CHARISMA study

Title: The Colchicine and High-risk plaque Assessed by peRIcoronary adipoSe tissue inflamMAtion Study

Project Sponsor:	Monash Cardiovascular Research Centre (MCRC)
Principal Investigator:	A/Prof Dennis Wong
Site Name:	Monash Medical Centre – Monash Health

Information to Participants

You are being invited to participate in this research study. Outlined below is information about the study, it explains the tests and treatments involved. Knowing what is involved will help you make an informed decision about whether you want to take part in the research. Please read this Participant Information Sheet carefully. Feel free to ask any questions or have anything explained that you do not understand. You may wish to discuss this research study with a relative or friend.

Participation in this research is voluntary. If you agree to participate in this study, it will be necessary that you and the investigator sign this document. By signing the Consent Form, you are indicating that you understand the information and that you freely give your consent to participate in the research study. You will be given a copy of the Participant Information Sheet and Consent Form to keep. Your general practitioner will be notified if you agree to participate. If you do not wish to take part, you do not have to. You will receive the best possible care whether you take part or not.

What is the purpose of the research?

You are being asked to participate in this study because your CT coronary angiogram (CTCA) showed that you have plaque(s) in your coronary artery (blood vessels that supply blood to the heart) that is not severe but have features identified to be high-risk for causing future heart attack. This research study aims to see if a new treatment affects the plaque in your coronary arteries.

This new treatment is called Colchicine.

Colchicine is a medicine currently used for inflammatory conditions such as gout. It has a broad anti-inflammatory effect and previous research has shown Colchicine to reduce adverse cardiovascular events in patients with coronary artery disease.

The purpose of the CHARISMA research study is to look at the effect of Colchicine in patients with coronary artery disease with non-severe but high-risk plaques. The main cause of heart disease is from blockages in the heart arteries caused by atherosclerosis. Atherosclerosis is a chronic inflammatory disease of the blood vessels, where plaques form. These plaques can cause clots to form which can block blood flow completely. In the case of the coronary (heart) arteries this results in heart attack. Current treatment options against atherosclerosis include cholesterol lowering drugs such as statins and blood thinning drugs like Aspirin. This study aims to see how Colchicine acts on the coronary plaque, so we can better understand how Colchicine can lower adverse cardiovascular events such as heart attack. The results of this study will help to provide information about whether Colchicine should be recommended as a medicine against high-risk plaques, and form part of the treatment for patients with high-risk plaques in the future.

What is the number of study participants and what is the duration of my participation?
This trial will involve 100 participants from Monash Health. The expected duration of your participation is 6 months.

What are the study treatments?
You will be randomised (allocated by chance, like flipping a coin, not by the doctor´s decision) to one of two groups. If you are randomised to the Colchicine group, you will receive a 0.5mg Colchicine (Colgout) tablet to take once a day for 12 months. If you are randomised to the placebo (has no active ingredients) group, you will receive a placebo tablet to take once a day for 12 months.

The treatment will be provided to you for 6 months. In addition to the study drug, you will receive the current recommended therapies according to local and international guidelines for high-risk coronary atherosclerotic plaques. Your study doctor will provide you more with information about colchicine (Colgout) which you should read before agreeing to take part in the study.

What does participation in this research involve?
If you agree to participate in this research study, you will be asked to sign this informed Consent Form. You must meet specific entry criteria. In addition, you must be available for the clinic visit at 3 and 6 months after your inclusion in the study to receive the study drug and have all the study procedures performed. The clinic visits will take approximately 30 minutes and may be done as virtual visits via telehealth (e.g. telephone or video contact) rather than on-site visits and the study drug may be sent to you. The final clinic visit at 12 months after your study inclusion will involve a repeat CT scan of the heart and it will take approximately 4-5 hours. There will also be a phone call at 1 and 9 month after your study inclusion.

You will be participating in a randomised controlled research study. Sometimes, we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). You will be randomised to receive a Colchicine tablet or placebo (has no active ingredients) tablet to take orally once a day for 12 months. You will have a 1 in 2 chance (50%) of receiving Colchicine or placebo.

Your treatment allocation will be double-blind. That is, neither you nor the study doctor can choose the group you will be in or will know which treatment you receive. In the event your doctor needs to know which treatment group you have been assigned to, this information can be provided once your doctor has contacted the study team and discussed the reason with a clinician involved in the study.

This research study has been designed to make sure the researchers interpret the results in a fair and appropriate way.

