INFORMED CONSENT FORM

1. Study Information

Protocol Title:

Sirolimus coated angioplasty versus plain balloon angioplasty in the treatment of dialysis access dysfunction

Site Principal Investigator (PI) & Contact Details:

A/Prof Jackie Ho Pei
National University Hospital
Department of Cardiac, Thoracic and Vascular Surgery
CTVS office, CTVS office, Level 9, NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228
Principal Investigator Contact: 67722076

Study Sponsor:

This is an investigator-initiated study with fundings from Concept Medical.

2. Purpose of the Research Study

You are invited to participate in a research study. It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you take part in this research study, the study will be explained to you and you will be given the chance to ask questions. After you are properly satisfied that you understand this study, and that you wish to take part in the study, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

You are invited because you meet our inclusion criteria of needing to undergo balloon angioplasty for dysfunctional AVF.

This study is carried out to find out the effectiveness of two different treatments for stenosis in arteriovenous fistulas (AVF). Stenosis (narrowing) within the AVF is a common cause of dysfunction of AVF (failure of the AVF to meet the requirement of haemodialysis). The standard of care for treating stenosis in AVF is angioplasty (dilatation) with conventional plain (uncoated) balloons. However, there is often recurrence of stenosis due to neointimal hyperplasia (growth of cells and tissue that result in decreased size of the vessel lumen), which is the body's response to injury and expected changes to blood flow within the AVF.

Sirolimus-eluting balloons are coated with a drug (sirolimus) which inhibits neointimal hyperplasia thereby prolonging the success and durability of treatment. Sirolimus is a drug used in transplant to inhibit cell growth. Sirolimus-eluting balloons have been shown to allow localised release of a dose of Sirolimus into the vessel wall with minimal exposure to the rest of the body. They have also proven effectiveness and safety in the treatment of stenosis in arteries of the heart and lower limb. We hope to learn if the use of sirolimus-eluting balloons will lead to improved treatment results of dysfunctional AVF compared to treatment with plain balloons.

This study will recruit 170 subjects from Singapore General Hospital, Sengkang General Hospital and National University Hospital.

3. What procedures will be followed in this study

If you take part in this study, you will first undergo balloon angioplasty procedure to treat all the narrowings within your AVF with conventional plain balloons as per standard hospital protocol. During angioplasty, angioplasty balloon are inflated to open up narrowed segment of the AVF. These balloons are then deflated and removed from your body after treatment.

After successful angioplasty of the narrowings with conventional plain balloons, you will be enrolled into the study. You will then be randomised to receive either uncoated plain balloons (Placebo), or sirolimus-eluting balloons to treat for all the stenosis (narrowing) in your AVF again. Randomisation means assigning you to one of 2 groups by chance, like tossing a coin or rolling dice. You will not know the treatment balloon you have received. This is to ensure the scientific validity of this study. If the narrowings within the AVF cannot be successfully treated with conventional plain balloons as per standard hospital protocol, you will not proceed with randomisation and your participation in the study will end.

If you are assigned to the sirolimus-eluting balloon arm, all the stenosis (narrowing) that were treated with conventional plain balloon will be treated again with the sirolimus-eluting balloon. The purpose is to coat the treated segment with the medicine called sirolimus. If you are enrolled into the placebo plain balloon arm, all the stenosis will be treated with an uncoated plain balloon (placebo) again.

Your participation in the study will last approximately 12 months. You will be reviewed in NUH clinic as standard care for your fistula condition after the intervention. Besides clinic review, you will need to return to NUH for ultrasound scan at 3, 6 and 12 months after intervention to assess the effect of the treatment on the AVF.

Follow-up visit 1: 3 months after intervention for ultrasound scan of the AVF

Follow-up visit 2: 6 months after intervention for ultrasound scan of the AVF

Follow-up visit 3: 12 months after intervention for ultrasound scan of the AVF and end of study

If for any reasons you have to undergo repeat angioplasty of the AVF because of recurrence of AVF dysfunction before the scheduled ultrasound scan (within 1 week of visit 1 and 4 weeks of visit 2 and 3), then you will not need to attend the further scan appointments.

Additional Study Procedures

Ultrasound scan of the AVF at 3, 6 and 12 months.

We will also review your medical records to collect data such as demographics, medications, treatment and scan information. In the event that you have to undergo repeat angioplasty of the AVF due to recurrence of AVF dysfunction during your study participation, we will seek your consent to continue tracking your progress and collecting your data, by telephone call and reviewing your medical reocrds, for the intended 12 month participation period.

In addition, your data collected during the study may be kept for future research beyond the completion of the study. The data will be de-identified for future research use. For this purpose, consent for future research will be sought from you.

During the course of the study, there is a possibility that we might unintentionally come to know of new information about your health condition from the angiogram and ultrasound scans that /are conducted as part of the study. These are called “incidental findings”.

