quality of life, thus it is not a hand specific measure. EQ-5D is designed for self-completion by respondents and is ideally suited for use in surveys [34]. The EQ-5D consists of 2 pages – the EQ-5D-3L descriptive system (page 1) and the EQ Visual Analogue scale (EQ VAS) (page 2). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Standardized answer options are given (3 Likert boxes) and each question is assigned a score from 1 to 3. It is simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled '*the best health you can imagine*' and '*the worst health you can imagine*'. This information can be used as a quantitative measure of health as judged by the individual respondents. A Danish version of the EQ-5D is available and a Danish valuation set for reference is also available [35].

6.5.1.5 Joint count

Joint assessment includes bilateral examination of the first carpometacarpal (CMC-1) and first interphalangeal (IP) joints as well as second to fifth MCP, PIP and DIP joints. Joints will be assessed by the investigator or his/her delegate for swelling and tenderness according to the European League Against Rheumatism (EULAR) handbook [36] in a dichotomous manner. Both hands will be scored.

6.5.1.6 Grip strength

Changes in the hand function are associated with changes in grip strength [37]. Grip strength measurements provide objective data on the muscular performance of the hand. Grip strength is assessed using the Grippit instrument that records grip force in Newtons. Three measurements are performed on each hand and averaged separately for each hand.

6.5.1.7 OMERACT-OARSI responder criteria

To assess treatment response, the validated OMERACT-OARSI criteria will be applied [27]. The criteria combine target hand specific measures with measurement that apply to both hands.
Participants will be classified as a responder if:

1. the relative change in VAS finger joint pain of the target hand or AUSCAN function of both hands is ≥ 50% and the absolute change is ≥ 20; or
2. at least 2 of the following applies:
    a. the relative change in VAS finger joint pain of the target hand is ≥ 20% and the absolute change is ≥ 10.
    b. the relative change in AUSCAN function of both hands is ≥ 20% and the absolute change ≥ 10.
    c. the relative change in VAS patient global assessment is ≥ 20% and the absolute change ≥ 10.

The absolute change is equal to the change from baseline to week 12. The relative change is the absolute change divided by the baseline score.

6.5.1.8 HADS

HADS consists of two subscales with seven questions concerning anxiety and seven questions concerning depression [38]. The recall period is 1 week. The tool aims to help distinguish physical illness from mental, and can also assess symptom severity [39]. Each item is scored on a 0-3 scale. A cut-off value of 8 on each subscale suggest possible illness [39]. A Danish version of the questionnaire is available and have been validated among cardiac patients [40]. HADS is not a hand specific measure.

6.5.1.9 PSQI

PSQI consist of 11 items, two of which contain multiple sub-questions [41]. In the PSQI scoring the questions are pooled into 7 components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. Each component is scored

on a 0-3 scale providing a total score of 0-21. Higher scores indicate worse sleep quality. The Danish translation is limited by lack of validation. PSQI is not a target hand specific measure.

6.5.1.10 Brief IPQ

The brief IPQ is a scale assessing cognitive and emotional representation of illness. It is reliable and valid when compared to relevant measures. It contains eight numerical rating scale questions that each assess one dimension of illness perception and a memo field based on patients' own beliefs about their condition. Dimensions are scored separately (1–10) [42]. The Danish translation is limited by lack of validation. Brief IPQ is not a hand specific measure.

6.6 Description of imaging measures

6.6.1 X-ray

Existing hand radiographs will be used in case these are not longer than 6 months old at the time of the screening visit. If there are no existing hand radiographs these will be obtained for both hands in a standard anterior-posterior projection at the Department of Radiology X-ray's will be used to describe degenerative status, image scoring will be described in a the SAP or the image analysis plan (IAP).

6.6.2 Ultrasound

Ultrasound (US) examinations will be performed with a Logiq E10 using a 15 MHz linear transducer. US-examinations will be performed by Karen Ellegaard (KE), who has more than 15 years of experience in musculoskeletal US. The US pre-set will be fixed during the study. The grey scale will be optimized for detection of signs of crystal deposits and only the gain and focus can be adjusted in order to optimize the image. The Doppler settings will be optimized for detection of slow flow [43]. Only the target hand will be assessed with US. The joints assessed will be DIP and PIP 2-5, IP-1, MCP 1-5 and CMC-1. The joints will be scanned both from the volar and dorsal aspect with the hand lying relaxed on the examination table. The joints will be scanned in the longitudinal plane and the transverse plane will be used to confirm abnormal findings.

In the US examination at baseline will address crystal deposits (yes/no), inflammation and bony changes. US examination at week 12 will only assess inflammation. Scoring will be described in the SAP or the IAP. US findings will be registered in the CRF. US stills will be used to document findings and re-score images.

6.6.3 Dual energy CT

Target hand will be examined with a dual-source dual-energy CT scanner (Siemens Somatom Force, Siemens Healthineers, Forchheim, Germany). Data acquisition settings and image reconstruction parameters are presented in **table 2**, Sn indicates use of a Tin filter to increase the spectral separation. Dual energy CT image reading will score for crystal deposits (yes/no) and crystal characterisation (MSU/CPP/HA). Software will be calibrated to crystal detection by scanning several crystal calibration phantoms at different known crystal concentrations. Image reading will be described in the SAP or IAP.

Table 2: Dual-energy computed tomography data acquisition and image reconstruction parameters

Scanner	Force
Tube voltage combination	80/sn150 kV
Collimation	64 x 0.6 mm
CTDi	8 mGy
Rotation	0.5
Pitch	0.3
CT image Slice thickness	0.5 mm
CT image voxel size	0.325 x 0.325 mm^2

CTDi: Computed tomography dose index. CT: Computed tomography. Sn: Tin filter.

6.6.4 Cone beam CT

Non-contrast CBCT of the target hand will be performed in all participants on a Carestream OnSight® scanner. The CBCT scanner can perform a 3-dimensional scan of the target joint by rotating three X-ray emitting tubes 270 degrees around the anatomy of interest in approx. 20-25 seconds. CBCT has the advantage of low dose and very high resolution (isotropic voxel size less than 0.3 mm). Software will be calibrated to crystal detection by scanning several crystal calibration phantoms at different known crystal concentrations. CBCT will be used to score degenerative status and crystal depositions (yes/no) and crystal characterization (MSU/CPP/HA). Scoring will be described in the SAP or IAP.

6.7 Description of safety outcome measures

6.7.1 Adverse event

An AE will be defined by any untoward medical occurrence, any unfavourable and unintended sign, symptom, or disease. Worsening of a pre-existing condition will also be considered an AE. AE will be

registered regardless of any causal relationship to the allocated treatment. Any AE with onset or worsening reported by a participant during the study period will be considered a treatment emergent AE.

AE will be rated by severity, see **table 3**.

Table 3: AE severity

Mild	Transient AE easily tolerated by the participant
Moderate	AE leading to participant discomfort and interrupt the participant's usual activities.
Severe	AE leading to considerable interference with the participant's usual activities and may be incapacitating or life-threatening.

Known AEs related to the intervention are described in **table 6**. Laboratory monitoring at visit 6 will be used to assess hepatotoxicity (alanine transaminase [U/L]), bone marrow depression (haemoglobin [mM], thrombocytes [$*10^9$/L], differentiated leucocytes [$*10^9$/L]), rhabdomyolysis (creatine kinase [U/L]), and reduced kidney function (creatine clearance [mL/min], potassium [mM], and sodium [mM]). A complete list of blood samples throughout the trial is available in **Appendix 1.** Blood will be sampled and analysed at the central laboratory at Bispebjerg and Frederiksberg Hospital and destroyed after evaluation according to standard clinical procedures, thus blood will not be stored in a biobank. Approximately 20-25mL of blood will be drawn. Laboratory results will be available to the physician in charge in the patient health file (Sundhedsplatformen) immediately upon analyses and will be reviewed for abnormal findings.

