Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Title:	A randomised double-blind placebo-controlled trial of topical sirolimus in chemoprevention of facial squamous cell carcinomas
HREC Reference Number:	HREC/2021/QMS/77134
Project Sponsor	The University of Queensland (Diamantina Institute)
Coordinating Principal Investigator	Professor Kiarash Khosrotehrani
Location	Princess Alexandra Hospital The Prince Charles Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project because you are a solid organ transplant recipient (that is, kidney, liver, lung, heart) who has subsequently had multiple skin cancers such as BCC (basal cell carcinoma) or SCC (squamous cell carcinoma). The research project is testing whether sirolimus cream applied to the skin can help in the prevention of skin cancers in solid organ transplant recipients (SOTRs).

To be eligible you must:

- be aged 18 years or older
- have received an organ transplant 12 months ago or earlier
- have had at least 1 SCC or BCC in the past 5 years
- currently have at least 5 keratotic lesions on your face. These are typically scaly, sun-exposed lesions that may increase your risk of skin cancers.

However, you *may not* be eligible if:

- you have received or are receiving sirolimus or everolimus orally
- you have a skin cancer on your face that requires treatment
- you have an open wound on your face that requires treatment
- you are pregnant or planning to become pregnant in the next 6 months
- the researchers consider you medically unstable
- you have difficulty understanding and signing this document (if you are non-English speaking or intellectually impaired)

You are still eligible if you have used topical fluorouracil (e.g. Efudix) in the past 12 months or if you are currently taking nicotinaminde or acitretin (neotigason).

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.

2 What is the purpose of this research?

The main idea of this research is to determine the effectiveness of topical sirolimus cream in reducing the occurrence and number of skin cancers in solid transplant recipients at high risk of skin cancer.

Background

Keratinocyte cancers (e.g. BCC or SCC) are by far the most common form of cancer and are caused by ultraviolet (UV) light from the sun People who have had an organ transplant (e.g. lung or kidney) are much more likely to get SCCs or BCCs compared to people who have never needed one. Transplant patients require lifelong medication to prevent organ rejection but unfortunately these drugs can interfere with the normal working of the immune system. Cells damaged by UV may develop into cancer, instead of being repaired or destroyed as usual. As a result, these skin cancers become a major cause of poor health, hospitalisation and financial cost.

A newer immunosuppressant drug – sirolimus – has actually been seen to *reduce* skin cancer rates. Dermatologists in recent years have also used sirolimus as a cream in some genetic skin disorders. Our research team has recently completed a similar trial to test the safety of topical sirolimus – cream applied directly to the skin - in transplant patients. We found that the cream caused few side-effects, that the cream was safe when used for long periods and that the amounts of surface skin cancer were reduced.

This study is designed to test whether long term use of topical sirolimus will reduce the number of facial SCCs in a cost-effective and safe manner.

The initial 20 participants recruited will form a pilot study and will be provided with an additional questionnaire to answer at three months. This will determine how acceptable it is to apply the cream every night to the face. You will be informed when you are recruited if you are one of the first 20 participants.

This research has been initiated by the study doctor Professor Kiarash Khosrotehrani. The research is being conducted by a team of researchers based at UQDI (the University of Queensland Diamantina Institute) in Woolloongabba, Brisbane and has been funded by the Metro South Study, Education and Research Trust Account (SERTA). This research is not sponsored by any commercial entity or industry.

3 What does participation in this research involve?

A dermatologist has considered you eligible for this trial. Once you have read this Information Sheet you will be asked to sign a consent form.

Application of creams

This is a randomized placebo-controlled trial. This simply means that the hospital pharmacy will randomly choose if you will be in the group using sirolimus cream or the group using placebo (the cream which contains *no* medication). You will apply the creams to your whole face, avoiding your eyes. You will be required to apply the cream every night at bedtime for six months. No-one knows which patients receive the sirolimus and it is only at the end of the study that this information will be shared with you and the research team. **It is extremely important for the success of the study that the creams are applied as directed by the dermatologist.**

Visits to the Transplant Skin Clinic at PAH or TPCH

To monitor changes to the skin on your face, several clinic visits will be necessary: your initial appointment, then 3 and 6 months later. These visits will coincide with your usual 3-monthly visits to the Transplant Skin Clinic and will take less than 30 minutes. At each visit you will be monitored for any possible side effects (most commonly skin dryness and irritation).

On your first and 6-month visits your face will be photographed with a digital camera to record any changes on the surface and the number of lesions present.

