[](http://www.adelaide.edu.au/)

**A randomised trial of colchicine for osteoarthritis of the hand (COLAH)**

**PROTOCOL BOOK**

**Version 7, 26/06/2018**

**The Queen Elizabeth Hospital and Royal Adelaide Hospital**

Human Research Ethics Committee (TQEH/LMH/MH) Ref # Q20161109

The trial is registered on the ANZCTR: ACTRN12617001524381

Date of registration: 2/11/2017

**Principal investigators:**

Professor Catherine Hill (University of Adelaide)

Dr Carlee Ruediger (University of Adelaide)

**Associate investigators:**

Dr Scott Graf

Dr Fin Cai

Dr Anita Lee

A/Prof Susanna Proudman

A/Prof Helen Keen (University of Western Australia)

**Study coordinators:**

Dr Carlee Ruediger (University of Adelaide)

Dr Courtney Davis (University of Adelaide)

**TABLE OF CONTENTS**

Contents

[BACKGROUND - 3 -](#_Toc517769991)

[Study aims - 3 -](#_Toc517769992)

[Study design - 3 -](#_Toc517769993)

[Intervention - 4 -](#_Toc517769994)

[Adverse events - 4 -](#_Toc517769995)

[Participants - 4 -](#_Toc517769996)

[Inclusion criteria - 4 -](#_Toc517769997)

[Exclusion criteria - 4 -](#_Toc517769998)

[Outcomes - 5 -](#_Toc517769999)

[Investigative product (COLCHICINE) - 5 -](#_Toc517770000)

[Head Office and Manufacturing - 5 -](#_Toc517770001)

[Statistics and sample size calculations - 6 -](#_Toc517770002)

[Statistics - 6 -](#_Toc517770003)

[Power calculations - 6 -](#_Toc517770004)

[Informed consent - 7 -](#_Toc517770005)

[Recruitment - 8 -](#_Toc517770006)

[Telephone screening protocol - 8 -](#_Toc517770007)

[Screening visit protocol - 9 -](#_Toc517770008)

[Prior to the screening visit - 9 -](#_Toc517770009)

[Pre-visit paper work - 9 -](#_Toc517770010)

[Screening visit - 10 -](#_Toc517770011)

[PARTICIPANT – Screening visit - 10 -](#_Toc517770012)

[Visit 1 – Screening - 10 -](#_Toc517770013)

[Visit 2 – Baseline Visit - 10 -](#_Toc517770014)

[Visit 3 – (Week 6) - 11 -](#_Toc517770016)

[Early Termination Visits - 12 -](#_Toc517770017)

[Dispensing protocol - 12 -](#_Toc517770018)

[Participant IDs - 14 -](#_Toc517770019)

[Adverse events protocol - 14 -](#_Toc517770020)

[Recording of adverse events - 14 -](#_Toc517770021)

[Reporting of adverse events - 14 -](#_Toc517770022)

[Reporting of regular adverse events - 14 -](#_Toc517770023)

[Reporting of serious adverse events - 14 -](#_Toc517770024)

[Ultrasound protocol - 16 -](#_Toc517770025)

## BACKGROUND

**BACKGROUND***:* Osteoarthritis (OA) is the most common joint disease and frequently involves the hand. Painful hand OA is associated with a significant disease burden and reduced quality of life. Indeed, the effect of symptomatic hand OA on quality of life is comparable to rheumatoid arthritis, but affects considerably more people (prevalence ~20% versus ~1% in older adults)*[1,2]* With an ageing population, the burden and health-care costs related to hand OA will increase. Patients often rely on NSAIDs or opiates with concomitant adverse effects in this age group to control pain. Hand OA is a heterogeneous condition with approximately 50% of patients having evidence of synovitis *[3, 4]*. This phenotype of hand OA with inflammatory signs i.e. those with evidence of synovitis is associated with increased pain. In addition, hand OA joints with synovitis are 3.5 times more likely to experience rapid joint destruction and radiographic progression than those without synovitis *[3]*. Ultrasound (US) has been shown to reliably detect synovitis in the joints of the hand when performed by an experienced technician *[3]*. Therefore, this is the subgroup of patients with hand OA that are most in need of evidence-based therapies. Previous study to assess treatments for hand OA using of plaquenil, etanercept or adalimumab found not superior to placebo to alleviate pain *[5-7].* There is possible effect if structural modification with etanercept and adalimumab has been shown to be beneficial in erosive and inflamed hand OA *[6, 7]*. The cost however of these medications in 20K/per year, therefore there use is an expensive alternative.