6.7.2 AE and SAE recording

The investigator will assess and record any AE in detail including the date of onset, description, severity, duration and outcome, and any action(s) taken. Relationship of the AE to study treatment will be rated as described in section "Relationship to study treatment".

AE registration will start at baseline and continue post-study to week 16. AE will be recorded at week 4, week 12 and week 16. The participant can report an AE during the study period by contacting the investigator site by telephone.

All AE will be followed until they have abated, or until a stable situation has been reached.

AEs will be registered in the CRF.

6.7.3 Serious adverse events

Any AE meeting the following criteria are considered serious:

- Results in death

- Is life-threatening, i.e. any event in which the patient was at the risk of death at the time of the event. Events that hypothetically might have caused death if it was more severe is not covered by the term.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.

All SAE should be reported to sponsor as quickly as possible, and within 24 hours after the investigator (or his/her delegate) have been made aware of the incidence. Investigator (or his/her delegate) will evaluate whether the SAE is a serious adverse reaction (SAR), see next section. Sponsor will evaluate whether the SAE is a SAR and optionally a suspected unexpected serious adverse reaction (SUSAR), see next section. Once a year in the entire study period the sponsor will provide a list of SAR and general evaluation of safety in the study, that will be sent to Danish Medicines Agency and the Health Research Ethics Committee.

6.7.4 Suspected unexpected serious adverse reaction (SUSAR)

A SAR can be a SUSAR, which means that it is unexpected, as it is not consistent with current information. If the sponsor judge that a SAE is SUSAR he is responsible for reporting it to the Danish Medicines Agency and the local Health Research Ethics Committee. A SUSAR that is life-threatening must be reported to the national competence authority within 7 days (15 days in case of non life-threatening SUSAR).

6.7.5 Relationship to study treatment

All AE, SAE, SAR, SUSARs will be registered whether the event is known or unknown, reference will be the Danish Medicines Agency product resumé for tablet colchicine "Tiofarma" section 4.8, see **appendix 4**.

AE will be rated to study treatment in one of three groups, see **table 4**.

Table 4: Relationship of AE to study treatment

Probably related	An AE has a strong temporal relationship to study treatments or recurs on re-challenge and an alternate aetiology is unlikely or significantly less likely.
Probably not related	An AE has little or no temporal relationship to the study treatments and/or a more likely alternative aetiology exists.
Not related	An AE is due to an underlying or concurrent illness or effect of another exposure and is not related to the study treatments (*e.g.*, has no temporal relationship to study treatments or has a much more likely alternative aetiology).

If the first category is not chosen, an alternative aetiology must be provided by the investigator for the AE. Evaluation of relationship to study treatment must bear known side-effects in mind, see section "Risk associated with the intervention".

6.7.6 Participant withdrawal

Participants are free to withdraw from the trial at any time without reason. Withdrawal will not have any consequences for the participant in future investigations and/or treatments at the site. Withdrawn participants will not be replaced. Decision to withdraw can come from the participant or from the investigator in case of urgent medical reasons or SAE. Participants who withdraw from treatment will be requested to participate in week 4, week 12, week 16, week 20 and week 24 visits and efficacy assessment to minimize missing data.

6.7.7 Participant discontinuation

The investigator may discontinue the participant for any reason. Participants will be discontinued if any of the following occur

- Clinically significant AEs, which rule out continuation of the study treatment, as determined by the investigator.
- Other illness, which rule out continuation of the study treatment, as determined by the investigator.

If at any point in time between randomisation and week 12 the investigator feels that the participant's clinical course is not acceptable within the normally applied paradigms of hand OA, the participant will be requested to withdraw from treatment, and it will be evaluated whether the participant should be taken out of the study completely. The clinician's judgment will be required to decide on a case-by-case basis whether to implement this step or not.

6.7.8 Study discontinuation

The study can be terminated at any time if the incidence of AE in this or other studies indicate a potential health hazard to the participants.

6.8 Participant timeline

Participant timeline and study procedures are evident from **table 5** below.

6.8.1 Table 5: Participant timeline

Study phase	**Pre-screening**	**Screening**	**Baseline**	**Week 4**	**Week 8**	**Primary endpoint, week 12**	**Post-study, week 16**	**Post-study, week 20**	**Post-study, week 24**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Days	**≥ -7**	**-35 to -7**	**-7 to 0**	**21 to 35**	**49-63**	**77-84**	**105-119**	**134-148**	**162-176**
Oral information	x								
Written information	x								
Eligibility assessment		x							
Selection of target hand		x							
Informed consent		x							
Randomisation			x						
Medical history [1]		x	x	x		x	x		
Treatment									
• Colchicine			x -----	----------	----------	-------x			
• Placebo			x -----	----------	----------	-------x			
Patient reported outcomes									
• VAS finger joint pain scoring			x	x		x			
• VAS thumb base pain scoring			x	x		x			
• AUSCAN			x	x		x			
• HAQ-DI			x	x		x			
• EQ-5D			x	x		x			
• VAS fatigue			x	x		x			
• VAS patient global assessment			x	x		x			
• HADS			x			x			

• PSQI			x			x			
• Brief IPQ			x			x			
• Joint count			x			x			
Other examinations									
• Weight			x						
• Height			x						
• Blood pressure			x			x			
• Physical examination		x	x			x			
• Grip strength [2]			x			x			
• VAS physician global assessment			x			x			
Ultrasound			x			x			
X-ray [3]		x							
Dual-Energy CT			x						
Cone-beam CT			x						
Laboratory monitoring [4]		x				x			
Safety recording [5]				x		x	x		
Pregnancy screening [6]									
• Blood sample		x				x			
• Urine test			x	x	x		x	x	x
Assessment of treatment adherence				x		x			

Day 0 refers to the day study treatment is initiated.

1: Includes outcomes specified in section "Outcomes for descriptive statistics". Medical history is obtained at each visit and will be updated to adjust for any new events or treatments. At the post-study week 16 visit medical history will focus on study drug withdrawal symptoms and general hand-OA symptoms.

2: Measured on Grippit [Newtons].

3: Existing hand radiographs will be used in case these are not longer than 6 months old.

*4: A complete list of blood samples throughout the trial is available in **Appendix 1.***

5: AE, SAE, discontinuation of study drug, initiation of rescue treatment.

VAS: Visual analog scale (0-100 mm). AUSCAN: Australian/Canadian Osteoarthritis Hand Index pain, disability, and stiffness subscales. HAQ-DI: Health Assessment Questionnaire Disability Index. EQ-5D: European Quality of Life 5 Dimensions. HADS: Hospital Anxiety Depression Scale. PSQI: Pittsburgh Sleep Quality Index. IPQ: Illness Perception Questionnaire. CT: Computed tomography.

6: Only for female fertile participant. Urine screening will be done at home at visit 4, 5 and 8, and reported to the investigator or his/her delegate using telephone or email.

6.8.2 Assessment visit windows

Visit 1 will be performed at least 1 week prior initiation of treatment, corresponding to day ≥ -7. Visit 2 will be performed 1 to 5 weeks before initiation of treatment, corresponding to day -35 to -7. Visit 1 and visit 2 may take place on the same day. Visit 3 will be performed within a timeframe of 1 week prior initiation of treatment, corresponding to day -7 to 0. Visit 4, 5, 7 and 8 will be performed within +/- 1 week (7 days) for the scheduled visit. Visit 6 will be performed within a timeframe of 1 week before primary endpoint, corresponding to day 77-84.

