

Participant Information Sheet/Consent Form

Monash University

Title	Does statin use have a disease modifying effect in symptomatic knee osteoarthritis? A multicentre randomised, double-blind, placebo-controlled trial
Short Title	Osteoarthritis of the Knee Statin (OAKS) Study
Protocol Number	521/12
Project Sponsor	National Health & Medical Research Council
Coordinating Principal Investigator/ Principal Investigators	Dr Yuanyuan Wang, Professor Flavia Cicuttini, Professor Andrew Tonkin, Professor Graeme Jones, Associate Professor Catherine Hill, Associate Professor Changhai Ding, Associate Professor Anita Wluka
Associate Investigator(s)	Ms. Judy Hankin, Ms. Alice Noone, Dr Maureen Rischmueller, Dr Sarah Downie-Doyle, Dr Andrew Teichtahl, Dr Sharmayne Brady
Location	Melbourne

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 6 months or longer. The research project is testing a new treatment for symptomatic knee osteoarthritis. The new treatment is called atorvastatin calcium.

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. It is characterized by the loss of cartilage (the lining over the bones that gives a cushioning effect). Currently there is no treatment that slows the progression of knee osteoarthritis. Evidence suggests that lipid metabolism and inflammation play an important role in the development and progression of osteoarthritis. The most common drugs used to lower cholesterol levels (called statins) have a broad range of effects including anti-inflammatory effects. They have been widely used in people with heart disease, stroke or at high risk of these conditions. Recently, there is emerging evidence that statins may also have a role in slowing the progression of knee osteoarthritis. The Osteoarthritis of the Knee Statin (OAKS) Study is a randomised clinical trial with the aim to compare the effect of statins with an inactive dummy tablet (what is called a placebo) on knee cartilage and symptoms in people with symptomatic knee osteoarthritis. If statins are effective, they will offer a new way to slow the progression of knee osteoarthritis.

Atorvastatin calcium has been approved in Australia to treat hyperlipidemia (a condition with abnormally increased levels of lipids, a type of fat, in the blood) since 1998. However it is not approved to treat osteoarthritis. Therefore, it is an experimental treatment for symptomatic knee osteoarthritis. This means that it must be tested to see if it is an effective treatment for symptomatic knee osteoarthritis.

A total of 350 participants will participate in this project, approximately 120 participants in Melbourne. They will be randomly allocated into two groups; with one group receiving the treatment of atorvastatin and the other group receiving a placebo.

This research is a multicentre clinical trial being conducted by Monash University, University of Tasmania, and University of Adelaide. This research has been initiated by the study investigators, Dr Yuanyuan Wang, Professor Flavia Cicuttini, Professor Andrew Tonkin, Professor Graeme Jones, Associate Professor Catherine Hill, Associate Professor Changhai Ding, and Associate Professor Anita Wluka.

This research has been funded by the National Health & Medical Research Council.

3 What does participation in this research involve?

If you agree to participate in the study, we will ask you to do the following:

1. Participation in this trial will initially involve a screening process. You will be screened for your suitability for the study over the phone by answering simple questions about your health. If you meet the inclusion criteria, you will have an interview with a research nurse at Monash University during which any question can be answered. A Participant Information Sheet will be provided, and informed consent is taken in writing. In order to further assess your eligibility for the study, you will have a fasting blood test at your nearest Melbourne Pathology Laboratory or

the Alfred Hospital, and have a knee X-ray at your nearest Medical Imaging Australia, unless you have had a knee X-ray within the last 6 months.

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

- Severe knee osteoarthritis on X-ray, severe or very mild knee pain
- Rheumatoid arthritis, other inflammatory arthritis, psoriatic arthritis, or lupus
- Significant knee injury
- Previous or planned knee joint replacement, or knee arthroscopy in the last 12 months
- Current use of potent analgesics including opiates
- Taking any other study drug within the last 30 days
- An indication to take statins for heart or blood vessel disease, diabetes or currently taking lipid lowering therapy or have had a previous adverse reaction to statins
- A high estimated risk for heart or blood vessel disease of more than 15% within the next 5 years
- Fasting total cholesterol level >7.5 mmol/L
- Clinically significant renal or liver disease
- Current medical condition such as cancer in the past 5 years (other than non-melanoma skin cancer)
- Any contraindication to magnetic resonance imaging (MRI) scanning
- Pregnancy, breast feeding, or trying to become pregnant

2. If you are eligible to participate, a session will be organised for you to undergo clinical assessments and complete questionnaires at Monash University. You will then undergo an MRI of the study knee.