Currently, there are no proven pharmacological treatments for hand OA. The lack of categorization of hand OA according to inflammatory phenotype may have contributed to previous negative outcomes in clinical trials. Cost-effective therapies targeting synovitis may offer a novel approach for reducing disease burden from hand OA.

Colchicine is a low cost drug which has long been used in the anti-inflammatory treatment of acute gout. There has been recent renewed interest in this ancient drug, particularly its effects in cardiovascular diseases such as pericarditis. The primary mechanism of action of colchicine is tubulin disruption leading to subsequent down-regulation of multiple inflammatory pathways and modulation of innate immunity. Preliminary studies in knee OA have indicated that colchicine may have a beneficial effect on pain *[8-10]* and a larger randomized clinical trial of colchicine in knee OA is currently underway *[11]*. No studies of colchicine have been undertaken in hand OA.

## Study aims

Primary hypothesis:

Colchicine decreases pain (assessed by 100mm VAS) by 10mm more than identical placebo over 12 weeks in patients with clinical hand OA.

## Study design

Randomised, placebo-controlled double-blind clinical trial.

This study will be carried out at The Queen Elizabeth Hospital and Royal Adelaide Hospital.

**Study registration and reporting**:

The study is registered with the Australian Clinical Trials Registry (ACTRN12617001524381). The protocol will be reported according to CONSORT guidelines.

## Intervention

Colchicine (0.5mg twice daily) or identical placebo (cellulose). Allocation of participants to one of the two groups will be based on computer generated random numbers. Allocation concealment will be ensured by the use of identical placebo for each group. The use of a central automated allocation procedure with security in place will ensure allocation data cannot be accessed or influenced by any person. All assessors will be blinded to treatment allocation.

## Adverse events

Drug safety will be assessed by recording all important adverse events (AE’s), whether we think they are related to the study medications or not. Blood samples will be taken for assessing change inflammatory markers, full blood count and hepatic and renal function (screening, baseline, week 12). We will report incidence and number of regular AE’s, by treatment group, and categorised by type.

## Participants

### Inclusion criteria

1. Aged between 40 and 80 years old
2. Men and women with significant hand pain within the last 48 hours (defined as a VAS ≥ 40 mm) with a history of hand pain for minimum of 6 months.
3. Symptoms of more than half of days in the last 3 months
4. Meet American College of Rheumatology (ACR) clinical criteria for hand OA:

Hand pain, aching, or stiffness and 3 or 4 of the following features:

* Hard tissue enlargement of 2 or more of 10 selected joints
* Hard tissue enlargement of 2 or more DIP joints
* Fewer than 3 swollen MCP joints
* Deformity of at least 1 of 10 selected joints

\* The 10 selected joints are the second and third distal interphalangeal (DIP), the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands. MCP = metacarpophalangeal.

### Exclusion criteria

1. Concomitant inflammatory rheumatic disease (for example, gout, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, seronegative spondylarthropathy)
2. Oral, IM, IA or IV steroids during the last 1 month
3. DMARD or immunosuppressant therapy (e.g. cyclosporine, methotrexate, azathioprine, leflunomide, biologic agents)
4. Women who are pregnant or lactating
5. Any new hand OA treatment in the previous 1 month, including physiotherapy and provision of new hand splint
6. Allergy to colchicine
7. BMI <20 kg/m2 or weight <50 kg
8. Renal dysfunction (eGRF <50)
9. Haemoglobin ≤ 10 g/dl
10. White cell count <=3.5 × 109/l
11. Neutrophils ≤ 1.5 × 109/l
12. Platelets ≤ 100 × 109/l
13. ALT or AST  >2 times ULN for the laboratory conducting the test
14. Use of any investigational drug(s) and/or devices within 30 days prior to randomisation
15. Presences of any serious medical illness that may preclude 24 week follow up.
16. Inability to provide informed consent
17. Evidence of serious uncontrolled concomitant medical condition, including cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine, GI disease or epilepsy, which in the opinion of the investigator makes them unsuitable for the study