“Incidental findings” are findings that have potential health or reproductive importance to research participants like you and are discovered in the course of conducting the study, but are unrelated to the purposes, objectives or variables of the study. These findings may affect your current or future life and/or health insurance coverage.

You will be asked to indicate whether you wish to be re-identified and notified in the case of a clinically significant incidental finding that is related to you.

If you agree to be re-identified and notified, your study doctor/a qualified healthcare professional will explain the incidental finding to you and discuss and advise you on the next steps to follow. For this purpose, please inform the Principal Investigator or any of the study contact persons listed in this document whenever there are changes in your contact details. You may wish to do more tests and seek advice to confirm this incidental finding.

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

For study activity continuation during COVID-19
If there are measures which limit all hospital visits or prevent you from being able to complete the ultrasound scan in person at any hospital due to COVID-19, we will review your medical records and conduct telephone consult with you in place of the ultrasound scan.

4. Your Responsibilities in This Study

If you agree to participate in this study, you should follow the advice given to you by the study team. You should be prepared to visit the hospital 4 times (once for intervention, 3 time for follow up ultrasound scan) and undergo all the procedures that are outlined above. You should also:

- Keep your study appointments. If it is necessary to miss an appointment, please contact the study staff to reschedule as soon as you know you will miss the appointment.
- Inform the Principal Investigator as soon as possible about any side effects that you may have encountered.

5. What Is Not Standard Care or is Experimental in This Study

The study is being conducted because sirolimus-eluting balloons are not yet proven to be a standard treatment for dysfunctional AVF. We hope that your participation will help us to determine whether treatment with sirolimus-eluting balloon angioplasty is equal or superior to existing conventional plain balloon angioplasty alone.

Use of a placebo (inactive agent), blinding (one or more parties unaware of the treatment assignment), and randomization (study treatment balloon selection by chance) are only done for research studies.

Although ultrasound may be part of standard medical care, in this study these are being performed for the purposes of the research.You will be put on close monitoring of the AVF for the scan. Ultrasound scan of the AVF will be performed at 3, 6 and 12 months to determine if the stenosis has recurred. This is not routinely done in routine clinical practice.

6. Possible Risks and Side Effects

All angioplasty procedures have possible risk, discomforts and inconveniences which you may encounter regardless of enrolment into this study. The usual risks associated with fistulogram and balloon angioplasty are:

- Pain or discomfort with balloon angioplasty
- Injury to AVF, supplying artery or draining vein which may require further treatment (for instance with stents or surgery)
- Thrombosis of AVF which may require thrombectomy / thrombolysis (treatment targeted at clot removal / dissolution)
- Loss of AVF patency, necessitating a new method of dialysis (which may also include insertion of a vascular catheter for temporary access)
- Blood clots may form within the blood vessels and get displaced into the artery. This may result in blockage of the artery and injury to the tissue that is dependent of the artery for blood supply
- Localised bleeding or infection
- Recurrence of stenosis
- Surgery may be required for any of the complications
- Inpatient admission for observation or treatment for any of the complications
- Allergic reaction to contrast or medications administered

The effectiveness of sirolimus-eluting balloon is still being tested; therefore, you may experience other side effects that have not yet been reported. However, you will be kept informed of any significant new findings that may relate to your willingness to continue to take part in this study.

If you experience any new symptoms, you should contact your doctor or the Site Principal Investigator as soon as possible.

Contrast media or drug allergic reaction

A small percentage of patients react adversely to the contrast media or other drugs that are necessary for the procedure. Possible minor complications are flushing, nausea, vomiting, arm pain, pruritus (itching), headache, rashes and a warm sensation.

More serious complications are convulsion (epilepsy), unconsciousness, airway obstruction, pulmonary collapse, drop in blood pressure, heart failure and arrhythmia. Death has been reported but fortunately the risk is very low i.e. 1 in 170,000 to 200,000.

Sirolimus-eluting balloons:

- There might be a risk that the sirolimus eluting balloon may not work in the AVF.
- Treatment with sirolimus-eluting balloon may involve risks to you, which are currently unknown to the medical community and are unforeseeable.
- Systemic side effects related to sirolimus are highly unlikely due to the small dose used and local release to the vessel wall without significant exposure to the rest of the body.

7. Possible Benefits from Participating in the Study

If you participate in this trial you may reasonably expect to benefit from the trial in the following way:

If you are randomised to the sirolimus-eluting balloon group, you may experience better outcomes compared to conventional plain uncoated balloon which is the standard of care. Your AVF may last longer after interventions and it may also remain free from the need for repeat treatment for a longer period of time compared to treatment with conventional plain balloon angioplasty by delaying the narrowing of the AVF. However, there is no assurance

that you will benefit from this study or that treatment with sirolimus-eluting balloon will be better compared to conventional plain uncoated balloon.

