



## Participant Information Sheet/Consent Form

*Monash University*

<b>Title</b>	Does low dose amitriptyline reduce pain in knee osteoarthritis? A double blind, randomised, pragmatic, placebo controlled clinical trial of amitriptyline in addition to usual care
<b>Short Title</b>	Does low dose amitriptyline reduce pain in knee osteoarthritis?
<b>Project Sponsor</b>	Monash University
<b>Coordinating Principal Investigator/ Principal Investigators Associate Investigator(s)</b>	Assoc Prof Anita Wluka, Prof Flavia Cicuttini  Dr Donna Urquhart, Dr Andrew Teichtahl, Prof Andrew Forbes, Dr Carolyn Arnold, Dr Yuanyuan Wang, Dr Elspeth Hutton, Dr Sharmayne Brady, Ms Clare Bellhouse, Dr Louisa Chou, Ms Molly Bond
<b>Location</b>	Melbourne

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### Part 1 What does my participation involve?

#### 1 Introduction

You are invited to take part in this research project. This is because you have had symptomatic knee osteoarthritis for 3 months or longer. The research project is testing a new treatment for symptomatic knee osteoarthritis. The new treatment is called amitriptyline (tradename Endep).

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described

You will be given a copy of this Participant Information and Consent Form to keep. The Participant Information and Consent Form is 12 pages long in total. Please make sure that you have all the pages.

## **2 What is the purpose of this research?**

Knee osteoarthritis is a common disabling condition resulting in pain and impaired function. The main symptom of knee osteoarthritis is pain. There are drug and non-drug treatments for knee pain in osteoarthritis, however, most of these do not control pain well. This may be because whilst some pain comes from the changes at the knee, there is evidence that shows pain can also be related to changes that occur in the nervous system after pain has been present for some time. These changes are called pain sensitisation.

The changes of pain sensitisation occur in other conditions, such as after shingles. In these settings, a medication called amitriptyline can be used to control the pain related to pain sensitisation.

There is evidence that pain sensitisation plays a role in pain in knee osteoarthritis pain.

The aim of this clinical trial is to determine whether low-dose amitriptyline is more effective than placebo (an inactive substance) in the management of pain in people with knee pain related to knee osteoarthritis. Amitriptyline is approved in Australia to treat depression. However, it is not approved to treat knee pain. Therefore, it is an experimental treatment for knee pain. This means that it must be tested to see if it is an effective treatment for this condition.

If this study finds amitriptyline to be effective, it will potentially enable this treatment to be considered by more individuals. It will also tell us more about why people have pain in knee osteoarthritis which may help us to find even more effective treatments for this condition.

Information obtained in this study will also be used to examine factors that affect how pain osteoarthritis changes over time.

160 participants will participate in this project and attend one site. They will be randomly allocated into two groups; with one group receiving the treatment of amitriptyline and the other group receiving a placebo.

There are a number of hospitals and medical, specialist and allied health clinics involved with this trial in Melbourne.

This research is being conducted by the Musculoskeletal Unit at Monash University in collaboration with researchers from the Alfred Hospital and Caulfield Hospital Pain Management Service.

The research has been initiated by investigators, Assoc Prof Anita Wluka and Prof Flavia Cicuttini.

The research is being funded by the National Health and Medical Research Council.

No member of the research team will obtain any financial benefit from their involvement in this project (other than their ordinary wages).

### **3 What does participation in this research involve?**

Participation in this trial will initially involve a screening process.

A research nurse will phone you to determine whether you meet the eligibility criteria for the trial.

During these screening procedures, if any of the following applies to you, you will not be asked to continue in the study.

- Very mild knee pain
- If you have another form of arthritis.
- Previous or planned knee joint replacement in the next 4 months
- Knee arthroscopy or knee injection in the last 3 or next 4 months
- Current use of strong pain medications including opiates
- if you have been involved in another clinical trial, and taken another study medication within the last 30 days
- Any reason why you should not be taking amitriptyline, such as trouble passing urine, cancer, taking medications that may not be safe to take if you are taking amitriptyline
- Clinically significant renal or liver disease
- Pregnancy, breast feeding, or trying to become pregnant

If you are eligible to participate, then a session will be organised for you to meet with study personnel, to ask questions about the study. At this stage you will be asked whether you agree to take part in the study. Only when you have agreed, that is when you have provided consent to participate in the study, will any examination or investigations be performed.

After you have provided consent, you will undergo a clinical assessment by a doctor and complete a questionnaire at the Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, Commercial Road. Measures relating to your experience of pain will be made.

If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project.