## Outcomes

**Primary Outcome measure:** Change in VAS pain scores at 12 weeks

**Secondary Outcome measures:**

1. Change in AUSCAN scores at 12 weeks.
2. Change in ultrasound measurement of synovitis
3. Adverse effects (measured by patient report, renal, haematological and hepatic function) at all time points and 4 weeks after drug cessation.
4. Change in Michigan Hand Outcomes Questionnaire

# Investigative product (COLCHICINE)

Colchicine is currently TGA approved for “the relief of pain in acute gout”. It is not currently TGA approved for the use in OA.

**Colchicine Manufacture information:**

Pharmaceutical packing professionals will be making and packing the colchicine and the placebo tablets for use in this study. Pharmaceutical Packaging Professionals (PPP) Pty Ltd provides cGMP finished product manufacturing, labelling, packaging, warehousing and distribution services (cold chain and ambient) for companies and research institutes undertaking clinical trials.

PPP manufacturing and warehousing facilities in Melbourne manufacture, warehouse and distribute clinical supplies for use in Australia, New Zealand, Asia and North America. Pharmaceutical Packaging Professionals (PPP) Pty Ltd has both a Licence to Manufacture Therapeutic Goods and Certificate of GMP Compliance of a Manufacturer available on their website. http://www.pharmpackpro.com/

### ****Head Office and Manufacturing****

Pharmaceutical Packaging Professionals Pty Ltd

3/31 Sabre Drive  
Port Melbourne VIC  
Australia 3207

**Phone**: +61 3 9673 1000  
**Fax**: +61 3 9646 3103

**Email:**[info@pharmpackpro.com](mailto:info@pharmpackpro.com)

Please direct all Post to the Melbourne Head Office.

## Statistics and sample size calculations

## Statistics

An intention-to-treat approach will be taken, consistent with CONSORT guidelines. Baseline characteristics between groups will be analysed by unpaired t test. For the primary endpoint, the proportion of participants with change in VAS pain score of 10mm will be compared between treatments using logistic regression model. Safety data will be analysed by means of descriptive statistics. Subgroup analysis will be performed for those participants with synovitis identified by ultrasound (exploratory analysis).

## Power calculations

**Sample Size**

The average VAS in a previous RCT of symptomatic hand OA similar to the proposed study was 67.1mm (standard deviation 13.1mm) *[12]*. With 31 in each group, the study will have 80% power to detect a VAS pain difference of 10mm, including projected 10% drop-out rate.

**DATA SAFETY MONITORING BOARD**

No Data Safety Monitoring Board will be convened during the study.

All Adverse events and Serious Adverse events will; be recorded and documented through Ethics at The Queen Elizabeth Hospital.

**QUESTIONNAIRES**

**VAS and AUSCAN**

VAS

The Visual Analogue Scale (VAS) is measurement intensity “ worst pain” the amount of pain in the participants had within the last 48 hours at screening, baseline week 6, 12 and 16. Week 12 is the primary endpoint. At week 6 and week 16, the VAS questionnaire will be posted to the participant, to be complete at home. A reply paid envelope will be provided to enable return of the questionnaire.

AUSCAN

The AUSCAN™ Index is a self-administered questionnaire that assesses the three dimensions of pain, disability and joint stiffness in hand osteoarthritis using a battery of 15 questions. A 100mm Visual Analog Score will; be used in this measurement and participants will be within the last 48 hours at baseline, week 6, 12 and 16. Week 12 is one of the secondary endpoints. At week 6 and week 16, the AUSCAN will be posted to the participant, to be complete at home. A reply paid envelope will be provided to enable return of the questionnaire.