6.8.3 Recruitment

Participants will be recruited from the Parker Institutes outpatient OA clinic. Patients who are followed at the clinic and known to have hand OA will be invited to participate in the trial. Please see section below on pre-screening in the outpatient clinic.

If further recruiting is required, we will place an advert in the local free-of-charge newspaper MetroXpress. Please see section on telephone pre-screening.

6.8.4 Pre-screening in the outpatient clinic

The number of individuals pre-screened in the OA outpatient clinic will be registered. For individuals not proceeding to screening, the reason for drop-out will be registered.

Potential trial participants will be identified by the investigator in the outpatient osteoarthritis clinical at Bispebjerg Frederiksberg Hospital. The identification of potential participants may occur during regular clinical visits.

When a potential trial participant is identified by an investigator or a treating medical doctor in the clinic, a brief oral information about the trial is provided and the written information material will be handed out.

If the potential participant is identified by a medical doctor that is not an investigator of the current trial, the potential participant will be asked if he/she accepts that his/her information is transferred to an investigator, so the investigator can initiate contact with the potential participant. The information that will be transferred will be restricted to:

- Name
- CPR-number
- Contact information (telephone, email, postal address)

Furthermore, the potential participant is asked if he/she wishes to schedule an appointment for the oral information visit and/or a screening visit. It must be ensured that the potential participant is provided an opportunity to have at least 24 hours of reflection time before the screening visits.

Patient in the out-patient clinic who may be eligible for the study can also be contacted by the investigator or his/her delegate by telephone, see next section.

6.8.5 Telephone pre-screening

Advertisements will encourage potentially eligible individuals to contact the Parker Institute secretariat via telephone for further information and scheduling of an oral information visit and a screening visit upon answers to a few simple questions regarding key eligibility criteria.

The written information material will be sent by e-boks (national secure postal service) to the potential trial participant and the scheduling of a screening visit will ensure that he or she is provided with an opportunity to have at least 24 hours of reflection time (to read the material) before the oral information visit.

6.8.6 Visit 1: Oral information visit (pre-screening)

The oral information visit will be organised as an individual session with the investigator (or his/her delegate) in the out-patients clinic. Potential participants have the right to bring next of kin or another person of the participant's choice with him/her to the oral information visit.
The following will be emphasized:

- Participation in the trial is voluntary.
- Participants have the right to minimum 24 hours reflection time before deciding to sign the informed consent or not.
- Participants can at any time and without giving any reason, withdraw from the trial without affecting the potential participant's right to current or future treatment.

Further, the oral information will include: aim, procedures, potential benefits and risks when participating in the trial, procedures for random findings during the project, procedures for securing the participants privacy and data protection, information on the trial organisation, funding, as well as contact information on the primary investigator and other key investigators.

The investigator will make sure that participants have received and understood the information given to them. The investigator will make sure they are aware that they have the right to minimum 24 hours reflection time before signing the informed consent.

The written information material will be provided.

If participant decline the right to 24 hours reflection, visit 2 can take place immediately after visit 1 on the same day.

6.8.7 Visit 2: Screening visit

Potential participants will be requested to refrain from food and drinks 10 hours before visit 2 in order to ensure fasting blood sample, water intake is accepted within the fasting period. At the screening visit the following procedures will be done in this order. Signed informed consent is necessary to proceed to the following steps.

1. Provision of signed informed consent
2. Assessment of in- and exclusion criteria.
3. Registration of background information, see section “Outcomes for descriptive statistics”
4. Physical examination:
    - Heart and lung auscultation
    - Joint examination, see section “Joint count”.
3. Laboratory test: Blood sample, cf. exclusion criteria and parameters for exploratory outcome. For fertile female participants, this will also include pregnancy screening. A complete list of blood samples throughout the trial is available in **Appendix 1.** Parameters ≤ 1 week old need not be repeated, except anti-cyclic citrullinated peptide, were measures ≤ 1 year old need not be repeated.
4. X-ray. Existing hand radiographs will be used in case these are not more than 6 months old.
5. Selection of target hand.

6.8.8 Visit 3: Baseline visit

Participants will be asked to refrain from paracetamol and NSAID 24 hours prior baseline visit. Participants will also be asked to avoid any oral steroid, intramuscular steroids or steroids injections in other joints within 30 days prior visit 3. At the baseline visit the following procedures will be completed in this order:

1. DECT
2. CBCT
3. Pregnancy screening. Female fertile participants will be screened for pregnancy by testing for urine human chorionic gonadotropin.
4. Patient reported outcomes: See **table 5**.
5. Update medical history to adjust for any new events or treatments.
6. Hand photos

7. Objective examination: See **table 5**.
8. Ultrasound
9. Randomization
10. Scheduling of next visits

6.8.9 Visit 4: Week 4 telephone visit

The week 4 visit will be a telephone visit. Participants will be asked to refrain from medication as described at the baseline visit 3. Following procedures will be completed in this order:

1. Patient reported outcomes: See **table 5**. Scoring will be done by emailing individual internet hyperlink questionnaires. Participants will be directed to a secure webpage for online answering and the electronic system RedCap will be used for capture of data. If participants do not have access to email or online scoring of questionnaires, the questionnaires can be filled out by telephone interview.
2. Pregnancy screening. Female fertile participants will be screened for pregnancy by testing for urine human chorionic gonadotropin. Urine screening will be done at home and reported in the RedCap questionnaire. If participants fail to fill out test results, this will be requested upon telephone interview.
3. Safety recording: See **table 5**. Recording will be done by telephone interview.
4. Assessment of treatment adherence by telephone interview.

6.8.10 Visit 5: Pregnancy home screening

Female fertile participants will be screened for pregnancy by testing for urine human chorionic gonadotropin, urine screening will be done at home and reported to the investigator or his/her delegate using telephone or email. If the participant fails to contact the investigator within the timeframe, the investigator or his/her delegate will contact the participant.

6.8.11 Visit 6: Week 12 visit

Participants will be asked to refrain from medication as described at the baseline visit 3. The primary endpoint at week 12 will assess the following in this order:

1. Laboratory test: Blood sample, cf. safety and exploratory outcomes. For fertile female participants, this will also include pregnancy screening. A complete list of blood samples throughout the trial is available in **Appendix 1.** Parameters ≤ 1 week old need not be repeated.
2. Patient reported outcomes: See **table 5**.
3. Update medical history to adjust for any new events or treatments.

4. Safety recording: See **table 5**.
5. Assessment of treatment adherence
6. Objective examination: See **table 5**.
7. Ultrasound

6.8.12 Visit 7: Post-study week 16

At week 16 a post-study telephone visit take place. The visit is not part of the study. The following will be assessed:

1. Updated medical history with focus on study drug withdrawal symptoms and general hand OA symptoms.
2. Safety recording: See **table 5**.
3. Pregnancy screening. Female fertile participants will be screened for pregnancy by testing for urine human chorionic gonadotropin. Urine screening will be done at home and reported by telephone interview.
4.

6.8.13 Visit 8: Pregnancy home screening

Female fertile participants will be screened for pregnancy by testing for urine human chorionic gonadotropin, urine screening will be done at home and reported to the investigator or his/her delegate using telephone or email. If the participant fails to contact the investigator within the timeframe, the investigator or his/her delegate will contact the participant.

6.8.14 Visit 9: Pregnancy home screening

Identical to visit 8, please see description above.

