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Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Monash Health

Title	The efficacy and acceptability of enoxaparin administration via a subcutaneous catheter vs subcutaneous injections in both prophylactic and therapeutic settings
Short title	Butterfly
Protocol Number	4
Project Sponsor	Monash Health Haematology Research Unit
Principal Investigator	Dr Emma Leitinger
Associate Investigator(s)	A/Prof Sanjeev Chunilal, Dr Zane Kaplan
Location	*Monash Health*

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project because you require subcutaneous low molecular weight heparin (LMWH) (e.g. enoxaparin (Clexane) or dalteparin (Fragmin)) therapy either to treat or to prevent a blood clot in the legs (deep vein thrombosis, DVT), or the lungs (pulmonary embolism, PE). This project will study whether a catheter (Insuflon) placed under the skin (Insuflon) which can stay in for up to 1 week is an acceptable alternative to regular daily or twice-daily injections under the skin. The Insuflon catheter is widely used in paediatric patients to administer enoxaparin (Clexane), and is also used in adults for various medications, but has not specifically been assessed for enoxaparin (Clexane) or dalteparin (Fragmin).

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and research 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. This decision will not affect the quality of medical care that you receive.

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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?

Low molecular weight heparins, such as enoxaparin (Clexane) or dalteparin (Fragmin), are medications used both to treat and prevent blood clots. They are administered as an injection under the skin either once or twice per day. Long term use of these medications can result in complications at the sites of injection, including pain, bleeding, bruising, inflammation and infection. The use of a catheter (Insuflon) that is inserted under the skin and can stay in place for up to 7 days is a method used in children, and has also been used in adults for many medications, however not specifically with low molecular weight heparin therapy. This study aims to see whether using a subcutaneous catheter (Insuflon) reduces the complications seen with regular enoxaparin (Clexane) or dalteparin (Fragmin) injections, and also whether the amount of drug exposure is the same between the two methods of administration. Based on knowledge of how enoxaparin (Clexane) and dalteparin (Fragmin) are absorbed by the body, no difference in drug exposure is anticipated. However, to confirm this, drug levels will be measured to ensure there is no increased or decreased exposure. This will help guide doctors in the future when treating patients who require long term enoxaparin (Clexane) or dalteparin (Framgin) therapy. This research is being conducted by researchers at Monash Health.

3 What does participation in this research involve?

Patients who are receiving enoxaparin (Clexane) or dalteparin (Fragmin) therapy for at least 4 weeks, either to treat or to prevent a blood clot are invited to participate. There are no additional upfront blood tests required before starting the study, however, there are additional blood tests required for the study itself. If you are willing to participate in this study, you will be asked to sign the consent form at the back of this booklet.

If you consent to participate, a separate clinic visit will be arranged where the study doctor will ask you questions about your medical history (e.g. prior medical problems, medications used, family history of medical problems, smoking status, pregnancy status), and will perform a physical examination (e.g. height, weight, checking heart rate and blood pressure, and examining your heart, lungs, abdomen). If you have not had the appropriate standard blood tests done within 4 weeks of review you may require an additional blood test. You will also be reviewed by the nursing staff who will demonstrate use of the subcutaneous catheter and allow you to practice administering medication through it. If you are happy to proceed, a catheter (Insuflon) will be inserted under the skin and kept in place with a sterile dressing. The nursing staff will provide education and equipment if required on how to care for the catheter. You will be asked to self-administer your enoxaparin (Clexane) or dalteparin (Fragmin) dose through the subcutaneous catheter with nursing staff observing to ensure you are comfortable and using correct technique. You will have several blood tests done to measure medication levels as part of the study (see below for details). We expect that there will be no difference in medication levels between using the subcutaneous catheter (Insuflon) as compared to subcutaneous injections, however, this has not been directly assessed in adults. There is a theoretical risk of increased or decreased exposure to enoxaparin (Clexane) or dalteparin (Fragmin), however based on current data we believe this risk is very low.

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This study is a crossover study, meaning that you will receive both therapy via a subcutaneous catheter, and via subcutaneous injections in turn. Written medication information on enoxaparin (Clexane) and dalteparin (Fragmin) can be provided on request. You will meet with the study investigators to discuss this project and sign the consent form at the back of this document if you wish to participate.

Study visits day 2, 5, 7, 13, 16

Initial study visits will occur on days 2, 5 (+/- 1 day) and 7 if the catheter remains in for a full week. During these visits, nursing staff will review the catheter site for any complications and take a blood test (approximately 10mL, or 2 teaspoons) to check blood levels of enoxaparin (Clexane). If there are concerns with the catheter at any time, a doctor will review the site and discuss removal of the catheter as necessary. Another catheter can be inserted at this time if you wish to proceed (the day of the new catheter insertion will be "day 1"), otherwise you can resume subcutaneous injections if you prefer. For those receiving twice-daily dosing, a second catheter can be inserted from day 2 to allow alternation of which catheter is used. At day 5 you will be provided a brief survey on how the catheter has affected you and your daily life. You will be seen by the doctor on the day the catheter is removed (either at day 5 or 7).