Repeat CTCA scan procedure
This is a non-invasive test with a minimal side-effect profile. You will be required to fast for about 2 hours prior to the test. You will have a cannula placed in a vein in your arm.
When we do a CT scan, we are essentially taking a photograph of the blood vessels of your heart. If the heart is beating too quickly, the photo may be blurry and hard to interpret. Therefore, you may be given a tablet to slow your heart rate a bit so we can take good quality images of your heart.

Screening for eligibility
If you do qualify, you will also have the following performed:

- Medical history
- Physical examination
- Blood pressure, heart rate, respiratory rate and temperature
- Blood tests (approximately 50mls which is equivalent to 3 tablespoons) taken, including pregnancy test if you are a woman of child-bearing potential
- Review of your other medications

Study procedures

Baseline visit (within 1 week of your CTCA)

- Randomisation to Colchicine 0.5mg or Placebo
- Review of other medications you are receiving
- Review of any adverse events
- Supply of Colchicine or Placebo

Month 1 (telephone review)

- Review of other medications you are receiving.
- Review of any adverse events.

Month 3

- Blood pressure, heart rate, respiratory rate and temperature.
- Review of other medications you are receiving.
- Review of any adverse events.
- Supply of Colchicine or Placebo.

Month 6

- Fasting blood tests
- Blood pressure, heart rate, respiratory rate and temperature.
- Review of other medications you are receiving.
- Review of any adverse events.
- Supply of Colchicine or Placebo.

Month 9 (telephone review)

- Review of other medications you are receiving.
- Review of any adverse events.

Month 12 / Final visit

- Repeat CTCA
- Fasting blood tests
- Blood pressure, heart rate, respiratory rate and temperature
- Review of other medications you are receiving
- Review of any adverse events

At month 1 you will receive a phone call from a study coordinator to review other medication you are receiving and to review any adverse events.

What are the possible benefits of taking part in this study?

We cannot guarantee or promise that you will receive any benefits from this research. Your condition may get better but it could stay the same or even get worse. The information from this study might help to develop better treatments in the future for patients with cardiovascular disease.

What are the possible risks of taking part in this study?

Medical treatments can often cause side effects. You may have none, some or all of the effects listed below, 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.

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. Your study doctor will discuss the best way of managing your side effects with you.

Risk associated with repeat CT coronary angiogram

You are constantly monitored for any adverse event in a hospital environment with medical help immediately available. The risks with CTCA are rare. The contrast contains iodine and accordingly if you are allergic you will be ineligible. Around 1 in 200 people may get a minor itching reaction. If the contrast escapes from the vein it may cause some swelling and bruising. More severe reactions are very rare (1 in 5-10000) such as laryngospasm, bronchospasm or hypotension. Your kidney function will be checked before the scan as in a small number of patients the contrast can damage the kidneys.

CT scans involve exposure to a small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisievert (mSv) each year. The dose from this whole study is about 4 mSv. At this dose, no harmful effects of radiation have been demonstrated as any effect is too small to measure.

Risks of having blood samples taken

You will have your blood taken during the study. Possible side effects of having blood taken are tenderness, pain, bruising, bleeding and/or infection where the needle goes into the skin and blood vein. Having your blood taken may also cause you to feel nauseated and/or lightheaded.

Risk associated with taking Colchicine

The risks associated with taking Colchicine may include the following:

Common side effects (at least 10% chance):
Gastrointestinal symptoms such as nausea, vomiting, abdominal pain or diarrhea. If this happens, you will need to discuss with your doctor as soon as possible.

More serious side effects (less than 1% chance):
Loss of appetite or loss of hair. If this happens you will need to tell your doctor as soon as possible.

Very serious side effects (less than 0.1% chance):
Burning feeling in the stomach or throat, severe stomach pain, nausea or vomiting, severe diarrhea with bloody or black tarry stools, itchy skin, skin rash, hives, unusual bleeding or bruising under the skin, difficulty passing urine or blood in urine, confusion or convulsions, fever, muscle weakness, numbness or weakness in the fingers or toes. Tell your doctor immediately or go to the Emergency department at your nearest hospital.

All medicines have side effects, and you may experience unwanted side effects or you may not experience any of them. The elderly may have an increased chance of experiencing the side effects.

Risk of Colchicine to an unborn or breastfed baby

If you are a woman of childbearing age and decide to participate in this study, you should be sure that you are not pregnant and it is recommended that you do not get pregnant during the study, because

the effects of the medication on the baby are unknown. Potential risks could include the loss of the pregnancy (a miscarriage) or birth defects. Therefore, pregnant women or women planning to become pregnant should not participate in this study. If you are currently breastfeeding you also cannot participate in this study, because the risks to your baby are unknown. Your doctor will discuss this subject with you. If you or your partner gets pregnant during this study, you should inform the study doctor immediately. Any study medications that you (or your partner) are taking will be discontinued. You (or your partner) and your baby will be followed-up and will have assistance for as long as necessary.