Michigan Hand Outcomes Questionnaire *[13]*

The Michigan Hand Outcomes Questionnaire (MHOQ) is a validated hand-specific outcomes instrument to assess quality of life and functionality variables amongst patients with hand disorders *[13]*. It assesses 6 domains; overall hand function, activities of daily living, pain, work performance, aesthetics and patient satisfaction. Each question is answered on a 5-point Likert scale. The questionnaire takes approximately 10 minutes to complete. Scores can be used to track progress over time *[13]*. It will therefore be administered at baseline and week 12 appointments to determine whether there are changes in any of the 6 domains due to the intervention. Data will be compared to results collected using the AUSCAN for validation purposes.

## Informed consent

Informed consent will be obtained in writing with a participant information consent form approved by HREC. The signed consent forms will be archived securely. With a copy of the fully signed PICF given to the participant.

**SCHEDULE OF ASSESSMENTS**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Visit** |  | **1** | **2** | **3** | **4** | **5** |
| **Week** | **phone screen** | **screen** | **0** | **6** | **12** | **16** |
| **Informed Consent**  **Clinic measurements** |  | **X** |  |  |  |  |
| **Physical measurements a** |  | **X** | **X** |  | **X** |  |
| **Grip strength (3 trials)** |  |  | **X** |  | **X** |  |
| **Hand x-ray** b |  |  | **X** |  |  |  |
| **Hand ultrasound** |  |  | **X** |  | **X** |  |
| **Full Laboratory exam** c,d |  | **X** | **X** |  | **X** |  |
| **Pill counts** |  |  |  | **X** | **X** |  |
| **Phone Calle** | **X** |  |  | **X** |  | **X** |
| **Questionnaires** |  |  |  |  |  |  |
| **VAS-pain** | **X** | **X** | **X** | **X** | **X** | **X** |
| **AUSCAN questionnaire [12]** |  |  | **X** | **X** | **X** | **X** |
| **MHOQ [13]** |  |  | **X** |  | **X** |  |
| **Safety (AEs)** |  |  |  | **X** | **X** | **X** |

a Full physical examination, blood pressure, tender and swollen joint count (hand only), height, weight, waist circumference

b Only do hand x-ray at baseline if they have not had one within 12 months of baseline appointment c Only do laboratory exam at screening if they have not had one within 3 months of screening appointment. Baseline appointment will include lipids, so should be fasted.

d CRP, FBE, electrolytes, creatinine, urea (ECU), liver function tests (LFTs), creatinine kinase (CK).

eA courtesy call at 2 weeks may be performed to ensure there have been no adverse effects of study drug.

# Recruitment

1. A list of potential trial participants may be provided to the trial staff by the Principal Investigator. This list will contain the names of individuals whom the Principal Investigator (or another referring rheumatologist) has spoken to about the possibility of participating in the trial. These individuals have expressed an interest in participating.
2. Potential trial participants will also be collected via advertisement in local press.
3. Details of potential participants are to be entered into an excel spreadsheet.
4. Once the participant passes the telephone screening (see below) their information is to be entered in the central access database, where they will receive a participant ID.

## Telephone screening protocol

1. Phone the participant (noting details of call – including unsuccessful contacts- on their “Individual Participant Log”.)
2. Explain that you are calling on behalf of the Principal Investigator regarding the possibility of them participating in a clinical trial investigating the effect of colchicine in hand osteoarthritis. To assist with possible questions, familiarise yourself with the details of the trial (number of visits, number of infusions, length of trial, purpose of the different measures etc.) before calling.
3. In order to facilitate screening, please follow this telephone pre-screening list of inclusion and exclusion criteria.

**AGE** - ask for birth date (enter on potential participants.xlsx)🡪 should be 40-80 years

- if <39yrs old 🡪 excluded

**HAND PAIN** - Ask if they have had significant hand pain on most days for at least one month.

Complete VAS (ask for a pain rating (on a scale from 0 [no pain] to 10 [The highest you would rate your hand pain over the last 48 hours.]])

If less than 4 🡪 excluded

**Ask about other medical illnesses, gout and other inflammatory arthritis** - colchicine may be contra–indicated in people with renal, liver and haematological disease.