Once the subcutaneous catheter is removed, you will continue enoxaparin (Clexane) or dalteparin (Fragmin) injections for at least 5 days before any further study visits are required. There will be 2 visits required while you are receiving subcutaneous injections at days 13 and 16 (the exact days may vary to accommodate weekends). At these visits you will have a blood test (around 10mL or 2 teaspoons each time), and nursing staff will review the previous catheter site, and the current injection sites. You will be asked to complete 3 short surveys about how you found the subcutaneous catheter, and which method you preferred. You will also see the doctor on the day 16 visit.

Extension phase

This is an optional phase for participants who would like to continue using the subcutaneous catheter for enoxaparin (Clexane) or dalteparin (Fragmin). Before starting the extension phase, you will need to be seen by a doctor who will review your medical history and blood test results, including enoxaparin (Clexane) blood levels, to ensure that you are safe to continue using the catheter. The catheter will be inserted by trained nursing staff in the Clinical Trials Centre, and you will have a doctor assessment every 4 weeks with a blood test to check enoxaparin (Clexane) levels (approximately 5mL or 1 teaspoon of blood). After 4 weeks, you will have the option to insert the insuflon catheters yourself if you prefer. If you choose to do this, clinical trial staff will supply you with the appropriate materials (insuflon catheters, dressings, alcohol wipes, sharps disposal container), and supervise you inserting the catheter the first time you do so. If you have any issues doing this at home, you may change back to nursing staff inserting the insuflon at any time. You may decide to change back to regular subcutaneous injections at any time, at which point you will enter the follow-up phase outlined below. If you do not wish to enter the extension phase, you will move to the follow-up phase once you have completed the initial study visits.

Follow-up phase

You will receive a phone call on day 3, 30, 60 and 90 to check how you are and whether you have had any issues with bleeding or new clots. There are no costs associated with participating in this research project, nor will you be paid. However your participation will help benefit future patients who require enoxaparin (Clexane) or dalteparin (Fragmin) therapy.

There are no significant restrictions on daily activity except for while the subcutaneous catheter is in (swimming and bathing restrictions to keep the catheter clean). Participants will need to attend the review visits, and be contactable by telephone. There will be no changes required in your diet or usual medications with this study.

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4 Other relevant information about the research project

We aim to include around 35 participants (20 receiving enoxaparin (Clexane) or dalteparin (Fragmin) to treat a clot, and 15 receiving enoxaparin (Clexane) or dalteparin (Fragmin) to prevent clots) managed through Monash Health. Participants referred from external health services will be managed through Monash Health for the duration of the study.

Enoxaparin (Clexane) and dalteparin (Fragmin) are anticoagulant drugs used to treat and/or prevent blood clots administered as an injection under the skin. The main side-effects of treatment include pain/bruising/bleeding and inflammation around the site of injection. Other side effects may include nausea, fever, and inflammation of the liver (detected on blood testing). The major risk of treatment is an increased risk of bleeding. If you experience any bleeding or require any procedures (surgeries, tooth extractions), or sustain any trauma (falls, motor vehicle accidents, hits to the head), it is important to seek medical attention urgently. Additional written information on other side effects can be provided on request.

5 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 alter change your mind, you are free to withdraw from the project at any time. 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, or to take part and then withdraw, will not affect your treatment, your relationship with those treating you, or with Monash Health.

6 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this Health Service. If you choose not to participate, you will receive the usual care by your treating doctors.

7 What are the possible benefits of taking part?

The purpose of this project is to see whether subcutaneous catheters are preferred by participants as compared to injections, therefore you may have access to a less painful and invasive method of treatment for a week during your participation. The main anticipated benefits of this research will be for future patients requiring therapy with enoxaparin (Clexane) or dalteparin (Fragmin) if this method reduces the number of injections required and does not compromise the effectiveness of treatment.

If you wish to continue using the subcutaneous catheter to administer enoxaparin (Clexane) or dalteparin (Fragmin), there will be an option to do so. You will need to see a doctor beforehand, who will review your history and blood tests results to ensure it is safe for you to continue using the subcutaneous catheter. You will be reviewed every 4 weeks with a blood test (around 5mL or 1 teaspoon) each time. You may choose to change back to subcutaneous injections at any time.