6.8.15 Delegation of study visits

Investigator can delegate visit 1-9 to any medical doctor affiliated with the Parker Institutes outpatient OA clinic who is familiar with the project and GCP guidelines. Visit 4, 5 and the post-study visits 7-9 can also be delegated to a nurse with research expertise affiliated with the Parker Institutes outpatient OA clinic who is familiar with the project and GCP guidelines.

6.8.16 Study completion

The end-of-study is defined as the date of the last participant's last scheduled visit.

6.8.17 Protocol violations

Protocol violations will be registered in the CRF, but participants may continue the study, i.e. participants with protocol violations and deviations will still be invited for outcome collection and follow-up. Participants with protocol violations occurring after randomization, will not be replaced by new participants.

6.8.18 Participant retention and follow-up (drop-outs)

Participants will schedule study visits over the phone. Visits will be confirmed by emailing appointments via the public secure mail system, e-boks. If participants fail to meet the appointment, they will be contacted by telephone and rescheduled for a new appointment. If the participant is prevented from attending the appointment, telephone consultation will be used to minimize missing data. If a participant fails to attend a study visit three times in a row and cannot be reached by telephone when contacted on three separate days, they will be sent a letter of notification. The letter will state that unless they contact the department within 14 days, they will be terminated from the trial and no further contact attempts will be made. Drop-outs after randomisation will not be replaced by new participants.

6.9 Allocation

A computer-generated randomisation sequence will be produced before patients are enrolled, allocating participants to treatment with oral colchicine 0.5 mg bid or placebo (1:1). Randomisation will be in permuted blocks; block sizes will be unknown to the investigator and his/her delegate. The randomisation will be stratified on age (<75, ≥75), BMI (<30, ≥30) and gender (male/female).The randomisation sequence is generated by a biostatistician (RC), both the biostatistician and the central pharmacy of the capital region stores the randomisation list. Subjects will be assigned individual treatment numbers. Numbers will be listed on the study treatment etiquettes, to ensure that subjects are receiving the study drug or placebo according to the treatment allocation. Treatment number will be registered in the eCRF once participant has been randomised.

The study utilizes a computer-generated allocation concealment process, which ensures that the group to which the patients is allocated is not known before the patient is entered into the study.

6.10 Sample size and power considerations

We set minimal clinical important difference for change in finger joint pain from baseline to week 12 to 15 mm (VAS 0 to 100 scale), as used in previous hand OA trials [44, 45]. Based on previous trials [44, 45] we assume a standard deviation (SD) of 22 for the change in VAS finger joint pain over time. The standardised

Cohens effect size 0.7 (mean difference divided by SD) is equivalent to a medium to large effect when using Cohens' cut-off sizes (0.2: small, 0.5: medium, 0.8 large) [46].

At a power of 90% and 80% and a p-value of 0.05 a sample size will be needed of at least 46 and 35 per group respectively. To take loss-of-follow up into account we aim to include 100 patients. Sample size calculations were performed in R studio (Version 1.2.1335, RStudio Team (2018). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL, http://www.rstudio.com/).

7 METHODS: Assignment of interventions

7.1 Blinding

By providing a placebo identical to the intervention we aim to achieve blinding of participants, care providers and outcome assessors. Data analysists will be blinded throughout analysis. The data manager will provide a blinded data output for analyses.

All participants are assigned a participant number and a treatment number upon randomisation. Both are unique. Study medication is labelled with the treatment number. The pharmacy provides sealed envelopes marked with a treatment number alongside study medication. The sealed envelopes will be stored separately from the medicine in a locked room at the Parker Institute.

7.2 Unblinding

Unblinding can occur immediately and without restrictions if necessary, by contacting the investigator. The investigator can look up the participants treatment number in the eCRF. The investigator can then open a physical envelope labelled with the treatment number and the envelope will contain information of the true content of study medication (colchicine or placebo). Each treatment number has its own envelope and unblinding of a participant does not collaterally unblind other participants.

8 METHODS

8.1 Data collections methods

Data collection methods are specified in the outcomes section.

8.2 Data management

Data management will adhere to the standard requirements for Good Clinical Practice (GCP)-compliant data management in clinical trials. Sponsor will organize GCP monitoring together with the GCP-unit (address on the title page).

8.2.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, participants' diaries or evaluation checklists, health professionals' records or charts, and other records, recorded data from automated instruments, and X-rays.

The investigator(s)/institution(s) will permit study-related monitoring, audits and regulatory inspection(s), providing direct access to source data documents.

DECT and CBCT will be made available for further imaging analyses in collaboration with the Department of Radiology, Bispebjerg and Frederiksberg Hospital, headed by MB. The imaging-analyses team will be blinded to other clinical trial data. The results will be transferred back to the data management team for further processing and subsequent analyses.

8.2.2 Case Report Forms

The study will use electronic case report forms (eCRF) using an on-line web-based clinical trial management application (RedCap) and an in-house custom-built electronic data capture system (Cirkeline).
RedCap allows individual patients to supply data from home and clinical and data can be entered by staff who has been granted permissions.
Cirkeline allows individual patients to supply questionnaire data at clinical visits via touch-screens in the clinic, as well as entering of study related data by the staff.
At the end of the trial, all data will be merged and stored in the RedCap application. Upon completion of data entry, the database will be checked to ensure acceptable accuracy and completeness. System backups and record retention for the study data will be consistent with The Parker Institutes standard procedures. The applications meet all regulatory standards and allow management of all activities related to clinical trials that ensures optimal resource use and safety according to good clinical practice and data protection legislation.

8.2.3 Data management upon completion of data entry

Upon completion of data entry, the databases will be checked to ensure acceptable accuracy and completeness. System backups and record retention for the study data will be consistent with The Parker Institute standard procedures. All clinical data will be made available in an anonymised state to the data management team, led by the investigator. The team will make available a dataset for the statistical analysis. The statistician will be blinded throughout the analyses-phase.

The source data and documents, protocol and amendments, drug accountability forms, correspondence, patient identification list, informed consent forms, and other essential GCP documents will be retained for at least 10 years after the study is completed at the study site. Any data captured electronically will be stored electronically in a separate database according to standard procedures at The Parker Institute.

The data collected in the clinical trial will upon request be made available for further exploitation in the research community upon publication of the main results of the studies. The Parker Institute guarantees to ensure future data storage, protection, and availability.

8.2.4 Data Protection Act and General Data Protection Regulation

The study will be conducted in accordance with the Data Protection Act and follow the General Data Protection Regulation. The study data management and data security procedures are approved by the Regional Knowledge Centre on Data Protection Compliance (Videnscenter for dataanmeldelser i Region Hovedstaden) on behalf of the Danish Data Protection agency (file no.: P-2020-138).

8.3 Statistical methods

Categorical data, e.g. the number of randomised patients will be summarized as total by using counts and percentages. Continuous variables will be presented as means with corresponding variation presented as SD, for skewed data medians and percentiles will be considered instead.

8.3.1 Analysis population

Efficacy and safety analysis will use the intention-to-treat population (ITT) for primary analysis. The ITT population will also be used for calculating percentages in categorical data. The ITT population consist of all randomised patients irrespective of whether the patient received study intervention or the patient's compliance with the study protocol, in the treatment group to which the participant was assigned at randomisation. A patient will be considered randomised as soon as a treatment is assigned by according to the allocation sequence.

Sensitivity analysis will also be done on the as-observed population (AO) and the per protocol population (PP). The AO population consists of participants who has the outcome of interest assessed at any given time point of interest (i.e. no imputation of missing data will be done). The PP population consist of all patient meeting the study criteria, with no protocol violation, who completed the study. As drop-out or protocol violation may occur throughout the trial, the AO and PP population can differ at varying timepoints. The AO and PP population can be identical if all participant in the AO population adhered to protocol.