3. Following these you will be randomly assigned to either the treatment or the control group. This means you will not have a choice regarding which group you are in and you will have equal chance of receiving the active study medications. The treatment group will receive atorvastatin (40 mg once daily) and the control group will receive a placebo (40 mg once daily). A placebo is a medication with no active ingredients. It looks like the real thing but is not. As this is a double-blind trial, neither you or the investigator will know which treatment you are receiving until the study is completed. However, in certain circumstances the investigator may find out which treatment you are receiving.

4. The trial will go for two years as the effects of atorvastatin on cartilage take this long to be measured adequately. During the trial you will attend 4 study visits in total: at screening, baseline, 1 year and 2 years, and have a telephone interview at 6 month. Each study visit will take about 40 - 50 minutes, and the telephone interview will take about 20 minutes. We can provide an attendance certificate signed by the research investigator for each study visit.

5. The following measurements will occur during the study period.

- 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 you have used at each visit.
- Measurement of height, weight, girth (hip and waist), and body composition (fat and muscle mass) at baseline and final visits.
- Blood (fasting or non-fasting, 5 - 10 ml) will be taken to examine serum lipids, liver function, creatine kinase (a test for muscle function), and renal function at screening, 4 weeks, 6 months, 1 year, and final visit, at either your nearest Melbourne Pathology Laboratory or the Alfred Hospital.
- Knee X-ray at screening.
- Knee MRI at baseline and final visits. The MRI scan will take about 20 minutes.

- Measurement of physical activity using a brief International Physical Activity Questionnaire (IPAQ) at baseline and final visit.
- Measurements of blood pressure, adverse events and pill counts will occur at all visits.

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.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You will be reimbursed for any reasonable travel and parking associated with participating in the research project (maximum \$10 per study visit).

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

4 What do I have to do?

You will be required to swallow one whole tablet every evening with a drink of water, with or without food, for 2 years. You will need to commit to taking the investigational drug regularly. You will need to attend all the study visits.

Whilst involved in this study, do not take more than one or two small glasses of grapefruit juice per day as large quantities of grapefruit juice can change the effects of atorvastatin. You should avoid drinking too much alcohol since drinking large quantities of alcohol may increase your chance of atorvastatin causing liver problems.

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 atorvastatin or may affect how well atorvastatin 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 350 participants with symptomatic knee osteoarthritis, aged 40-70 years will be recruited from the community, about 120 participants from each study site – Melbourne, Hobart, and Adelaide. The project will have 2 groups, with one group receiving atorvastatin and the other group receiving a placebo. All participants will be followed up over 2 years to examine whether atorvastatin affects the changes in knee cartilage and symptoms. The project involves researchers from multiple institutes including Monash University, University of Tasmania, and University of Adelaide.

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.

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 atorvastatin is effective in slowing the progression 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 MRI, X-ray and other tests, 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.

Use of atorvastatin is an established safe and well-tolerated treatment to lower cholesterol. The doses of atorvastatin we use in the study are commonly used for heart disease. Atorvastatin can cause a range of side effects, although not everybody gets them.

Most common side effects (affects 1 in 100 to 10 in 100 users) include:

- some inflammation of the nasal passages, pain in the throat, nose bleed
- allergic reactions
- some increases in blood sugar levels, increase in blood creatine kinase levels
- headache
- nausea, constipation, wind, indigestion, diarrhoea
- muscle pain
- blood test results that show your liver function can become abnormal

Uncommon or rare side effects (affects 1 in 100 to 1 in 10,000 users) include:

- anorexia (loss of appetite), weight gain, decreases in blood sugar levels
- having nightmares or some trouble with sleeping
- dizziness, numbness or tingling in the fingers and toes, reductions of sensation to pain or touch, change in sense of taste, loss of memory
- blurred vision
- ringing in the ears and/or head
- vomiting, belching, abdominal pain upper and lower, inflammation of the pancreas
- hepatitis (liver inflammation)
- rash, skin rash and itching, hives, hair loss
- neck pain, muscle fatigue
- fatigue, feeling unwell, weakness, swelling especially in the ankles, raised temperature
- serious allergic reaction which causes swelling of the face, tongue and throat
- muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown which can lead to kidney problems
- unexpected bleeding or bruising
- jaundice
- gynecomastia (breast enlargement in men and women).