**Already using colchicine**. 🡪 excluded.

**Ask about other medications –**check unfamiliar medications for contra-indications in the “Colchincine Product Information” sheet and the “Colchicine Consumer Medicine Information” sheet. If found send to Principal Investigator (with screen shot including which section of info sheet the medication was listed under) to determine if medication is safe for consideration with colchicine. [Note this process is to be followed at any time during the screening process or trial if the participant notifies us of new medication]

1. If the participant remains eligible, explain that you will post out to them the Patient information sheet about the study.
2. Make a time for them to attend a Screening Clinic Visit where they can ask questions about the study. Explain that at this screening visit they will be asked questions about and be assessed for a number of things (including their hand OA, and ALL current medications (prescription, over–the–counter, natural therapies, herbal remedies etc) – which they will need to bring to the Screening Visit) to determine whether or not they may be eligible to participate. If they have any previous hand x-rays scans ask them to bring these to the Screening Visit as well.
3. Check that you have their correct postal address details.
4. Using “*Colchicine in hand OA* Contact Letter (template)*.docx*” complete mail merge and print out letter for potential participant and the information sheet.
5. Place individual “Contact Letter” and an “Information Sheet” (“Participant  *Information Sheet (latest version)*.docx”) into envelope and post. Record postal details (date and what was posted) on “Individual Participant Log”.

# Screening visit protocol

For potential participants who have qualified through the phone screening a screening visit will be made with the clinical trial coordinator and PI to further discuss the study and obtain consent

## Prior to the screening visit

1. Post out a reminder letter to the participant before to remind them of the date and time of their SCREENING VISIT. **Remind them to bring in ALL current medications (prescription, over–the–counter, natural therapies, herbal remedies etc) and any previous x-ray results.**

## Pre-visit paper work

1. The following paperwork is needed for the Screening Visit:
   1. “*Participant CRF – Screening visit*”
   2. “Participant  *consent (latest version)*”
   3. Blood request forms (if necessary)

## Screening visit

In attendance with be clinical trial coordinator or Nurse and the Principal Investigator (PI))

1. Greet the participant and thank them for attending the Screening Visit. Introduce them to the PI and ask participant to take a seat.
2. Complete the details on the front of the *“Participant CRF – Screening visit”* Teleform.
3. Use the protocols listed below to complete the clinic measures required for the Screening Visit.

## PARTICIPANT – Screening visit

Please note that the Inclusion Criteria and Exclusion Criteria do not necessarily need to be completed in order listed on Participant CRF. It may be more convenient for the trial staff to complete the questionnaires and the non-PI required elements before the PI makes their assessments

1. Consent:
   1. PI to answer any questions that participant may have and to determine that the consent is informed and that the participant is aware of and able to meet all the study requirements.
   2. Ask participant to complete the *“P*articipant *Consent”.*
   3. Ensure the PI signs *“Consent Form”.*
   4. Make a copy of the form for the participant to take with them. Original to be filed.
   5. GP information: Determine the name and address of the participants GP for follow up contact.

**Full visit details**

**Visit 1 – Screening**

After reading and signing the informed consent document, the following tests and procedures will be performed by the PI or trial coordinator or nurse to determine if the participant qualifies to participate, this visit will take approximately 30 minutes:

* Review participant as per inclusion/exclusion criteria
* Collect personal information, such as name, date of birth, sex
* Review medical and medication history. Obtain their current primary care physician and permission obtains copies of your medical records from their primary care physician.
* Physical exam including an assessment of weight, height and vital signs (blood pressure, heart rate). There is a need for the participant to wear loose clothing as will require lifting of shirt for chest examination
* Assess osteoarthritis symptoms and complete a hand joint count of tender and swollen joints
* A blood sample will be collected (20 mL) for clinical laboratory tests.
* Ask participant to complete a VAS to assess hand pain.

**Visit 2 – Baseline Visit**

Once eligibility has been confirmed from screening a baseline visit will be organised. During this visit the following procedures and tests will be performed.