For analysis concerning inflammation analysis population will only include participants who refrained from anti-inflammatory medication (i.e. NSAID and corticosteroids) prior baseline visit 3 and the week 12 visit, this population will be referred to as per ultrasound protocol. Thus, they will still be included in inflammation analysis if other protocol violations occur.

8.3.2 Missing data

Missing data will not be imputed for descriptive statistics. Missing outcome data will be handled by multiple imputation.

8.3.3 Primary outcome

Assessments of changes from baseline and construction of CIs for continuous measures will be based on a repeated measures analysis of covariance (ANCOVA; including group as the main factor and baseline measure as covariate). Outcome will be presented as point estimate of the differences between the two treatment arms. Corresponding CI of 95% and two-sided p-value will be presented. A p-value < 0.05 is considered significant. A difference in treatment effect between colchicine and placebo can be considered truly present, if CIs does not overlap between two treatment arms. Superiority will be claimed if the computed 95% confidence interval of the estimated group difference in the change from baseline in the VAS pain scale does not include 0 in the ITT population. The primary analysis will be adjusted for baseline VAS pain. In case of relevant between-group differences at baseline in other important covariates, the primary analysis will be adjusted for those. Statistical analysis will be done in R studio (Version 1.2.1335, RStudio Team (2018). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL, http://www.rstudio.com/).

8.3.4 Secondary outcomes

Secondary outcomes will be analysed analogous to the above model for the continuous outcomes. Dichotomous endpoints will be presented as categorical data and compared using a two-sided significance test. The OMERACT-OARSI responder criteria incorporate changes from baseline, so there is no need to adjust for baseline data.

8.3.5 Exploratory outcomes

Exploratory outcomes will be analysed analogous to the above model for the continuous outcomes. Stratified subgroup analysis will also adhere to the ITT population as defined. To avoid type I errors due to multiple comparisons, efficacy will only assess the primary outcome VAS finger joint pain. Analysis will be stratified based on inflammation (yes/no), crystal (yes/no), and type of crystal (MSU/CPP/HA). The latter will only be performed on the population who have crystals.

8.3.6 Statistical analysis plan

The statistical analysis plan will be reviewed again and described in detail before execution of analysis and before unblinding the treatment allocation.

9 RESEARCH ETHICS

Prior to screening, all potential trial participants are informed, both orally and in writing, about the purpose of this trial, its process and potential risks, as well as costs and benefits of participation. In addition, the leaflet ”Rettigheder som forsøgsperson i et sundhedsvidenskabeligt forskningsprojekt [Rights as a participant in a health research project]” will be handed out. All participants are informed of their rights to withdraw from the study at any time without this impacting on any future investigations and/or treatments at any site or by some of the members of the study group. After the information is delivered, read and understood, voluntary informed consent is given by the participant by signing a consent form before trial participation can take place.

9.1 Oral information

Oral information will be provided in agreement with the guideline presented in **appendix 5**. When a potential participant contacts the trial, an appointment for an information interview is made. It will be stressed that the investigator is asking the participant to consider participation in the trial, and that the potential trial participant has the right to bring a companion to the information interview. The written information material will be handed out or sent by e-boks to the potential trial participant so that he or she has at least 24 hours to read the material before the information interview.

The oral information is based on the written information and will be given in a language easily understood without technical or value-laden terms. The information will be given in a considerate way that is tailored to each potential trial participants. The aim is that the conversation takes place without interference. It is the responsibility of the interviewer to ensure that the potential trial participant has understood the information. The information interview is performed by the investigator or his/her delegate.

9.2 Written information

A written information material for the patient is available in **appendix 6.**

9.3 Informed consent

Consent to participation in the trial is given based on the written and oral information.

An informed consent form (ICF), **appendix 7,** has been prepared. The form must be signed and dated by the participants prior to participation in the trial. A copy of the form is provided to the participants. The investigator or his/her delegates can receive the signed consent form. Prior to consent, it must be ensured that a potential participant has been given enough time to consider his or her participation.

The source documentation and CRFs will document for each participant that informed consent was obtained prior to participation in the study. The signed ICF must remain in each participant's study file and must be available for verification by study monitors at any time.

9.4 Risk associated with the intervention

There are well known AEs related to oral colchicine treatment, mainly from the gastrointestinal system (loose bowel movements, abdominal pain, dyspepsia). All studies have reported occurrence of these events but have found them to be mild and without significant difference between tablet colchicine and comparator arm [23-26]. No serious AEs have been reported in recent clinical trials [23-26]. Oral colchicine 0.5 mg bid is therefore considered safe and well-tolerated. The participants are followed closely and will have the ability to contact the study investigator or delegates, if they need help managing AE or if unforeseen AE should occur.

In case of AE participants will be evaluated by a medical doctor and assessed individually. Dose modification may be necessary.

According to the Danish Medicines Agency Product Resumé for tablet colchicine (appendix 4) animal studies have shown reproductive toxicities related to colchicine. In humans, rare cases of reversible oligospermia or azoospermia have been described among men. Among pregnant women current data indicate that malformations and foetal or neonatal toxicities does not occur due to treatment with colchicine. In case of pregnancy within the treatment period or respectively 3 and 6 months after end of treatment for female and male participants, the couple will be referred to genetic counselling.

The intervention is considered justifiable in a health research ethics perspective. Known AEs are summarized in **table 6**.

9.4.1.1 Table 6: Colchicine AEs

Frequency	Side-effect
1-10%	Abdominal pain. Diarrhea. Nausea. Vomiting

Unknown	Gastrointestinal hemorrhage. Hepatotoxicity. Bone marrow depression. Myopathy. Rhabdomyolysis. Neuropathy. Peripheral neuritis. Alopecia. Amenorrhea. Reduced kidney function. Oligospermia.

Colchicine AE. Table reproduced from pro.medicin.dk without editing [47].

9.4.2 Colchicine safety in drug-drug interactions

Treatment with drugs known to inhibit cytochrome P450 3A4 and P-glycoprotein can increase the plasma concentration of colchicine [48], increasing the risk for colchicine related adverse effects. The United States Food and Drug Administration (FDA) recommends that P-glycoprotein inhibitors and strong CYP3A4 inhibitors are not co-administered with oral colchicine in people with impaired kidney or liver function. In case of normal kidney and liver function, concomitant treatment are accepted, but dose reduction of oral colchicine is recommended [49]. Grapefruit is a moderate CYP3A4 inhibitor. The FDA advise for dose-reduction when consuming grapefruit, while Danish recommendation consider it safe [50]. The pharmacokinetics of oral colchicine was not altered when 240 mL of grapefruit juice was consumed twice a day [51], and consumption within this range will be accepted in the current study. The potential interaction between statins and oral colchicine is not clear. Danish recommendations advise caution, allowing concomitant treatment but advise focus on symptoms related to acute myopathy [50]. Previous studies of oral colchicine 0.5 mg bid for knee OA did not exclude participants receiving statins and none of these trials have reported cases of acute myopathy nor a significant increase in symptoms related to myopathy such as myalgia or musculoskeletal pain [23-26]. In a trial assessing the efficacy and safety of continuous treatment with oral colchicine 0.5 mg once daily after myocardial infarction, 98.9% of the 2339 participants treated with oral colchicine where taking statins. The trial had no separate report on AE such as myopathy or myopathy related symptoms, but noteworthy there was no difference in occurrence of any AE or any SAE between intervention and placebo group [52]. We will adhere to national recommendations and allow concomitant treatment with statins, along with careful participant information. All participants will be provided with a study-participant card, to be always carried, which will contain information of the current study and study medication. The study-participant card contains contact information of a study investigator that can be contacted, see **appendix 8**.