Highly effective methods of birth control

You and the study doctor should discuss and agree on how you will prevent pregnancy. If you plan to have vaginal sex during this study, you should understand that even with the use of highly effective birth control there is still a small chance that a pregnancy could occur. Highly effective forms of preventing pregnancy include not having sex (abstinence) or birth control methods that work at least 99% of the time when used the right way every time you have vaginal sex, and include:

- use of hormonal birth control methods: pills, shots, implants (placed under the skin by a health care provider) or patches (placed on the skin)
- intrauterine devices (IUDs)
- sexual activity with a male partner who has had a vasectomy (surgery to become sterile)
- condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide

Females

If you become pregnant or think you are pregnant during this study or within twelve weeks after stopping the study drug, please tell the study doctor or his/her study staff right away. The use of the study drug(s) may be stopped. We will discuss any follow-up with you and ask you for information on the pregnancy outcome.

Males

If you are male and your partner becomes pregnant during this study, please tell the study doctor or his/her study staff. The study doctor will discuss any follow-up with you (and/or your pregnant partner) and ask you for information on the pregnancy outcome.

Do I have to take part in this research study?

Participation in this study 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 study at any stage.

If you 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, relationship with those treating you or your relationship with the Monash Health

What are the alternatives to participation?

If you do not take part in this research study you will still receive guideline-based treatment by your Cardiologist. It is very important to understand that irrespective of whether you participate in the study or not, you will receive current standard of care and treatment for high-risk coronary plaques. This usually involves taking a number of long-term medications such as aspirin and one or more cholesterol lowering medications, including a statin. The use of these medications will be decided upon by your treating Cardiologist in consultation with you and occurs completely independently of this study. If you

do participate, you will still be treated with these other tablets as per usual care, whether you are assigned to the Colchicine or placebo group.

Will I be reimbursed for harms related to the study?
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 in 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.

Will I be paid or reimbursed for any costs resulting from my participation?
There are no additional costs associated with participating in this research study, nor will you be paid. All medications, tests and medical care required as part of the research study will be provided to you free of charge.

Who will have access to my medical records? Is my information confidential?
All records containing personal information will remain confidential and no information which could lead to your identification will be released, except as required by law.

Under Australian privacy law all information collected about you must be kept confidential, unless you agree to it being released. If you consent to take part in this study, your medical records and the data collected for the study will be looked at by the research team and authorised persons for the company sponsoring the research. They may also be looked at by representatives of regulatory authorities and by authorized people from the hospital to check that the study is being carried out correctly. All these people will have a duty of confidentially to you as a research participant and no information that could identify you will be given to anyone else. By signing this document, you are authorizing such access. We will keep the records of this study private and confidential; they will be maintained within a separate secure research file in a locked office, in a secure research building that cannot be entered without approval, in accordance with the Monash Health's policy.
Records and data about your participation in this study may be used for study purposes, to obtain regulatory approval for the study drug, or for further analyses in the future. All such records and your right to them will be protected in accordance with Australian law.
With your consent, your general practitioner will be informed of your participation in this study so that, if you need to see him/her for any reason, he/she will be aware of your involvement.

You have the right to ask the study doctor about the data being collected on you and have the right to ask the study doctor to allow you to see **your personal health information** and to have any necessary corrections made

Besides the above described procedures, some medical data from your hospital records will be collected. All medical information will be confidential and only the study staff will have access to it. Your data may also be reviewed by regulatory agencies or ethics committees for audit purposes. At any time, your name or any other information about your health will not be given to any person that is not from the study staff. The information is confidential and used only for the purposes of this study, and will only be disclosed with your permission, except as required by law. The study results will be released, for academic and scientific purposes, without the identification of any data that discloses the participants' identity.

This study is being conducted by the Monash Cardiovascular Research Centre (MCRC). MCRC staff may require access to your medical record for onsite monitoring of the conduct of the study and potential audit. Again, all information will remain confidential.
A description of this clinical trial and the results will be available on http://www.anzctr.org.au The website will not include information that can identify you.

Name of General Practitioner:_____

Address:_____ Post Code: _____

Phone: _____

What will happen to my blood samples?
This study involves the collection of blood samples for testing as part of routine care and for research purposes. The research samples collected at Baseline and Month 6 (final visit) will be used to investigate exploratory endpoints including analysis on biomarkers of heart disease. Biomarkers are characteristics that are measured and evaluated as indicators of normal biological processes or disease processes. The blood sample will be used to analyse these markers related to blood lipids and inflammation.

