

PARTICIPANT INFORMATION SHEET

A randomised trial of *Curcuma Longa* for treating symptoms and effusion-synovitis of knee osteoarthritis (CurKOA trial)

1. Invitation

You are invited to participate in a research study investigating an experimental treatment for knee pain because you have osteoarthritis of the knee. The study is being conducted at the Menzies Institute for Medical Research (Hobart) by Dr Benny Eathakkattu Antony, Prof Graeme Jones, Prof Changhai Ding, Prof Tania Winzenberg, Dr. Dawn Aitken and Dr. Laura Laslett.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

2. What is the purpose of this study?

This study will examine a new treatment for knee pain. The treatment is the natural extract of *Curcuma Longa* (turmeric). This study will determine whether treating people with *Curcuma Longa* will improve knee pain, reduce swelling and slow down the progression of knee osteoarthritis.

3. Why have I been invited to participate?

We will be studying up to 70 people. People can be included in the study if they:

- ✓ Are ≥ 40 years;
- ✓ Have significant knee pain on most days for more than 6 months;
- ✓ Have a swelling (effusion-synovitis) present on an ultrasound (US imaging) scan; and
- ✓ Have clinically defined knee osteoarthritis

You will not be eligible to participate if you are pregnant, planning to be pregnant during the study period or breastfeeding.

4. What knee abnormality do I need to be eligible to participate?

We are interested in people with increased fluid inside their knee joint (effusion), or swelling of the lining of the joint (synovitis) [Figure 1]. This is known to be related to inflammation and to be a significant contributor to knee pain. This is commonly seen in people with knee pain and will be evaluated as an outcome using MRI scans.

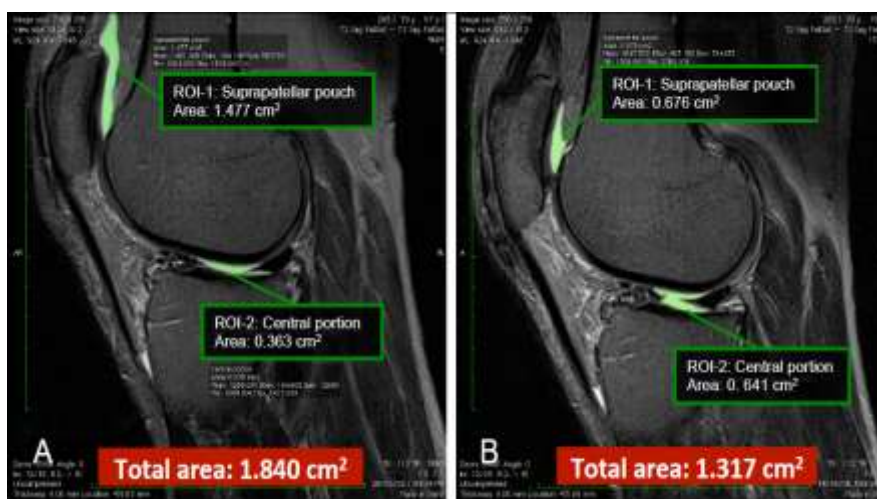


Figure 1: Example of changes in effusion-synovitis area (cm²) in MRI. Effusion-synovitis size decreased from baseline to follow-up 2.6 years later (A-B). Effusion-synovitis are present in both the area above patella and central region. Overall, effusion size is smaller at follow-

Baseline

2.6 years later

5. What type of drug is *Curcuma Longa*?

Curcuma Longa (turmeric plant) grows mainly in India, and is traditionally used in Chinese and Indian Ayurvedic medicine to treat arthritis and pain. Turmeric contains naturally occurring polyphenols termed curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin) and non-curcuminoid fractions such as polysaccharides. Curcuminoid and non-curcuminoid fraction of *curcuma longa* is effective for reducing knee pain and inflammation. Therefore, the whole extract of *curcuma longa* should have the ideal therapeutic effect. *Curcuma longa* extracts are being marketed in several countries including Australia in different forms such as capsules, tablets, ointments, energy drinks, soaps, and cosmetics.

Curcuma Longa has been gaining popularity in osteoarthritis treatment despite the lack of evidence to modify disease progression. Studies suggest that *Curcuma Longa* has multiple effects such as anti-inflammatory, hypoglycemic, antioxidant, lipid lowering, wound healing, and antimicrobial activities. These

properties make *Curcuma Longa* an ideal treatment for osteoarthritis patients with other co-existing diseases. Laboratory studies suggest that curcumin show a protective effect on joints through anti-inflammatory, anti-oxidative stress, and anti-catabolic mechanisms. Animal studies suggest that oral administration of curcumin suppressed pro-inflammatory mediators and significantly reduced osteoarthritis disease progression including synovitis reduction.

6. What if I don't want to take part in this study, or if I want to withdraw later?

Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

New information about the treatment being studied may become available during the course of the study. Should any significant new findings that may affect your willingness to continue in the study, you will be kept informed.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. The participants can withdraw their study data at any time during the study and they are not obliged to explain the reason.

7. What does this study involve?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form.

Screening visit

All participants will be asked about their previous medical history and a medical examination of your knees will be performed. You may be asked to have a knee x-ray. All participants will be asked to complete a survey relating to knee pain. This survey has questions on symptoms, the degree of knee stiffness and pain and the effect the condition has on a patient's daily activities and quality of life. Participants will also be asked a separate

question to assess the amount of knee pain they have. Those with a pain score in the moderate range will undergo an ultrasound scan of the knee.