* Review any changes in health or medications since last visit.
* Final review of inclusion/ exclusion criteria
* A review of medications use.
* X-ray of the study hand, done at TQEH on the same day as the baseline appointment
* Vital signs (blood pressure, heart rate)
* Completion of questionnaires to evaluate participant’s pain and symptoms of osteoarthritis, and how they affect your activities of daily living.
* Participants will then be randomly assigned (from pharmacy) either to COLCHICINE or to a matching placebo.
* A fasting blood sample may be required if non-fasting bloods were taken at screening, or if ≥3months since screening visit.

Prior to the baseline visit the hand ultrasound will be organised through Dr Jones and Partners Medical Imaging. Participant contact details will be emailed to enable Dr Jones and Partners to contact and arrange a baseline and week 12 ultrasound. The baseline ultrasound will occur before or on the same day as the baseline visit, before the participant begins taking the medication/placebo tablets.

**Visit 3 – (Week 6)**

This visit will be done via a phone call; this will take approximately 15 minutes (done by study coordinator)

* Review any changes in health or medications since last visit phone call
* A count of the medication taken / remaining (by participant)
* Assess any adverse events recorded and reviews by PI
* If necessary, remind participant to complete AUSCAN and VAS and return via reply-paid envelope.

**Visit 4 - (Week 12)**

* Physical exam including an assessment of participant weight, height and vital signs (blood pressure, heart rate cardiorespiratory health). Participant needs to wear loose clothing as will require lifting of shirt for chest examination.
* Assessment of hand osteoarthritis symptoms
* Review any changes in health or medications since last visit
* Participant to complete of questionnaires to evaluate participant pain and symptoms of osteoarthritis, and how these affect participant ‘s activities of daily living and complete a hand joint count to tender and swollen joints
* Assess any adverse events recorded and reviews by PI
* Schedule follow-up an ultrasound of study hand.
* A count of the medication taken / remaining

**Visit 5 (Week 16 - Final Study Visit)**

Phone call one month later for participant final visit (done by study coordinator)

* Review any changes in health or medications since previous study visit
* Assess any adverse events recorded and reviews by PI
* If necessary, remind participant to complete AUSCAN and VAS and return via reply-paid envelope.

**Early Termination Visits**

If the participant chooses to discontinue taking study medication for any reason from the study, they will be asked to return to the study doctor for a final visit and final procedures.

# Dispensing protocol

Colchicine will be obtained from TQEH pharmacy, and identical placebo will be obtained from Pharmaceutical Packaging Professionals (PPP) Pty Ltd.

In this parallel-group randomized study, participants who meet study entry criteria will be randomly assigned in a 1:1 ratio to colchicine or to placebo. The Queen Elizabeth Hospital Clinical trial Pharmacy will be providing the randomisation of participants. Participants will be given a two digit randomisation code. (01, 02….45+). The randomization schedule will be prepared before the start of the study. No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. No participant will be randomized into this study more than once.

Study participants will need to be dispensed enough tablets to last the duration of the study (12 weeks). They will need to return any unused product at the week 12 visits for destruction with TQEH clinical trial pharmacy,

**Blinding and Unblinding Treatment Assignment**

All participants, Investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified clinical supply manager and pharmacy that will have access to the randomization code.

The unblinded study personnel will not otherwise participate in study procedures or data analysis before unblinding of the study data to all study related personnel.

Study personnel will strive to safeguard the integrity of the study blind to minimize bias in the conduct of the study.

Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject’s treatment assignment. For emergency unblinding, study personnel will use the Unblinding envelope provided by pharmacy. The Investigator or designee must record the date and reason for study drug discontinuation on the appropriate CRF for that subject. If treatment assignment is unblinded for an individual participant , study personnel will be notified of that participant’s treatment assignment without unblinding those of the remaining participants in the study. Thus, the overall study blind will not be compromised. If a participant’s treatment assignment is unblinded, he or she may or may not be asked to withdraw from the study. The Investigator will make this decision after consultation with the medical monitor.