Your muscle strength will be measured. Your pressure pain threshold will be measured over your knee, elbow, and over the fleshy muscle at the base of the thumb. This session will last for about 1 hour.

Following the assessment you will be asked to undergo an xray at an MIA Radiology site (one close to your home).

Once we receive a copy of your xray, we can determine whether you are eligible to be in the study or not. We will contact you to tell you whether you are eligible or not.

a) If you do not have xray findings of osteoarthritis, you are not eligible for this study. We may use your information to help understand knee pain better and may contact you in the future for future studies. If you do not want to be contacted please let study personnel know.

b) If you do have xray findings of osteoarthritis, you will be randomised to the treatment or the control group. This means you will not have a choice regarding which group you are in. The treatment group will receive low-dose amitriptyline (25 mg) and the control group a placebo called benztrapine. Both medications are well tolerated. Benztrapine has been chosen as the placebo, as both benztrapine and amitriptyline can make a person feel drowsy and have a dry mouth. This means that neither you, nor the investigators will know whether you are receiving amitriptyline or the placebo until the study is completed. However, in certain circumstances the investigator may find out which treatment you are receiving.

The trial is for 12 weeks (3 months). If you are eligible for the study, we will post you your study medication, either amitriptyline or the placebo. You will be required to take this during the study period. Once you receive the study medication, for the first 2 weeks of the study you will be required to take one tablet every second nights. We will contact you after 2 weeks to make sure that you are not having any problems. If all is going well, you will be asked to take one tablet each night for the rest of the study, 10 weeks.

During the trial you will be in contact with study personnel by phone on 3 occasions to monitor your progress and any side effects of the treatment. This will take place when you receive your study medication (you will be asked to contact study personnel to let them know that you have started to take medication) and also at 2 and 6 weeks, when you will be called. These sessions will take 2-10 minutes and will involve completing questionnaires over the phone with one of the research personnel.

At the end of the study, at 12 weeks, you will be asked to return to the Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, so that your pain and type of pain can be assessed, and to return your pill containers. This visit will take approximately 45 minutes.

The measures that will be taken during the study at the beginning and the end include

- Questionnaires that will collect information about yourself (date of birth, gender, education, occupation), then ask about joint symptoms, smoking, history of knee injury and surgery, health status, other medical conditions and medications. Also about other factors that may impact on your experience of pain such as sleep, your general health status.
- Measurement of height, weight, blood pressure and muscle strength at the beginning and end of the study
- Knee X-ray at screening.
- Measurement of pain using questionnaires and also pain testing. This will be determined at three sites: over the knee, over the elbow, and over the fleshy muscle at the base of the thumb. This test involves applying gradually increasing pressure using a rubber pad 1cm2 in diameter over the test site. You will be asked to tell the examiner as soon as the pressure becomes painful, at which point the pressure will immediately be released. The testing will be done at the initial and final study visits. This test is used to determine whether the level at which mechanical pressure is painful varies in patients with OA, and whether this increased sensitivity improves with treatment with amitriptyline. This is important in order to understand the mechanisms of pain in osteoarthritis and how we may best treat them.
- Measurement of physical activity using a brief International Physical Activity Questionnaire (IPAQ)
- Assessment of adverse events will occur at all contacts.
- Measurements of pill count will occur at the final visit.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

You will not be paid for your participation in this research, but you will be reimbursed for any of the following costs that you incur as a result of participating in this research project (\$10 for parking or transport costs per visit).

#### **4 What do I have to do?**

For the first 2 weeks, you will be required to swallow one whole tablet every SECOND evening with a drink of water, with or without food. If you are not having any problems at 2 weeks, we will ask you to start swallowing one whole tablet every evening for the next 10 weeks. You will need to commit to taking the investigational drug regularly. You will need to attend all the study visits

(at the beginning of the study, and after 12 weeks of taking study medication) and answer the study phone calls (2 and 6 weeks after starting study medication).

Whilst involved in this study, you can take your regular medications. We will screen for medications unsuitable for this study. You will need to record all medications and complete a questionnaire at study visits. Your involvement does not affect your ability to donate blood.

You should tell your doctor and study personnel if you are taking any other medications, including any that you buy without a prescription from a pharmacy, supermarket or health food shop. Some medications may be affected by amitriptyline or may affect how well amitriptyline works. It is also important not to start taking any other medications during the study without talking to your doctor and research staff.