If you have a normal minimal or no fluid levels /synovitis of the knee on your ultrasound scan you will not be asked to continue in the study. If you have elevated fluid levels or synovitis in your knee you will be eligible to participate.

Continuing in the study

This study will go for 3 months. We will need to see you at the start of the study (month 0), and at month 3. Measures will be done at the Menzies Institute for Medical Research, Hobart.

The following procedures/measures will be performed:

- A blood and urine sample will be collected at baseline and month 3. These will be stored for analysis of inflammatory and cartilage biomarkers and may be transported to overseas labs for analyses. ;
- An MRI scan will occur at baseline and month 3
- Participants will receive either *Curcuma Longa* capsules or a matching placebo treatment (a capsule filled with an inactive substance that contains no medicine) at baseline;
- Questionnaires about knee pain, knee function, your views on overall improvement in pain, and pain at other sites will be asked in clinic (baseline and month 3) or posted to you monthly (months 1 and 2);
- Clinic visits will occur at baseline and month 3. At this time, we will measure height and weight, and ask about pain elsewhere. We will also send you questionnaires about your use of medications, any side effects, wellbeing, joint replacement and quality of life;
- Physical function tests will occur at baseline and month 3. These include a 30s chair stand, 40m fast-paced walk and stair climb tests.

Randomised trial

Sometimes doctors don't know the best way of treating patients with a particular condition so comparisons need to be made between different treatments. To do this, study participants are put into groups and given

different treatments, and the results are compared to see whether one treatment is better. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the study investigators nor the study participant can decide which treatment the participant receives.

All study participants will receive bottles of identical capsules to take daily. These capsules will contain either *Curcuma Longa* or placebo. As this is a 'blind trial' all study patients will be unaware whether the capsules they receive will contain active (*Curcuma Longa*) or inactive ingredients (placebo) until we have completed all data collection for the entire study.

8. How is this study being paid for?

The study is partially funded by Menzies Institute for Medical Research, UTAS and Natural Remedies Ltd. *Curcuma longa* extract (provisionally patented by the company) and placebo capsules are provided by the company. The company may use the published data or results of the study for their advertisement purpose and may commercially benefit from this study. However, the company will not have any access to the individual data and any data (generated with the help of the company) communicated will be in a de identified manner only. The company will not have any role in the design, conduct, analyses and publication of the study.

All of the money being paid to run the trial will be deposited into an account managed by the University of Tasmania. No money is paid directly to individual researchers.

9. Are there risks to me in taking part in this study?

Curcuma Longa is a very safe medication, with no known side effects attributable to the drug. *Curcuma Longa* treatments in clinical trials have reported mild fever and throat infection, gastrointestinal symptoms, tachycardia, hypertension, and redness of tongue. However, the control groups such as placebo and pain medicine (ibuprofen and diclofenac) also showed similar adverse effects. Thus, turmeric preparations were considered

to be safe at doses not exceeding 1200 mg/day for up to 4 months. The current study will use two 500mg capsules (1000 mg/day) daily for 12 weeks.

If you have previous reported allergies to turmeric or curcumin containing tablets, you will not be able to take part in this study.

There is no radiation exposure associated with ultrasound. A small amount of radiation exposure is associated with a knee x-ray. MRI scans may be claustrophobic, but are considered safe. There may be the possibility of injury during completion of physical function tests. Having blood taken causes minimal risk, but there may be a chance of discomfort, feeling faint and bruising. The effect of the study medication on an unborn or breast fed baby is unknown and women who are pregnant or breastfeeding will not be able to take part in this study. If you are a woman of childbearing age and there is any possibility that you are pregnant, the researchers will need to perform a urine pregnancy test before you start in the study. We are asking questions about health and wellbeing in this study. Some people find that focusing on aspects of ill health raises concerns for them. If you have any concerns about health issues please contact your GP.

In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study.

10. What happens if I suffer injury or complications as a result of the study?

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those

compensation monies. You do not give up any legal rights to compensation by participating in this study.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

11. Will I benefit from the study?

This study aims to further medical knowledge and may improve future treatment of knee osteoarthritis. If the treatment is effective, then patients in the active treatment group may experience reduced knee pain and swelling. However, it is possible you may not directly benefit regardless of your treatment group.

12. Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything, and we do not pay study participants to take part in the study.

13. How will my confidentiality be protected?

Of the people treating you, only study staff will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the study researchers will have access to your details and results that will be held securely on confidential password protected databases and access will be limited to the researchers and support staff only. Biological specimens taken from patients will be destroyed after biochemical tests and any biological samples collected will be sent in a de-identified manner.

14. What happens with the results?

If you give us your permission by signing the consent document, we plan to discuss/publish the results with the ethics committee for monitoring purposes, peer-reviewed journals, presentations at conferences and/or other professional forums.

In any publication, information will be provided in such a way that you cannot be identified. Data sharing may be considered in rare circumstances, but any data shared will be in a de-identified manner. Results of the study will be provided to you, if you wish.

15. What happens to my treatment when the study is finished?

Curcuma Longa is available commercially. If you wish to continue using *Curcuma Longa*, you will need to purchase it.

16. What should I do if I want to discuss this study further before I decide?

When you have read this information, the study coordinator will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact the Clinical Trial Coordinator Gudrun Wells on 6226 4369 or email Gudrun.Wells@utas.edu.au or the Principal Investigator Dr. Benny Antony on 6226 4255 or email Benny.EathakkattuAntony@utas.edu.au.

17. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to **quote Reference # H0016713**.

Thank you for taking the time to consider this study.

This information sheet is for you to keep.