**Radiological measurements:**

1. Hand xray: These will be performed at TQEH or RAH radiology units. However, if participants have readable plain hand xrays in the past 12 months these will not be required. Hand xrays will be read by two musculoskeletal researchers experienced in xray reading. The radiographs will be scored for individual radiographic features according to the Osteoarthritis Research Society International atlas, including JSN (grade 0–3), osteophytes (grade 0–3) and erosions (absent/present). The readers will be blinded for clinical information and ultrasound findings.
2. Ultrasound: these will be performed by an experienced musculoskeletal ultrasonographer who will be blinded to treatment allocation, according to a protocol defined in Mathiessen (2015) *[3]*. This has been demonstrated to have good inter- and intra-reader reliability and this will be checked in our study using a rheumatologist experienced in musculoskeletal ultrasound. See Ultrasound Protocol.

# Participant IDs

Once the participant passes the telephone screening and is booked in for a screening visit they will receive a **unique participant ID**. This is their participant ID for the entire study which will be pre-populated on all their CRFs. This will be the number which a participant could be re-identified if needed.

**CASE REPORT FORM (CRF) MANAGEMENT**

Data will be recorded on CRFs and stored in a locked clinic room. Data will then be entered on a web-based custom designed system using ENVIDO software. ENVIDO software is password protected and allows efficient extraction of data for statistical analysis.

# Adverse events protocol

## Recording of adverse events

A specific *“Adverse Events”* form has been created to record and manage adverse events.

1. An *“Adverse Events”* form must be completed as soon as the trial staff are made aware that the participant has experienced an Adverse Event (AE). This needs to be done for each AE (unless the two or more AE’s are substantially related).
2. Complete all details of the *“Adverse Events”* form.
3. The Principal Investigator at each site must review the Adverse Events form.

## Reporting of adverse events

Adverse events must be reported to ethic committees, but what needs to be reported may vary between sites depending on the requirements of the local ethics committee.

### Reporting of regular adverse events

Regular adverse events (ie not SAE’s) need to be recorded via the system described above (page - 14 -).

### Reporting of serious adverse events

These need to be reported to the CALHN HREC *within 24 hours of study staff becoming aware of the issue*.

***Early participant withdrawal protocol***

Participants may wish to withdraw from the study prior to the 16 week visit. If the reasons for their withdrawal involve an adverse event, ensure that the *“Adverse Events”* form and appropriate notifications to ethics committees are completed.

Unblinding of individual participants can be arranged by negotiation with the staff member conducting the randomisation and dispensing at each site, after consultation with the site PI.

***Adverse events due to investigational product***

In the event that an adverse event is related to the study medication (i.e. a medication side effect has occurred), participants will be instructed to first reduce their does to half – that is, 0.25 mg/day rather than 0.5 mg/day. The participant will then contact us to inform us whether side effects have improved/changed. If we have not heard from the participant after 7 days of trying half-dose, we will follow-up via phone. It will be made clear to the participant at all times that if they wish to stop the medication they may do so at any time. If side effects are considered too severe by either participant or research staff after trying half-dose, they will be stopped completely. If side effects have abated after trying half-dose, a decision will be made by the principle investigator in consultation with the participant as to how best to proceed.

**GRIP STRENGTH PROTOCOL**

A study coordinator will illustrate the use of the instrument to the participant prior to testing.

* The participant should be in a seated position with their feet firmly on the ground and back straight against the chair (to prevent participant movement)
* The handle of the dynamometer is adjusted if required (for very large hands). Maximal grip strength most commonly occurs in the second or third position and is usually tested at the second position. The base should rest on first metacarpal (heel of palm), while the handle should rest on middle of four fingers.
* The participant t holds the dynamometer in the hand to be tested (starting with the unaffected (non-study) hand for pain free grip force), with the elbow extended and the forearm pronated (since this position was thought to be the most sensitive for testing).
* The participant squeezes until they can just start to feel the pain but no harder for 5 seconds. No other body movement is allowed. No encouragement is given.
* Three trials should be made with a pause of about 10-20 seconds between each trial to avoid the effects of muscle fatigue.
* Maximum grip strength is then recorded for the affected (study) hand. Participant squeezes the dynamometer with maximum isometric effort, which is maintained for 5 seconds. No other body movement is allowed. No encouragement is given.
* Maximum grip strength is then recorded for the unaffected hand. Participant squeezes the dynamometer with maximum isometric effort, which is maintained for 5 seconds. No other body movement is allowed. No encouragement is given.
* Record the result of each trial away from view of the participants. If the difference in scores is within 6.6 lbs. or 3 kgs., the test is complete. If the difference between any two measures is more than 6.6 lbs. or 3 kgs., then repeat the test once more after a rest period. Use the best 3 measurements (ie. the highest three) in your data report.
* When a 4th measurement is taken with the hand grip (when any of the 3 measurements are 3 kg apart) be sure the outlier (THE LOWEST VALUE) is crossed off with your initials so that the 3 HIGHEST measurements are clearly indicated for data entry.