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

Having a blood sample taken may cause discomfort, bruising and bleeding. If this happens, it is easily treated. The subcutaneous catheter may also result in discomfort, bruising, bleeding, inflammation and infection at the site. If this becomes an issue, you may request for the catheter to be removed. You will be unable to swim while the subcutaneous catheter is in place, and it will need to be covered while bathing/showering which may cause some inconvenience. Additional hospital visits can cause inconvenience and may have associated costs (e.g. parking). We are able to provide medical certificates and carers' certificates to try to minimise any inconvenience, however, are unable to cover parking costs

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directly. The subcutaneous catheters (Insuflon) and dressings will be supplied by the Clinical Trials Centre at no cost to you. The enoxaparin (Clexane) or dalteparin (Fragmin) injections will need to be supplied by yourself (through your referring doctor) with the costs as listed on the Pharmaceutical Benefits Scheme (estimated $42.50 per box).

There is a small risk that using the subcutaneous catheter may lead to higher or lower levels of enoxaparin (Clexane) or dalteparin (Fragmin) exposure, however, this does not seem to be likely based on what we know about the medication, and what has been seen in practice so far. We will be monitoring participants closely both clinically, and by testing drug levels for this. If there is any concern about increased bleeding or risk of blood clots, this study will be discontinued. If you experience any significant side effects during the study, you will be referred and managed as appropriate through Monash Health. A list of persons to contact are supplied at the end of this form in the event of any potential adverse reactions.

Potential side effects:

Very common (>10% or 1 in 10)

1. Increase in liver enzymes (commonly mild and self-limiting)

Common (1-10%, 1 in 100 to 1 in 10)

1. Anaemia (low red blood cells)
2. Nausea
3. Diarrhoea
4. Fever
5. Swelling of the legs (peripheral oedema)
6. Low blood platelet count
7. Minor allergic reactions including itch, erythema
8. Injection site reactions (e.g. pain, bruising, minor bleeding at the injection site)
9. Confusion

Uncommon (<1%, less than 1 in 100)

1. Severe skin irritation at injection sites (rash, urticarial, pruritis)
2. Heparin induced thrombosis and thrombocytopenia (HITT)

Rare (<0.1%, less than 1 in 1000)

1. Severe injection site reactions (bullae, necrosis, alopecia)
2. Severe allergic reactions and anaphylaxis
3. Elevated blood potassium levels
4. Severe bleeding

Safety during pregnancy

Enoxaparin (Clexane) is the preferred blood thinning medication in pregnancy and while breastfeeding. It is classified as “class C”, meaning that there is no evidence in animal studies of harm to the baby. The decision to use enoxaparin (Clexane) is made on a case by case basis by your treating doctor.

Dalteparin (Fragmin) is an alternative medication to enoxaparin (Clexane) which is also classified as “class C” in pregnancy.

9 What will happen to my test samples?

Routine blood tests will be analysed at Monash Health. Research blood samples will be processed, frozen and stored at Monash Health, then analysed at a later date (not on the day of collection). These analyses

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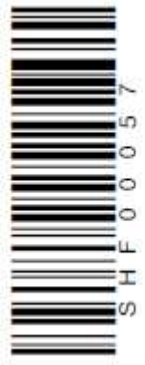
will not require any additional blood tests or study visits, and will not be used for genetic testing or commercial gain. Any future research will be reviewed and approved by a Human Research Ethics Committee. All stored specimens will be kept for at least 15 years following completion of this study.

10 What if new information arises during this research project?

Sometimes during the course of a research project, 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 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, they will explain the reasons and arrange for your regular health care to continue.

11 Can I have other treatments during this research project?



While you are participating in this research project, you will be able to take all of your usual medications and treatments. It is important to tell your study doctor and study staff of all treatments and medications you are taking, as well as any new ones, including over-the-counter medications, vitamins and supplements, herbal remedies, acupuncture or other alternative treatments. Use of any medications such as warfarin (Coumadin, Marevan), dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) is prohibited. Other regular medications including aspirin, clopidogrel (Plavix), ticagrelor (Brilinta), and Non-Steroidal Anti-inflammatory Drugs (e.g. neurofen, voltaren) may be used, however it is important you inform the research team of these medications first.

12 What if I withdraw from this research project?

If you decide to withdraw from this research project, please notify a member of the research team before you withdraw. A member of the research team will inform you if there are any special requirements withdrawing.

If you do withdraw your consent during the research project, the study doctor 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 investigators 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.

13 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/device being shown not to be effective
- The drug/treatment/device being shown to work and not need further testing

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14 What happens when the research project ends?

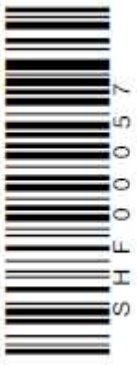
Once your involvement with the study is complete, you will continue to see your family doctor and haematology doctor if required.

If you choose to, you may contact the study team after the project has been completed and results have been published, to enquire about the study results and request a report of these results.

Part 2 How is the research project being conducted?