The study specific action for people taking treatment that inhibits P-glycoprotein or CYP3A4 are summarized in **table 7**.

9.4.2.1 Table 7: Colchicine drug-drug interaction

Classification	Drugs	Recommendation	Study specific

P-glycoprotein inhibitors	Cyclosporine* Ranolazine Tacrolimus*	Colchicine dose-reduction [48]. Potential interaction [50].	Excluded or treatment terminated 5 half-lifes before initiation of study drug.
Strong CYP3A4 inhibitors	Atazanavir Clarithromycin[1] Darunavir (with ritonavir) Indinavir Itraconazole Ketoconazole[1] Lopinavir (with ritonavir) Nefazodone Nelfinavir Ritonavir[1] Saquinavir Telithromycin Tipranavir (with ritonavir)	Colchicine dose-reduction [48]. Potential interaction, recommend control of creatine kinase [50].	Excluded or treatment terminated 5 half-lifes before initiation of study drug.
Moderate CYP3A4 inhibitors	Amprenavir Aprepitant Diltiazem[1] Erythromycin Fluconazol Fosamprenavir Verapemil[1] Grapefruit juice	Colchicine dose-reduction [48]. Colchicine and verapamil co-treatment should be avoided [50]. Colchicine and grapefruit juice is safe, no dose reduction required [50].	Excluded or treatment terminated 5 half-lifes before initiation of study drug. Grapefruit and grapefruit juice allowed but may not exceed 240 mL of grapefruit juice twice a day or equivalent.
Weak CYP3A4 inhibitors	Azithromycin[1]	No dose-reduction required of colchicine [48]. Caution for musculoskeletal side-effects [50].	Not excluded.

Uncategorized CYP3A4 inhibitors	Disulfiram Gemfibrozil Telapravir	Potential interaction with colchicine when kidney or liver function are impaired [50].	Not excluded.
Lipid-lowering CYP3A4 inhibitors	Simvastin Atorvastatin Pravastatin	Potential interaction with colchicine, focus on symptoms related to acute myopathy [50].	Not excluded. Careful participant information.

The table is modified from Terkeltaub et al., [1]refers to the drugs studied in the trial [48]. Third column summarizes recommendations from the Danish database of interactions, controlled and hosted by the Danish Medicines Agency [50] and from the Terkeltaub study [48] on which the U.S. Food and Drug Administration bases their recommendations. Fourth column summarizes the study specific action for people taking treatment presented in column two.

9.5 Risk associated with study participation

9.5.1 Questionnaires and physical examination

The methods are non-invasive and is not associated with any predictable risks. The procedures are considered justified in a health research ethics perspective.

9.5.2 Blood samples

Blood sampling can be associated with a short painful experience when the skin is penetrated by the sampling needle, and afterwards the participant may have a small subcutaneous haemorrhage and discoloration. This information will be included in the oral and written information.
The knowledge gained by this examination is commensurate with the efforts and difficulties associated with participation. The procedure is considered justifiable in a health research ethics perspective.

9.5.3 Radiation safety

The effective dose for a single X-ray image of a hand is approximately 3 µSv, in this study both hands will be X-rayed, so total effective X-ray radiation dose for participation in this trial will be 6 µSv. The total effective dose for DECT hand scans is 16 µSv. The effective X-ray dose for one scan of the hand with the CBCT (Carestream Onsight 3D Extremity System) equipment used is maximum of 40 µSv (5-40 µSv). The annual background radiation in Denmark is approximately 3000 µSv (≈ 8 µSv / day). When exposed to a dose of 1 Sv (1,000000 µSv), the risk of causing a cancerous disease increases by 5% over the average risk in the

population. The risk increments following exposure in this study is 6 µSv (X-ray both hands) + 16 µSv (DECT one hand) + 40 µSv (CBCT one hand) = 62 µSv can be calculated as 0.000062 Sv x 5% per Sv = 0.0000031% that should be added to the lifetime risk of dying from cancer of 25% in Denmark, that theoretically will change to 25.0000031%.

9.6 Benefit of study participation

Participants in this trial will receive special consultancies with a medical doctor with a special interest and knowledge of hand OA. Examinations in this trial exceeds standard hand OA examination and can give the participant a greater insight into their hand OA illness. Participants will not be financially compensated for participation.

9.7 Insurance

The participants are insured by the Danish Patient Insurance Association. Financing and insurance issues are addressed in the written information material.

9.8 Health Research Ethical approval

This protocol, the informed consent form, written patient information, any anticipated advertising materials, and relevant supporting information will be submitted to the Health Research Ethics Committee system, by the Sponsor, prior to study initiation. The study will be conducted in accordance with Danish law, the Helsinki declaration, and Health Research Ethics Committee requirements.
The Sponsor is responsible for keeping the committee informed of amendments or changes to the protocol, and the progress of the study, as appropriate.

10 PERSPECTIVE

If this study finds a positive effect of tablet colchicine on hand OA symptoms, it could lead the way for a new treatment option in patients with hand OA. This will benefit both the individual patient and society, as hand OA is a costly disease with the ability to invalidate patients. A negative finding will also be important. In clinical practice treating hand OA can be challenging, and when treatment options have been exhausted or are insufficient, clinicians and patients are often tempted to try off-label medication, which may include colchicine. A negative finding will hopefully limit off-label colchicine use and spare patients' unnecessary side-effects and medical expenses. In case of inconclusive results, this study may point the way for future

research as it includes a broad hand OA population, and will explore if subgroups differ in tablet colchicine treatment effects.

11 PATIENT INVOLVEMENT

Two patient research partners (PRPs), Ulla Dal and Kirsten Baldo, with hand OA were involved in the designing process of this study, which follows the EULAR recommendations [53]. The PRP work is voluntary. The PRPs were identified at the Parker Institutes outpatient clinic and invited to participate. Prior to their decision of participation, they received a written and oral task description that clarified their roles and expected contributions. They were invited to comment on the entire protocol and study design, and requested to focus on study relevance, outcomes and treatment duration. Both PRPs approved the design, intervention (dose and duration), outcomes and the remainder of the protocol, including appendixes. They supported pain as the primary objective and requested the secondary objective to be function. This request was met. Both PRPs were concerned about AE and underlined the importance of possible contact with the investigator (or his/her delegate) in case of AE. Both PRPs supported the current design with respect to safety.

The HAQ-DI questionnaire was criticised for not offering response option equal to “med lidt besvær [with little trouble]” but moves from “uden besvær [no trouble]” to “med noget besvær [with some trouble]”. The BIPQ was criticised for not including a self-centred reflection question on prevention “Tror du selv du kan gøre noget for at forebygge din sygdom? [Do you think you can do anything to prevent your disease?]”. Questionnaires were not altered but kept in original validated translations.

The PRPs will prospectively be invited to participate in discussion of results and contribute to the core publication. The PRP may contact the research group whenever needed. The PRP can be offered co-authorship in relation to publication according to the recommendations from the International Committee of Medical Journal Editors (ICMJE) criteria.

12 PUBLICATION

Development of the core publication will be coordinated by the executive committee, whose membership includes the investigator and delegates who provided significant input into study design, implementation, conduct and interpretation. Authors include the members of the executive committee and possibly other key study personnel (to be agreed upon by the executive committee) who has contributed significantly to the implementation and conduct of the study and non-site personnel who contribute substantially to the

design, interpretation or analysis of the study and fulfil the requirements for authorship as recommended by the ICMJE.