# Ultrasound protocol

Protocol designed by Assoc Prof Helen Keen

|  |  |  |  |
| --- | --- | --- | --- |
|  | SPP | Medial para patella | Lateral para patella |
| Hand position |  |  |  |
| Probe plane | Longitudinal | transverse | transverse |
| Probe position |  |  |  |
| Modes | GS and PD | GS and PD | GS and PD |
| Settings | To be optimised once machine known. | To be optimised once machine known. | To be optimised once machine known. |
| Probe sweep | Move lateral to medial side. | proximal to distal side. | move proximal to distal side. |
| Lesions to score | Synovitis (0-3)  Synovial Power Doppler signal (0-1) | Synovitis (0-3)  Synovial Power Doppler signal (0-1) | Synovitis (0-3)  Synovial Power Doppler signal (0-1) |
| Images to store | Midline longitudinal with the effusion depth measurement in situ | Representative image | Representative image |

Definitions:

SYNOVITIS (0-3) Grade 0 = no synovitis Grade 1= minimal distension of the recess by abnormal internal hypoechoic or anechoic (relative to subdermal fat tissue) material Grade 2= moderate distension or enlargement of the recess by abnormal internal hypoechoic or anechoic (relative to subdermal fat tissue) material with flat or concave superficial limit Grade 3= severe distension or enlargement of the recess by abnormal internal hypoechoic or anechoic (relative to subdermal fat tissue) material with bulging superficial limit

SYNOVIAL POWER DOPPLER SIGNAL (0/1) present/ absent

Score sheet:

|  |  |  |  |
| --- | --- | --- | --- |
| **HAND:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** | **Joint no.** | **GS synovitis (0-3)** | **PD signal (0-1)** |
| **Base of thumb** | 1 |  |  |
| **PIP** | 2 |  |  |
| 3 |  |  |
| 4 |  |  |
| 5 |  |  |
| **DIP** | 2 |  |  |
| 3 |  |  |
| 4 |  |  |
| 5 |  |  |

References

1. Haugen IK, et al. *Ann Rheum Dis*. 2011;70:1581-6.

2. Slatkowsky-Christensen B, et al. *Scand J Rheumatol.* 2009;38:342-8.

3. Mathiessen A, et al. *Ann Rheum Dis*. 2015 [epub ahead of print].

4. Kortekaas MC, et al. *Arthritis Rheumatol*. 2016;68:392-7.

5. Chevalier X, et al*. Ann Rheum Dis*. 2015 74:1697-705.

6. Kloppenburg M, et al, *Ann Rheum Dis*. 2016-eular.3663:90-1.

7. Verbruggen G, et al, *Ann Rheum Dis*. 2012 Jun;71(6):891-8

8. Aran S, et al. *Clin Exp Rheumatol*. 2011;29:513-8.

9. Das SK et al. *Arthritis Rheum*. 2002 Jun 15;47(3):280-4.

10. Das SK et al. *Osteoarthritis Cartilage* 2002;10:247-52.

11. Leung YY et al. *Trials* 2015;16:200.

12. Bellamy N, et al. *Osteoarthritis Cartilage*. 2002;10:855-62.

13. Chung KC, et al. *J of Hand Surgery*. 1998; 23A:575-587.