## **5 Other relevant information about the research project**

A total of 160 participants with symptomatic knee osteoarthritis, aged 40-70 years will be recruited from the community. The project will have 2 arms, with one arm receiving amitriptyline and the other arm receiving a placebo (benztropine). All participants will be followed up over 12 weeks to examine whether amitriptyline improves pain control in knee osteoarthritis.

## **6 Do I have to take part in this research project?**

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Monash University or the Alfred Hospital (if relevant).

## **7 What are the alternatives to participation?**

You do not have to take part in this research project to receive treatment. You can see your doctor or health care professional to discuss different treatment options for your knee osteoarthritis, such as weight loss, physiotherapy and medications for pain relief. Please feel free to discuss these with your healthcare worker before deciding whether or not to take part in this research project. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project.

## **8 What are the possible benefits of taking part?**

We cannot guarantee or promise that you will receive any benefits from this research. However, some participants may experience possible benefits, such as a reduction in knee cartilage loss and/or an improvement in their knee symptoms. If this study shows amitriptyline is effective in controlling the pain of knee osteoarthritis, it may enable this treatment to be available to more people in the future. We will inform you of any abnormal findings from knee xrays so that you can then consult with your doctor.

## **9 What are the possible risks and disadvantages of taking part?**

Medical treatments can cause side effects. You may have none or experience some, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Tell your doctor if you have any problems. Your study doctor will monitor for and discuss the best way of managing any side effects with you, should they occur.

Low dose amitriptyline is commonly used in general practice to treat pain sensitisation (eg related to shingles) and bed wetting in children. At higher doses it has been used to treat depression. At the low doses we will use, it is generally well tolerated. Any side-effects tend to be mild and may include dry mouth, constipation, fatigue, drowsiness, tremor and dizziness on rising.

Amitriptyline is dangerous in overdose and should be stored securely and out of reach of children.

The effects of amitriptyline on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are male, you should not father a child. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project.

Both male and female participants are strongly advised to use effective contraception during the course of the research and for a period of 1 month after completion of the study. You should discuss methods of effective contraception with your doctor.

If you do become pregnant whilst participating in the study, you should advise the study doctor immediately. The study doctor will withdraw you from the study and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

You should advise your treating doctor if you father a child while participating in the research project. Your doctor will advise on medical attention for your partner should this be necessary.

This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is less than 0.01 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be minimal.

Have you been involved in any other research studies that involve radiation? If so, please tell us.

Please keep information contained within the Patient Information and Consent Form about your exposure to radiation in this study, including the radiation dose, for at least five years. You will be required to provide this information to researchers of any future research projects involving exposure to radiation.

If you become upset or distressed as a result of your participation in the research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your doctor immediately about any new or unusual symptoms that you get.

If you become distressed during your participation in the study, you can suspend or end your involvement at any time.

#### **10 What if there is an unexpected finding on my imaging?**

This research project involves you having xrays of your knees. If we identify any unusual or unexpected findings, we will contact you and your general practitioner to discuss these and provide appropriate medical follow up.

#### **11 What if new information arises during this research project?**

Sometimes during the course of a research project, new information becomes available about the treatment being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/she will explain the reasons and arrange for your regular health care to continue.

#### **12 Can I have other treatments during this research project?**

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor will also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

It may also be necessary for you to take medication during or after the research project to address side effects or symptoms that you may have. You may need to pay for these medications and so it is important that you ask your doctor about this possibility.

#### **13 What if I withdraw from this research project?**

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study investigator and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the study investigator up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

#### **14 Could this research project be stopped unexpectedly?**

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The drug/treatment being shown not to be effective
- The drug/treatment being shown to work and not requiring further testing

## **15 What happens when the research project ends?**

At the completion of the trial, if you wish to know whether you received amitriptyline or the placebo, please contact the research personnel for further information. We will send you a follow up letter to inform you of the findings of the study.

Amitriptyline or placebo will be provided to you during the trial for a 12 week period at no cost. Once the trial has finished we will not be able to continue to provide this treatment to you. However, if your doctor is in agreement with continuing the treatment after the trial, he/she can provide you with a prescription for amitriptyline. From this point you will need to cover the cost of your medication.

## **Part 2 How is the research project being conducted?**

### **16 What will happen to information about me?**

By signing the consent form you agree to the study investigator and relevant research staff collecting and using personal information about you, the results of your questionnaires and xrays, for the research project, for extended related research and any future research into the symptoms of knee osteoarthritis. Any information obtained in connection with this research project that can identify you will remain confidential. For any future unrelated use of your information, we will seek the approval from the relevant ethics committees.