Development of secondary and/or substudy publication(s) will be coordinated by the executive committee. A named author approach will be utilized (authors to be agreed upon by executive committee) under the criteria recommended by ICMJE as above.

In accordance with the principles of the Helsinki declaration, all results of the study, positive as well as negative and inconclusive will be published.

Activities that alone (without other contributions) do not qualify a contributor for authorship include but are not limited to: acquisition of funding; general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading. Those whose contributions do not justify authorship may be acknowledged individually or together as a group under a single heading (e.g. "Clinical Investigators" or "Participating Investigators"), and their contributions will be specified (e.g., "served as scientific advisors," "critically reviewed the study proposal," "collected data," "provided and cared for study patients", "participated in writing or technical editing of the manuscript"). Written permission to be acknowledged from all acknowledged individuals will be collected prior to submission of a manuscript for publication.

13 FUNDING

The study is initiated by Professor Henning Bliddal and Ph.D. student Anna Døssing who has received funding from the IMK foundation (DKK 920.000 Ph.D. student salary), the A.P. Møller foundation (DKK 55.000 statistical assistance and database consultant), the Aase and Ejnar Danielsens Foundation (DKK 100.000 microscopy, publication fees, radiograph assistance, statistical assistance and database consultant), and the Danish Medical Association (DKK 100.000 radiograph assistance, statistical assistance and database consultant). The Parker Institute is also supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL). All funding is paid to the Parker Institute which administers the economy. None of the investigators have conflicts of interests related to the funding of this study. This information is disclosed to all participants in the written information material.

All sources of support (including technical and financial support) provided for this study is disclosed in the written information material and will be disclosed in publication of the study results. Funding is an ongoing process. All future financial and/or technical support to the study will be disclosed to all participants (previous, current and potential) in the written information material.

14 CONFLICT OF INTEREST

Anna Døssing: No conflict of interest.

Christoph Felix Müller: Employee of Siemens Healthineers.

Geraldine McCarthy: No conflict of interest.

Philip Conaghan: No conflict of interest.

Roy D. Altman: No conflict of interest.

Lisa Stamp: No conflict of interest.

Lene Terslev: Speakers fee from Novartis, Lilly, BMS, AbbVie, Roche and GE

Margreet Kloppenburg: No conflict of interest.

Ida Haugen: Research grant from Pfizer

Elisabeth Marie Ginnerup-Nielsen: No conflict of interest.

Mikael Boesen: No conflict of interest.

Robin Christensen: No conflict of interest.

Henning Bliddal: No conflict of interest.

Marius Henriksen: No conflict of interest.

Fabio Becce: Has received personal consulting fees from Horizon Therapeutics, unrelated to this work.

15 ROLES AND RESPONSIBILITY

All authors participated in study design. AD drafted the protocol. All authors critically reviewed and approved the protocol.

16 APPENDIXES

16.1 Appendix 1: Laboratory samples

Parameters ≤ 1 week old need not be repeated, except anti-cyclic citrullinated peptide, were measures ≤ 1 year old need not be repeated. Only female fertile participants will be pregnancy screened (human chorionic gonadotropin). Only female postmenopausal participants will have postmenopausal state confirmed by measurement of follicle stimulating hormone.

Blood sample	Unit	Purpose			Sample collected	
		Screening	Outcome	Safety	Visit 2	Visit 6
Urate	mM		X		X	X
Ionized calcium	mM		X		X	X
Magnesium	mM		X		X	X
C-reactive protein	mM		X		X	X
White-cell (leucocytes) differential count	$*10^9$/L	X		X	X	X
Haemoglobin	mM	X		X	X	X
Hematocrit	%	X			X	
Erythrocyte mean corpuscular volume	mM	X			X	
Platelet count (thrombocytes)	$*10^9$/L	X		X	X	X
Creatine kinase	U/L	X		X	X	X
Alanine transaminase	U/L	X		X	X	X
Creatine clearance	mL/min	X		X	X	X
Sodium	mM	X		X	X	X
Potassium	mM	X		X	X	X
Anti-cyclic citrullinated peptide	kU/L	X			X	
Human chorionic gonadotropin	IU/L	X		X	X	X
Follicle stimulating hormone	IU/L	X				

16.2 Appendix 2: Paracetamol and NSAID diary

MEDICINDAGBOG

Under hele forsøget bedes du dagligt angive brug af smertestillende medicin (præparat, dosis og antal)

Navn: _____ Id:_____

Dato	Har ikke taget nogen	Panodil		Pamol		Pinex		Ipren		Ibuprofen		Ibumetin		Andet		Årsag
		Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	

MEDICINDAGBOG

Under hele forsøget bedes du dagligt angive brug af smertestillende medicin (præparat, dosis og antal)

Navn: _____ Id:_____

Dato	Har ikke taget nogen	Panodil		Pamol		Pinex		Ipren		Ibuprofen		Ibumetin		Andet		Årsag
		Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	

MEDICINDAGBOG

Under hele forsøget bedes du dagligt angive brug af smertestillende medicin (præparat, dosis og antal)

Navn: _____ Id:_____

Dato	Har ikke taget nogen	Panodil		Pamol		Pinex		Ipren		Ibuprofen		Ibumetin		Andet		Årsag
		Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	

MEDICINDAGBOG

Under hele forsøget bedes du dagligt angive brug af smertestillende medicin (præparat, dosis og antal)

Navn: _____ Id:_____

	Har ikke	**Panodil**		**Pamol**		**Pinex**		**Ipren**		**Ibuprofen**		**Ibumetin**		**Andet**		**Årsag**
Dato	**taget nogen**	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	

MEDICINDAGBOG

Under hele forsøget bedes du dagligt angive brug af smertestillende medicin (præparat, dosis og antal)

Navn: _____ Id:_____

Dato	**Har ikke taget nogen**	**Panodil**		**Pamol**		**Pinex**		**Ipren**		**Ibuprofen**		**Ibumetin**		**Andet**		**Årsag**
		Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	Dosis (mg)	antal	

16.3 Appendix 3: Efficacy outcomes

Questionnaires and scoring sheets for efficacy outcomes are available as a separate document.

16.4 Appendix 4: Danish Medicines Agency Product Resumé for tablet colchicine "Tiofarma"

The product resume is available in Danish as a separate document. Product resume was updated 13.03.2020.

16.5 Appendix 5: Guideline for oral information

Guideline for oral information is available in Danish as a separate document.

16.6 Appendix 6: Written information

Written information for potential trial participants in Danish is available as a separate document.

16.7 Appendix 7: Informed consent form

An informed consent form in Danish is available as a separate document.

16.8 Appendix 8: Study participant card

A study participant card is available in Danish as a separate document.

17 REFERENCES

1. Zhang, Y., et al., Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. American journal of epidemiology, 2002. 156(11): p. 1021-1027.
2. Van Saase, J., et al., Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Annals of the rheumatic diseases, 1989. 48(4): p. 271-280.
3. Altman, R., et al., The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 1990. 33(11): p. 1601-1610.
4. Dahaghin, S., et al., Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). Annals of the rheumatic diseases, 2005. 64(5): p. 682-687.