Questionnaires

At each visit to the Transplant Skin Clinic, you will be asked to fill out the EuroQol 5-Dimensional and Basal and Squamous Cell Carcinoma QoL questionnaires, and then 6 months after you complete applying the cream. We will post these final questionnaires to you and ask you to return them in a reply-paid envelope. These questionnaires are used to assess the effects of the cream on your health and take less than 10 minutes to complete. The initial 20 participants of the study will complete an additional questionnaire to see how acceptable nightly cream application is. You will be informed when you are recruited if you are one of the first 20 participants.

Phone/email contact

You will receive either an email, phone call or text message to see how you are going applying the cream every night and if you have had any issues.

Blood tests

Approximately 6 months after the first cream application, blood will be collected to check sirolimus levels i.e. to check that you are not absorbing significant amounts of the medication. There have only been a few cases of sirolimus being present in the blood, even after prolonged use of sirolimus cream. However, if this was to occur, the Transplant Skin Clinic and research team will monitor you and your blood. It is expected the levels will decrease as soon as you stop using the cream. Electrolytes and other blood components that may indicate changes in your kidney or liver function will also be monitored as part of your routine care. The dermatologist will issue you with pathology request forms. These bloods can be done at the same time as your routine bloods. Fasting is not required.

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

Reimbursement.
You will be volunteering to participate in a research project which is a 'phase 3' clinical trial for which you will not be reimbursed. Clinical trials are research investigations in which people volunteer to test new treatments or tests to see if they prevent or manage a disease a medical condition. Oral sirolimus has been shown to be safe and effective in preventing keratinocyte cancers in previous clinical trials. This study is the next step in the research process and its purpose is to examine the suitability of a new chemoprevention method as a cream for transplant patients at high risk of skin cancer.

4 What do I have to do?

- You must apply the cream to your face as directed by your dermatologist.
- You must document every application on the sheet provided.
- You are required to attend 2 sessions at the Transplant Skin Clinic at PAH or TPCH within 6 months.
- At your clinic reviews, you will be required to fill out questionnaires and have photos taken of your face and report any skin cancer that may have occurred.
- You do not need to change your routine treatment or medications.

5 Other relevant information about the research project

- A total of 146 participants will be taking part in the project and they will be recruited over a 2-year period. The first 20 participants recruited will form part of a pilot trial.
- The project involves researchers from the Princess Alexandra Hospital, The Prince Charles Hospital and the University of Queensland (Diamantina Institute) working in collaboration
- If a skin cancer develops on your face during the study, it will be treated as usual (but sirolimus cream will not be applied to that area of the face)

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. Your decision will not affect your routine treatment, your relationship with those treating you or your relationship with the Princess Alexandra Hospital or The Prince Charles Hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital or any other Queensland hospital. The alternative is not to participate in this research. You will receive the same treatment and care as usual regardless of your decision.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research however: There may be a reduction in your risk of developing further skin cancers on your face.

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

- There is the possibility of an allergy to the sirolimus cream e.g. dermatitis, asthma, allergic rhinitis (runny nose, sneezing)
- There is a chance that the treatment may fail (that is, it will not result in any reduction in your skin cancer risk).
- Side-effects of Sirolimus are usually minor and include skin dryness, irritation and folliculitis (small pimples).
- Blood sampling may cause discomfort and bruising.

IMPORTANT: In the unlikely event of a life-threatening reaction to sirolimus cream (e.g. difficulty breathing, facial swelling) Emergency Services should be contacted by phoning 000. For all other possible side-effects and concerns please contact the Research Assistant, Charlotte Cox (phone numbers on page 7).

10 What will happen to my test samples?

If your face requires any biopsies or skin excisions during the study, small samples will later be sent to the researchers for studying. This will not affect your skin lesion diagnosis as they will be sent after your diagnosis has been made.

Skin samples are an essential part of the research. The skin samples obtained for the purpose of this research project will be transferred to University of Queensland PC2 certified facility located at the Translational Research Institute (TRI) in Woolloongabba, Brisbane QLD. Storage within a secure laboratory can be assured as access is limited to authorised personnel only. All samples will be given a unique code (study number) and only the research team will be able to re-identify them (i.e. trace them back to you). As per QLD Government retention policy, this document will be scanned into your ieMR record. In addition, samples and RCT documentation will be stored for 25 years before being destroyed by incineration.

Your samples will not be used for commercial or profit-making purposes.

We are not performing any genetic testing on your skin or blood samples therefore there are no implications for you or your family.