The data we collect or use will be individually identifiable or re-identifiable (i.e. coded). All electronic data will be kept in password protected databases, separate from identifying information. Hard copies of data will be kept in locked filing cabinets with restricted key access, at the Department of Epidemiology & Preventive Medicine, Monash University. Your knee xrays will be name-identified in accordance with standard clinical practice, and will be stored securely. Access to data will be limited to the chief investigators and support staff only.

Identifiable information will not be released to anyone outside the research team, with the exception of PPP (Pharmaceutical Packaging Professionals), who will be dispensing the study medication, and will not be used for any other purpose. Your information will only be used for the purpose of this research and related projects and it will only be disclosed with your permission, except as required by law.

By signing the consent form you consent to the study investigator using your data collected for this project for extended (related research) or unspecified (any future research) use.

Information from questionnaires and examinations will be retained for 15 years. This research project may retain your information for related use in the future regarding symptoms of knee osteoarthritis. If it is proposed to be used for other unrelated reasons, your consent will be obtained.

It is desirable that your local doctor be advised of your decision to participate in this research project. By signing the consent section, you agree to your local doctor being notified of your



decision to participate in this research project. As such, information about your health and your participation in this research project may be obtained and recorded in your health records.

It is anticipated that the results of this research project will be published and presented in a variety of forums. In any publication, report, or presentation, information will be provided in such a way that you cannot be identified, except with your permission. This confidentiality will be maintained by presenting aggregate data.

## **17 Injury**

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

## **18 Access to my information**

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information with which you disagree be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

## **19 Who is organising and funding the research?**

This research project is being conducted at Melbourne by Associate Professor Anita Wluka, Professor Flavia Cicuttini, Dr Donna Urquhart, Dr Andrew Teichtahl, Professor Andrew Forbes, Dr Carolyn Arnold and Dr Elspeth Hutton, funded by the National Health & Medical Research Council.

You will not benefit financially from your involvement in this research project even if, for example, your xrays (or knowledge acquired from analysis of your information) prove to be of commercial value to Monash University.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to Monash University, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries. No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

## **20 Who has reviewed the research project?**

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this project have been approved by the Alfred Hospital Ethics Committee.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

## 20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you would like any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), please contact the principal investigators.

Associate Professor Anita Wluka (Monash University): 9903 0994, [anita.wluka@monash.edu](mailto:anita.wluka@monash.edu)  
Professor Flavia Cicuttini (Monash University): 9903 0158, [flavia.cicuttini@monash.edu](mailto:flavia.cicuttini@monash.edu)

If you have any other questions you wish to be answered before consenting or during the course of the study, you can also contact the project officers.

Ms Molly Bond and Ms Clare Bellhouse on 03 9903 0553 (Melbourne)  
Email: [jointstudy@monash.edu](mailto:jointstudy@monash.edu)

If you have medical concerns outside office hours, please contact Rheumatology Registrar at the Alfred Hospital (9076 2000).

Telephone: 03 9076 2000 (Ask to speak to Rheumatology Registrar)

For matters relating to research at the site at which you are participating, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, you may contact

Name: Ms. Emily Bingle,  
Position: Research Governance Officer, Alfred Health  
Tel: (03) 90763619  
Email: [research@alfred.org.au](mailto:research@alfred.org.au).

You will need to tell Ms Bingle the following Alfred Health project number: 512/14

# Consent Form

**Title** Does low dose amitriptyline reduce pain in knee osteoarthritis? A double blind, randomised, pragmatic, placebo controlled clinical trial of amitriptyline in addition to usual care

**Short Title** Does low dose amitriptyline reduce pain in knee osteoarthritis?

**Project Sponsor** National Health & Medical Research Council

**Coordinating Principal Investigator/  
Principal Investigators  
Associate Investigator(s)** Assoc Prof Anita Wluka, Prof Flavia Cicuttini  
Dr Donna Urquhart, Dr Andrew Teichtahl, Prof Andrew Forbes, Dr Carolyn Arnold, Dr Yuanyuan Wang, Dr Elspeth Hutton, Dr Sharmayne Brady, Ms Clare Bellhouse, Dr Louisa Chou, Ms Molly Bond

**Location** Melbourne

## Declaration by participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Monash University, concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status.

I consent to the storage and use of information I have provided, questionnaire results and physical measures made on me, as described in the relevant section of the Participant Information Sheet.

Name of participant (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

**Declaration by researcher<sup>†</sup>**

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of researcher<sup>†</sup> (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

<sup>†</sup> A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

**Declaration by study physician**

I have discussed the clinical aspects of the research project, its procedures and risks, and I believe that the participant has understood that explanation.

Name of study physician (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_