5. Hunter, D.J. and S. Bierma-zeinstra, Seminar Osteoarthritis. 2019.
6. Martel-Pelletier, J., et al., Osteoarthritis. Nature Review Disease Primers, 2016. 2: p. 16072-16072.
7. Brandt, K., et al., Yet more evidence that osteoarthritis is not a cartilage disease. 2006, BMJ Publishing Group Ltd.
8. Bijlsma, J.W., F. Berenbaum, and F.P. Lafeber, Osteoarthritis: an update with relevance for clinical practice. The Lancet, 2011. 377(9783): p. 2115-2126.
9. Haugen, I., et al., Synovitis and radiographic progression in non-erosive and erosive hand osteoarthritis: is erosive hand osteoarthritis a separate inflammatory phenotype? Osteoarthritis and cartilage, 2016. 24(4): p. 647-654.
10. Clague, R., et al., Absence of autoimmunity to type II collagen in generalised nodal osteoarthritis. Annals of the rheumatic diseases, 1991. 50(11): p. 769-771.
11. Wang, Q., et al., Identification of a central role for complement in osteoarthritis. Nature medicine, 2011. 17(12): p. 1674.
12. Robinson, W.H., et al., Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nature Reviews Rheumatology, 2016. 12(10): p. 580.
13. Stack, J. and G. McCarthy, Basic calcium phosphate crystals and osteoarthritis pathogenesis: novel pathways and potential targets. Current opinion in rheumatology, 2016. 28(2): p. 122-126.
14. McCarthy, G.M. and A. Dunne, Calcium crystal deposition diseases—beyond gout. Nature Reviews Rheumatology, 2018. 14(10): p. 592-602.
15. McCarthy, G.M. and H.S. Cheung, Point: Hydroxyapatite crystal deposition is intimately involved in the pathogenesis and progression of human osteoarthritis. Current rheumatology reports, 2009. 11(2): p. 141-147.
16. Pritzker, K.P., Counterpoint: hydroxyapatite crystal deposition is not intimately involved in the pathogenesis and progression of human osteoarthritis. Current rheumatology reports, 2009. 11(2): p. 148-153.
17. Gibilisco, P.A., et al., Synovial fluid crystals in osteoarthritis. Arthritis & Rheumatism, 1985. 28(5): p. 511-515.
18. Corr, E.M., et al., Osteoarthritis-associated basic calcium phosphate crystals activate membrane proximal kinases in human innate immune cells. Arthritis research & therapy, 2017. 19(1): p. 23.
19. Cunningham, C.C., et al., Osteoarthritis-associated basic calcium phosphate crystals induce pro-inflammatory cytokines and damage-associated molecules via activation of Syk and PI3 kinase. Clinical immunology, 2012. 144(3): p. 228-236.

20. Kloppenburg, M., et al., 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Annals of the rheumatic diseases, 2019. 78(1): p. 16-24.
21. Hochberg, M.C., et al., American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis care & research, 2012. 64(4): p. 465-474.
22. National, C.G.C.U., Osteoarthritis: care and management in adults. 2014.
23. Leung, Y., et al., Colchicine lack of effectiveness in symptom and inflammation modification in knee osteoarthritis (COLKOA): a randomized controlled trial. Osteoarthritis and cartilage, 2018. 26(5): p. 631-640.
24. Aran, S., S. Malekzadeh, and S. Seifirad, A double-blind randomised controlled trial appraising the symptom-modifying effects of colchicine on osteoarthritis of the knee. Clinical and Experimental Rheumatology-Incl Supplements, 2011. 29(3): p. 513.
25. Das, S.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 & Research, 2002. 47(3): p. 280-284.
26. Das, 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 and cartilage, 2002. 10(4): p. 247-252.
27. Pham, T., et al., OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis and Cartilage, 2004. 12(5): p. 389-399.
28. Chan, A.-W., et al., SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Annals of Internal Medicine, 2013. 158(3): p. 200-207.
29. Chan, A.-W., et al., SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ : British Medical Journal, 2013. 346: p. e7586.
30. Allen, K., et al., Validity and factor structure of the AUSCAN Osteoarthritis Hand Index in a community-based sample. Osteoarthritis and cartilage, 2007. 15(7): p. 830-836.
31. Bellamy, N., et al., Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. Osteoarthritis and Cartilage, 2002. 10(11): p. 855-862.
32. Bellamy, N., et al., Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. Osteoarthritis and Cartilage, 2002. 10(11): p. 863-869.

33. Thorsen, H., et al., Adaptation into Danish of the stanford health assessment questionnaire (HAQ) and the rheumatoid arthritis quality of life scale (RAQoL). Scandinavian journal of rheumatology, 2001. 30(2): p. 103-109.
34. Rabin, R. and F.d. Charro, EQ-SD: a measure of health status from the EuroQol Group. Annals of medicine, 2001. 33(5): p. 337-343.
35. Wittrup-Jensen, K.U., et al., Generation of a Danish TTO value set for EQ-5D health states. Scandinavian Journal of Public Health, 2009. 37(5): p. 459-466.
36. van Riel, P.L., A.M. van Gestel, and D.L. Scott, EULAR Handbook of Clinical Assessments in Rheumatoid Arthritis: On Behalf of the EULAR Standing Committee for International Clinical Studies Including Therapeutic Trials-ESCISIT (Chairman, Piet LCM Van Riel). 2000: Van Zuiden.
37. Allen, K., et al., Relationship of global assessment of change to AUSCAN and pinch and grip strength among individuals with hand osteoarthritis. Osteoarthritis and cartilage, 2006. 14(12): p. 1281-1287.
38. Zigmond, A.S. and R.P. Snaith, The hospital anxiety and depression scale. Acta psychiatrica scandinavica, 1983. 67(6): p. 361-370.
39. Bjelland, I., et al., The validity of the Hospital Anxiety and Depression Scale: an updated literature review. Journal of psychosomatic research, 2002. 52(2): p. 69-77.
40. Christensen, A.V., et al., Psychometric properties of the Danish Hospital Anxiety and Depression Scale in patients with cardiac disease: results from the DenHeart survey. Health and Quality of Life Outcomes, 2020. 18(1): p. 9.
41. Buysse, D.J., et al., The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry res, 1989. 28(2): p. 193-213.
42. Broadbent, E., et al., The brief illness perception questionnaire. Journal of psychosomatic research, 2006. 60(6): p. 631-637.
43. Torp-Pedersen, S.T. and L. Terslev, Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. Annals of the rheumatic diseases, 2008. 67(2): p. 143-149.
44. Kroon, F.P., et al., Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. The Lancet, 2019.
45. Wenham, C.Y., et al., A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. Rheumatology, 2012. 51(12): p. 2286-2294.
46. Cook, J.A., et al., DELTA2 guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. BMJ, 2018. 363: p. k3750.

47. Friis, H., et al. pro.medicin.dk. 21.05.2019 [cited 2020 04.04.]; Available from: http://pro.medicin.dk/Medicin/Praeparater/8954#a060.
48. Terkeltaub, R.A., et al., Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. Arthritis & Rheumatism, 2011. 63(8): p. 2226-2237.
49. FDA. Postmarket Drug Safety Information for Patients and Providers: Colchicine Information. Retrieved 28.03.2020. Content updated 07.10.2015.; Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/colchicine-marketed-colcrys-information.
50. [Lægemiddelstyrelsen], D.M.A. Danish database for pharmacocinetic interactions [Interaktionsdatabasen.dk] established 2001 [cited 2020 03-03]; V3.3:[Available from: http://www.interaktionsdatabasen.dk/SearchResult.aspx?pids=28105830516.
51. Wason, S., J.L. DiGiacinto, and M.W. Davis, Effects of grapefruit and Seville orange juices on the pharmacokinetic properties of colchicine in healthy subjects. Clinical therapeutics, 2012. 34(10): p. 2161-2173.
52. Tardif, J.-C., et al., Efficacy and safety of low-dose colchicine after myocardial infarction. New England Journal of Medicine, 2019. 381(26): p. 2497-2505.
53. de Wit, M.P., et al., European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects. Annals of the rheumatic diseases, 2011. 70(5): p. 722-726.