These samples will be securely stored at the Monash Health Translation Precinct (MHTP) for up to 10 years following study completion to complete all analysis. Only study staff and students will have access to these samples. Your samples will be labelled with a code number instead of any identifying information.

These exploratory studies may provide additional information that will be helpful in understanding heart disease, but it is unlikely that these studies will have a direct benefit to you. The results of these tests will not have an effect on your care. Neither the investigator nor you will receive results of these exploratory research tests, nor will the results be put in your health record.

There will be a separate consent section for use of blood for exploratory research studies, you may refuse to sign it and still participate in the study.

What if new information arises during the research study?
Sometimes during the course of a research study, new information becomes available about the treatment that is 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 study.

Publication
The results of this study may be published in scientific journals at a later date. It is possible that the results may not be published for commercial, scientific or other reason. We will not publish anything that would let people know who you are.
Should any publication arise from the result of this study, a copy of the publication as well as a lay explanation of the study results may be sent to you. It is expected that any results will be published within a year of the conclusion of this study.

Who has reviewed the research study?
All research in Australia involving humans is reviewed by an independent group call a Human Research Ethics Committee (HREC). This study has been approved by the Monash Health Human Research Ethics Committee.

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

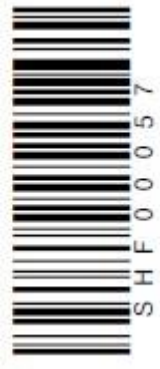
Further Information and who to contact

If you want any further information concerning this study or if you have any medical problems which may be related to your involvement in this project (for example, any side effects), you can contact any of the following people:

Clinical Contacts –

Assoc. Prof. Dennis Wong	03 9594 4543	Ms. Mary-Anne Austin	03 9594 4507
Dr. Kevin Cheng	03 9594 4543	Ms. Anne Tran	03 9594 3882

If you wish to speak to someone not directly involved in the study about any aspects of this study, the way it is being conducted, or any questions about being a research participant in general, then you may contact:



Reviewing HREC approving this study and HREC Executive Officer details

Reviewing HREC name	Monash Health HREC
HREC Executive Officer	Ms Deborah Dell
Telephone	03 9594 4605
Email	deborah.dell@monashhealth.org

Consent Statement

Title: The Colchicine and High-risk plaque Assessed by peRIcoronary adipoSe tissue inflamMAtion Study

Short Title: CHARISMA Study

Sponsor: Monash Cardiovascular Research Centre

Principal Investigator: A/Prof Dennis Wong

Location: Monash Medical Centre (Monash Health)

It is up to you to decide whether you want to take part in this study. If you want to take part, please read the statements below and sign the form if the statements are true.

1. The nature, purpose and risks of the research project have been explained to me. I understand them and agree to take part.

2. I understand that I may not benefit from taking part in the trial.

3. I understand that, while information gained during the study may be published, I will not be identified, and my personal results will remain confidential.

4. I understand that I can withdraw from the study at any stage and that this will not affect my medical care, now or in the future.

5. I understand that I should not become pregnant during the course of this trial. In the event of a pregnancy occurring, I agree to notify the investigator as soon as is practically possible.

6. I understand that I should not father a child during the course of this trial. In the event of a pregnancy occurring, I agree to notify the investigator as soon as is practically possible.

7. I understand the statement concerning payment to me for taking part in this study, which is contained in the Information Sheet.

8. I have not been a volunteer in any other research projects which have involved radiation exposure in the last twelve months.

9. I have had the opportunity to discuss taking part in this investigation with a family member or friend.

10. I agree to allow access to my medical records at any health care institution I may be admitted to for the purpose of collecting relevant information for this study.

Name of Participant

_____

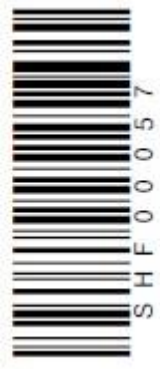
(please print)

Signature: _____ Date: _____

I certify that I have explained the study to the patient/volunteer and consider that he/she understands what is involved.

Name of Investigator: _____

Signature: _____ Date: _____



In addition to the main part of the research study, there is an optional part of the research. You can participate in the main part of the research without agreeing to take part in this optional part.

Optional De-Identified Databank Storage for Future Research Studies

I agree for my information to be stored in a de-identified databank for future research purposes

☐ Yes ☐ No

Participant: By signing below, you indicate that you have read the information written above and have indicated your choice for the optional part of the research study.

Participant's Name (print): _____

Signature: _____ Date: _____

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions about the research.

Investigator's Name (print): _____

Signature: _____ Date: _____