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.

If you have been involved in any other research studies that involve radiation, 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.

An MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used, for example, in X-rays. We will ask you to lie on a table inside the MRI scanner and make sure you are in a comfortable position so that you can keep still. The MRI is very noisy; earphones are supplied to minimise the noise. Some people may experience symptoms of claustrophobia from lying in a confined space although your head and shoulders will be clear of the MRI tunnel. If you do experience discomfort at any time during the scan, you will be able to alert staff by pressing on a call button provided to you.

There are no proven long-term risks related to MRI scans as used in this research project. MRI is considered to be safe when performed at a centre with appropriate procedures. We will screen you to ensure you don't have a pacemaker or any other metal objects in your body that may pose a safety risk.

The scans we are taking are for research purposes and are not intended to be used as a full clinical examination. The scans will not be used to help diagnose, treat or manage a particular condition. A specialist will look at your MRI scans for features relevant to the research project. On rare occasions, the specialist may find an unusual feature that could have a significant risk to your health. If this happens, we will contact you to talk about the findings. We cannot guarantee that we will find any/all unusual features.

Having blood taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated. Blood samples is collected by a qualified venpuncturist. We endeavour to make the collection process as simple and as stress free as possible.

10 What will happen to my test samples?

This research project involves the collection, storage, test and analysis of your blood samples. By signing the consent form you agree to the study investigator using your blood collected for this project and storing your samples for extended related research and any future research. For any future use of your blood samples, we will seek the approval from the relevant ethics committees. This research project does not involve the establishment of a tissue bank.

The collection and test of your blood sample are a mandatory component of the research. This is done to examine your liver function, kidney function, and blood lipids, in order to assess your suitability for the study and monitor the safety of the treatment.

Your blood samples will be re-identifiable (i.e. coded). These samples will be stored securely at each site and will only be accessible by senior researchers. The samples will be retained for at least 15 years.

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 atorvastatin 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.

Atorvastatin or placebo will be provided to you during the trial for a 2 year 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 atorvastatin. 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 for the research project. Any information obtained in connection with this research project that can identify you will remain confidential.

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. The MRI scans 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. Re-identified blood samples will be stored securely at Monash University and will only be accessible by senior researchers. Identifiable information will not be released to anyone outside the research team and will not be used for any other purpose. Your information will only be used for the purpose of this research project 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.

Blood samples, information from questionnaires and examinations will be retained for 15 years. This research project does not involve the establishment of a databank.

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.

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

17 Complaints and compensation

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 Who is organising and funding the research?

This research project is being conducted at Melbourne, Hobart, and Adelaide, by Dr Yuanyuan Wang, Professor Flavia Cicuttini, Professor Andrew Tonkin, Professor Graeme Jones, Associate Professor Catherine Hill, Associate Professor Changhai Ding, and Associate Professor Anita Wluka, funded by the National Health & Medical Research Council.

By taking part in this research project you agree that samples of your blood or knowledge acquired through analysis of your samples may directly or indirectly benefit Monash University financially.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) 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).

19 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, the Tasmanian Health & Medical Human Research Ethics Committee, and the Human Research Ethics Committee (TQEH/LMH/MH).

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.

Professor Flavia Cicuttini (Monash University): 9903 0158, flavia.cicuttini@monash.edu
Associate Professor Anita Wluka (Monash University): 9903 0994, anita.wluka@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. Judy Hankin or Ms. Alice Noone on 9903 0553
Email: judy.hankin@monash.edu or alice.noone@monash.edu

If you have medical concerns outside office hours, please contact Rheumatology Registrar.

Telephone: 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 Ms. Rowan Frew, Manager, Office of Ethics & Research Governance, 9706 3848 or research@alfred.org.au.

Reviewing HREC approving this research and HREC Executive Officer details:
Ms. Rowan Frew, Alfred Hospital Ethics Committee, 9706 3848, r.frew@alfred.org.au

Consent Form

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Associate Investigator(s)	Ms. Judy Hankin, Ms. Alice Noone, Dr Maureen Rischmueller, Dr Sarah Downie-Doyle, Dr Andrew Teichtahl, Dr Sharmayne Brady
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 blood samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

Name of participant (please print) _____

Signature _____ Date _____

Name of witness* to participant's
signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by researcher[†]

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[†] (please print) _____

Signature _____ Date _____

[†] 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.