Your participation may also contribute to the advancement of medical knowledge about the use of sirolimus-eluting balloon in dysfunctional AVF.

If you are randomised to the plain balloon (placebo) group, you will undergo angioplasty with placebo plain balloon which is established in the treatment of dysfunctional AVF.

8. Important Information for Women Subjects

The effect of sirolimus on a baby's development is not known. Therefore, pregnant and breast-feeding women may not take part in this study. Women who have a chance of becoming pregnant must have a negative pregnancy test at study entry and use birth control during the study. If you become pregnant during this study, you must call your doctor or the Principal Investigator immediately.

9. Alternatives to Participation

If you choose not to take part in this study, the alternative is to have what is considered standard care for your condition. In our institution this would be conventional plain balloon angioplasty.

This procedure has the following potential benefits:

- You will be receiving the standard of care.
- You will not experience the potential side effects of sirolimus (if you are randomized to the sirolimus-eluting balloon group)

10. Costs & Payments if Participating in the Study

If you take part in this study, the following will be performed at no charge to you and borne by Concept Medical:

- Sirolimus or plain placebo angioplasty balloon (depending on the treatment arm you are randomised to)
- Post procedure ultrasound, 3-month, 6-month and 12-month follow-up ultrasound

If you take part in this study, you will have to pay for the following:

- Routine blood tests (full blood count, PT/PTT, renal panel)
- Angioplasty procedure / hospitalisation (room, ward, etc) fees
    - Other conventional plain angioplasty balloons used during intervention (refers to the high pressure angioplasty balloons that have no drugs that are used to treat the narrowing vessels and to prepare the vessels before application of either the sirolimus balloon or placebo balloon)

You will be reimbursed for your time, inconvenience and transportation costs as follows:

- You will be paid $50 for each ultrasound scan follow-up visit you complete.

If telephone consult was done in replacement of ultrasound scan due to COVID-19 restrictions, there will not be any reimbursement for that follow-up visit completed via phone.

11. Voluntary Participation

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should tell the Principal Investigator.

If you withdraw from the study,

- You will discuss with your primary physician on how to continue management of your AVF or dialysis treatment.

However, the data that have been collected until the time of your withdrawal will be kept and analysed. The reason is to enable a complete and comprehensive evaluation of the study.

Your doctor, the Investigator and/or the Sponsor of this study may stop your participation in the study at any time if they decide that it is in your best interests. They may also do this if:

- You do not follow instructions required to complete the study adequately.
- Pregnancy
- You need treatment that is not allowed in the study.
- The study is cancelled.

If you have other medical problems or side effects, the doctor and/or nurse will decide if you may continue in the research study.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you (or your legally acceptable representative, if relevant) will be informed in a timely manner by the Principal Investigator or his/her representative.

12. Compensation for Injury

If you follow the directions of the doctors in charge of this study and you are physically injured due to the trial substance or procedure given under the plan for this study, National University Hospital will pay the medical expenses for the treatment of that injury.

Payment for management of the normally expected consequences of your treatment will not be provided by National University Hospital.

National University Hospital without legal commitment will compensate you for the injuries arising from your participation in the study without you having to prove National University Hospital is at fault. There are however conditions and limitations to the extent of compensation provided. You may wish to discuss this with your Principal Investigator.

By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

13. Confidentiality of Study and Medical Records

Your participation in this study will involve the collection of “Personal Data”. “Personal Data” means data about you which makes you identifiable (i) from such data or (ii) from that data and other information which an organisation has or likely to have access. This includes medical conditions, medications, investigations and treatment history.

Information and “Personal Data” collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available. Only your Investigator(s) will have access to the confidential information being collected.

However, Regulatory Agencies and NHG Domain Specific Review Board and Ministry of Health and National University Health System will be granted direct access to your original medical records to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you (or your legally acceptable representative, if relevant) are authorising (i) the collection, access to, use and storage of your “Personal Data”, and (ii) the disclosure to authorised service providers and relevant third parties.

Data collected and entered into the Case Report Forms are the property of National University Hospital which will contribute the data to the Lead PI at Singapore General Hospital to be used for research and analysis purpose. In the event of any publication regarding this study, your identity will remain confidential.

Research arising in the future, based on your “Personal Data”, will be subject to review by the relevant institutional review board.

Any information containing your “Personal Data” that is collected for the purposes described in this Informed Consent Form will be stored in Singapore. Only anonymised data will be transferred out of Singapore to Concept Medical Inc, United States of America.

By participating in this research study, you are confirming that you have read, understood and consent to the Personal Data Protection Notification available at http://www.nuh.com.sg/Pages/Personal-Data-Protection-Act.aspx.