The blood test taken will also be done by an external laboratory which is not affiliated with the research team. They will dispose of your blood samples in accordance with their usual practices.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new and important information becomes available about the treatment that is being studied. If this occurs you will be notified.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you will be able to use topical fluorouracil (Efudix) to treat a particular lesion as advised by your dermatologist. However, you will stop using the sirolimus cream in that location while you are applying the Efudix. You will also be advised to only continue to use the sirolimus cream after the skin has healed.

However, you may not be able to use other additional creams and laser or photodynamic therapy on the treated areas. These therapies may change the effectiveness of the cream and therefore the study results. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking.

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. You will be provided with a form to sign to withdraw your participation. Your decision to withdraw will not affect your routine care and your relationship with your doctor. If you withdraw, you can consent for the research team to continue to monitor, through your medical records, the number of your skin cancers that you develop.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include the treatment being shown to work and therefore not needing further testing, or publications of similar results which may seriously affect the significance of this study.

15 What happens when the research project ends?

Upon completion of the study the results will be published in a peer-reviewed journal. Information will be revealed for groups of participants: individual participants are never identified. All participants will receive a letter from the Principal Investigator.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project

The majority of information about you will be de-identified and receive a study number. Any remaining information that can identify you (i.e. the consent form) will remain confidential in a secure facility (swipe access only) or on password protected computer files and will only be used for the purpose of the research project. Consent forms will be scanned into your Queensland Health ieMR account before being stored in a locked compartment within the TRI facility. Your study records may be viewed for the purposes of auditing by members of the Ethics Committee.

Your skin samples will be given a study number or code (to match the code on the consent form) and only members of the research team will be able to access and re-identify them.

All information will be transferred to computer files that will be password protected and the entrance to the TRI facility will require key code access. This will ensure that only study

personnel will be able to access your information. All trial documentation will be kept for 25 years as per 2020 updated Queensland Government retention policy.

It is anticipated that the results of this research project will be published and/or presented in a variety of ways. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and QLD 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 by Professor Kiarash Khosrotehrani. The project is being funded by Metro South Study, Education and Research Trust Account (SERTA). 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 research project have been approved by the HREC of Metro South Health, Brisbane, QLD.

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 want 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), you can contact the principal study doctor on 3443 7088 or any of the following people:

Clinical contact person

Name	Dr Charlotte Cox
Position	Research Assistant
Telephone	0486 030 731
Email	charlotte.cox1@uq.net.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Position	Metro South HREC Co-Ordinator
Telephone	07 3443 8047
Email	MSH-Ethics@health.qld.gov.au

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, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC Name	Metro South Hospital and Health Service Human Research Ethics Committee (EC00167)
Position	Metro South HREC Co-ordinator
Telephone	07 3443 8047
Email	MSH-Ethics@health.qld.gov.au

Consent Form - Adult providing own consent

Title:	A randomised double-blind placebo-controlled trial of topical sirolimus in chemoprevention of facial squamous cell carcinomas
HREC Reference Number:	
Project Sponsor	The University of Queensland (Diamantina Institute)
Coordinating Principal Investigator	Professor Kiarash Khosrotehrani
Location	Princess Alexandra Hospital The Prince Charles Hospital

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 UQ Diamantina concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.
I consent to the storage and use of skin samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

• **This specific research project**

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.

Name of Participant (please print) _____

Signature_____ Date_____

Declaration by Study Doctor/Senior 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 Study Doctor/
Senior 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

Form for Withdrawal of Participation - *Adult providing own consent*

Title	A randomised double-blind placebo-controlled trial of topical sirolimus in chemoprevention of facial squamous cell carcinomas
HREC Reference Number	HREC/2021/QMS/77134
Project Sponsor	University of Queensland Diamantina Institute
Principal Investigator	Professor Kiarash Khosrotehrani
Locations	Princess Alexandra Hospital Brisbane QLD The Prince Charles Hospital Brisbane QLD

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with the Princess Alexandra Hospital/The Prince Charles Hospital, Brisbane QLD.

Name of Participant (please print) _____

Signature _____ Date _____

I wish to consent for the research team to continue to have access to my medical records at the Princess Alexandra Hospital/The Prince Charles Hospital, Brisbane QLD to monitor the number of skin cancers I develop for the duration of the trial. I understand that not consenting will not affect my routine treatment, my relationship with those treating me or my relationship with the Princess Alexandra Hospital/The Prince Charles Hospital, Brisbane QLD

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study doctor/Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

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