15 What will happen to information about me?

By signing the consent form, you consent to the study doctor and relevant study 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. Information will be stored by the Haematology Research Unit. Paper records will be stored in locked facilities (e.g. locked cabinets). Electronic records will be stored on password-protected computers, to be accessed only by study staff. Study participants will be assigned a unique alphanumeric code, such that their samples are information will be de-identified. 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. Data will be archived for at least 15 years following completion of the study and then confidentially destroyed (electronically or in confidential waste bins).



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 research team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection for the purpose of verifying the procedures and the data. This review may be done by the relevant authorities and authorised representatives of the investigators (the Monash Health Haematology Research Unit), the institution relevant to this Participation Information Sheet (Monash Health Human Research Ethics Committee), or as required by law. By signing the Consent Form, you authorise the release of, or access to, this confidential information to the relevant research personnel and regulatory authorities as listed above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission (e.g. de-identifying all participants).

Information about your participation in this research project may be recorded in your health records. In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

16 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

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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.

There are two avenues that may be available to you for seeking compensation if you suffer an injury as a result of your participation in this research project:

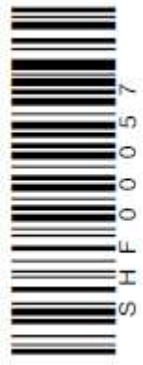
• The Clinical Trials Units and Monash Health

• You may be able to seek compensation through the courts.

17 Who is organising and funding the research

This research project is being conducted by Dr Sanjeev Chunilal and Dr Emma Leitinger of the Monash Health Haematology Research Unit. The Monash Health research department is providing funding to cover the costs associated with this project.

Monash Health may indirectly benefit financially from this research project if, for example, the project assists Monash Health obtain approval for new treatment or to secure grant funding for future research studies.



By taking part in this research project you agree that samples of your blood or tissue (or data generated from analysis of these materials) may be provided to Monash Health. Monash Health will not sell your samples for financial gain to any third parties.

You will not benefit financially from your involvement in this research project, even if your samples or knowledge acquired from analysis of your samples, prove to be of commercial value to Monash Health.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to Monash Health, the study doctors or their institutions, or Sanofi, there will be no financial benefit to you or your family.

No member of the research team will receive a personal financial benefit from your involvement in this research project (apart from their ordinary wages).

18 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 Monash Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018).* This statement has been developed to protect the interests of people who agree to participate in human research studies.

19 Further information and who to contact

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), you can contact any of the following people:

Trials coordinator contact (during office hours)

Name	Jacqueline Young
Position	Haematology Research Unit manager
Telephone	03 9594 4044

Clinical contact person (during office hours)

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Name	Dr Emma Leitinger
Position	Haematology Research Fellow
Telephone	03 9594 6666 (hospital switchboard)

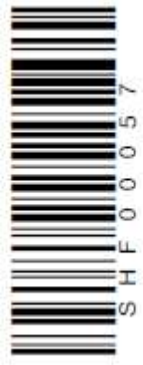
Clinical contact person (after hours and weekends)

Name	Clinical Haematology Registrar on call
Position	Monash Health Haematology registrar
Telephone	03 9594 6666 (hospital switchboard)

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

Name	Research Governance Manager
Position	Research Governance Manager
Telephone	03 9594 4611
Email	research@monashhealth.org



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	Monash Health Human Research Ethics Committee
HREC Executive Officer	HREC Executive Officer
Telephone	03 9594 4611
Email	research@monashhealth.org

Local HREC Office contact (Single Site -Research Governance Officer)

Name	Michael Kios
Position	Research Governance Manager
Telephone	03 9594 4611
Email	Michael.Kios@monashhealth.org

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Consent Form - *Adult providing own consent*

Title	The efficacy and acceptability of low molecular weight heparin administration via a subcutaneous catheter vs subcutaneous injections in both prophylactic and therapeutic settings
Short title	Butterfly
Protocol Number	4
Project Sponsor	Monash Health Haematology Research Unit
Principal Investigator	Dr Emma Leitinger
Associate Investigator(s)	A/Prof Sanjeev Chunilal, Dr Zane Kaplan
Location	*Monash Health*

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 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 project without affecting my future health care.

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

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

I consent to the samples being used in this research project ☐

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

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* 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 Study Doctor/Senior Researcher†

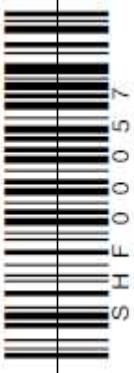
I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

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



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

Title	The efficacy and acceptability of low molecular weight heparin administration via a subcutaneous catheter vs subcutaneous injections in both prophylactic and therapeutic settings
Short title	Butterfly
Protocol Number	4
Project Sponsor	Monash Health Haematology Research Unit
Principal Investigator	Dr Emma Leitinger
Associate Investigator(s)	A/Prof Sanjeev Chunilal, Dr Zane Kaplan
Location	*Monash Health*

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 Monash Health.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

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.

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