14. Who To Contact if You Have Questions

If you have questions about this research study or in case of any injuries during the course of this study, you may contact the Site Principal Investigator:

A/Prof Jackie Ho Pei
National University Hospital
Department of Cardiac, Thoracic and Vascular Surgery
CTVS office, CTVS office, Level 9, NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228
Principal Investigator Contact: 67722076

The study has been reviewed by the SingHealth Centralised Institutional Review Board for ethics approval. This approval is mutually recognised by NHG Domain Specific Review Board (DSRB).

If you want an independent opinion to discuss problems and questions, obtain information and offer inputs on your rights as a research subject, you may contact the NHG Domain Specific Review Board Secretariat at 6471-3266. You can also find more information about

participating in clinical research, the NHG Domain Specific Review Board and its review processes at www.research.nhg.com.sg.

If you have any complaints or feedback about this research study, you may contact the Principal Investigator or the NHG Domain Specific Review Board Secretariat.

15. Consent to be Contacted for Future Research (optional)

You are being asked for permission to be contacted in the future for participation in research studies that you may be suitable for. If you agree to be contacted, your information and contact details will be entered and stored in a secured database in National University Hospital. Your information and contact details will not be released to any parties outside National University Hospital without your permission. When investigators from National University Hospital identify you to be suitable for a particular research study, the investigators or authorised personnel from National University Hospital will contact you to inform you about the research study. Your decision to be contacted for future research studies is completely voluntary and separate from your decision to participate in this study. Your decision will not affect your medical care or any benefits to which you are entitled. You may change your mind at any time by contacting A/Prof Jackie Ho Pei at 67722076.

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Principal Investigator & Contact Details:

A/Prof Jackie Ho Pei
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CTVS office, CTVS office, Level 9, NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228
Principal Investigator Contact: 67722076

I voluntarily consent to take part in this research study. I have fully discussed and understood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to my satisfaction. I have also been informed and understood the alternative treatments or procedures available and their possible benefits and risks.

By participating in this research study, I confirm that I have read, understood and consent to the National University Hospital Personal Data Protection Notification.

Consent to be Re-Identified and Notified in the Case of an Incidental Finding

☐ Yes, I agree to be re-identified and notified in the case of an incidental finding from this research.

In the event that I cannot be reached, please contact my next of kin

Name of next of kin:

Contact:

☐ No, I do not agree to be re-identified and notified in the case of an incidental finding from this research.

Consent to continue tracking your progress within the 12 month period (for situations where repeat angioplasty of the AVF is required)

As explained earlier, we would like to seek your consent to continue tracking your progress, in the event that you are not required to attend further scan appointments due to the need for repeat angioplasty of the AVF.

☐ Yes, I agree to allow continued tracking of my progress within the 12 month period

☐ No, I do not agree to allow continued tracking of my progress within the 12 month period

_____	_____	_____
Name of Participant	Signature	Date

Consent for the Use of Data for Future Research

☐ Yes, I agree to donate my data for future research.

Please also check one of these boxes:

☐ There are no restrictions on the kind of research that may be done with my data.

☐ The Investigator may use my data for future research as long as the research is related to the treatment of dialysis access dysfunction

☐ No, I do not agree to donate my data for future research.

Consent to be Contacted for Future Research

☐ Yes, I agree to be for contacted for future research that I may be eligible for.
I agree to be contacted via:

☐ Phone _____

☐ Mail _____

_____

☐ Email _____

☐ Others _____

☐ No, I do not agree to be contacted for future research.

_____	_____	_____
Name of Participant	Signature	Date

Translator Information
The study has been explained to the participant / legally acceptable representative in

_____ by _____
<insert language> *insert name of translator >*

Witness Statement
I, the undersigned, certify that:

- I am 21 years of age or older.
- To the best of my knowledge, the participant/ the participant's legally acceptable representative signing this informed consent form has the study fully explained in a language understood by him/ her and clearly understands the nature, risks and benefits of his/ her participation in the study.
- I have taken reasonable steps to ascertain the identity of the participant/ the participant's legally acceptable representative giving the consent.
- I have taken steps to ascertain that the consent has been given voluntarily without any coercion or intimidation.

Name of Witness	Signature	Date

1. In accordance with Section 6(d) of the Human Biomedical Research Act and Regulation 25 of the Human Biomedical Research Regulations 2017, appropriate consent must be obtained in the presence of a prescribed witness who is 21 years of age or older, and has mental capacity. The witness must be present during the entire informed consent discussion, and must not be the same person taking the appropriate consent. The witness may be a member of the team carrying out the research.
2. However, if the participant/ the participant's legally acceptable representative is unable to read, and/ or sign and date on the consent form, an impartial witness should be present instead. The impartial witness should not be a member of the study team.

Investigator Statement
I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of his / her participation in the study.

Name of Investigator / Person administering consent	Signature	Date