LOLIPOP
Long-term Outcomes of Lidocaine Infusions for Post-Operative Pain

Participant Information Sheet/Consent Form

Title	The Long-term Outcomes of Lidocaine Infusions for Post-Operative Pain Trial
Short Title	LOLIPOP Trial
Project Sponsor	Monash University
Coordinating Principal Investigator	Professor Tomás Corcoran
HREC Reference	HREC/74777/Alfred-2021

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project as you will be undergoing breast cancer surgery. After this type of surgery, some people experience persistent pain that lasts for 3 months or more. This research project is testing whether a new treatment can reduce the number of people experiencing persistent pain one year after breast cancer surgery. The new treatment involves an infusion (or steady dose administration) of lidocaine (a commonly used local anaesthetic drug) into your body for a period of up to 24 hours after surgery.

This Participant Information Sheet and 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?

After breast cancer surgery almost 50% of women will continue to have some degree of persistent or chronic pain which can last for a year or more. This pain can be mild, but up to a quarter of patients may have moderate or severe pain. We are interested in finding out if there are medications that can be given around the time of surgery to prevent the development or reduce the severity of chronic pain.

Lidocaine infusions have already been tested in a few small studies of patients undergoing breast cancer surgery. The LOLIPOP Trial team have completed a study themselves looking at lidocaine infusions in 150 patients undergoing breast cancer surgery in three hospitals in Western Australia. The results have shown that the methods are safe but a larger international trial is required to provide a clear answer if lidocaine is effective in preventing chronic pain.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Lidocaine is approved in Australia as a local anaesthetic drug, but it is not approved to prevent pain after breast cancer surgery. It is therefore an experimental treatment in this study and must be tested to see if it is an effective treatment.

This research has been initiated by the study doctor, Professor Tomás Corcoran and has received $4.3 million AUD in funding from the Medical Research Future Fund (MRFF) in Australia. The trial has also received £1.8 million GBP funding from the National Institute for Health and Care Research in the United Kingdom.

This research is being conducted by the Australian and New Zealand College of Anaesthetists (ANZCA) Clinical Trials Network (CTN), Monash University and Royal Perth Hospital. Monash University is the sponsor of this trial, with overall responsibility for it.

3 What does participation in this research involve?

If you agree to participate in this project, you will be participating in a randomised controlled research project. 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, much like a coin toss).

If you join this study, you will be randomly assigned to either receive:

- lidocaine during surgery and up to 24 hours afterwards ***OR***
- placebo (inactive saltwater solution with no drug) during surgery and up to 24 hours afterwards

A placebo is a medication with no active ingredients. It looks like the real thing but is not. You would have a 1 in 2 (50%) chance of receiving lidocaine, and a 1 in 2 (50%) chance of receiving the placebo.

The way you receive the lidocaine infusion will be slightly different, depending on how long you will be staying in hospital after your surgery. Some patients may stay in hospital for the day of surgery and not stay overnight (Day-case), while other patients may stay in hospital overnight (Overnight stay). The infusion will be administered into your veins from the start of your general anaesthetic until you arrive in the recovery area. If you are a day-case your infusion will continue until you are discharged from the recovery area. If you are staying overnight after your surgery at this point the infusion will be continued via a small plastic tube (cannula) placed under the skin of your stomach for up to 24 hours after your surgery (or earlier if you are ready for discharge). This infusion will be controlled by a small pump that

can be placed in a small pouch and worn over your shoulder. Your mobility will not be restricted.

You will be participating in a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving.

Before surgery the research team will review your medical record and you will be asked some questions about your health using brief questionnaires related to your quality of life and if you are experiencing any pain. We will also ask you for your contact details (name, mobile number and email address) so that we can follow you up at 3 months and 1 year after surgery. This will take about 10 minutes. We will review your medical history; ask you about any medications you are taking or may have taken, and ask about your ethnicity. Your height and weight will also be measured as per routine care. Information about your surgery such as start and stop time and any medication you are given will also be collected.

We will also ask you some questions when you are in the postoperative recovery area and on the first day after your surgery (if you are still in hospital). These will include questions about any pain that you may be experiencing and any medications that you may be receiving after your surgery. During the lidocaine or placebo infusion you will also be asked some Yes/No style questions at four hourly intervals to assess whether you are experiencing any side-effects from your study treatment. Routine observations (pulse rate, blood pressure, temperature and oxygen levels) are always taken every four hours in the early period after surgery, and so we will ask the side-effect questions at the same time.

Following your discharge from hospital you will be followed up with a telephone call at 3 months and 1 year after your surgery. We will ask whether you are experiencing any pain, taking any medications, and if you have required further surgery or admissions to hospital. We will also ask you which way you would prefer to complete research surveys like this in the future, via telephone or by using an online survey.

After 1 year, your involvement in the study will be over although the research staff will still be available to answer your questions should you have any.

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

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.
It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

Within the main study there are optional components known as “substudies” that you can choose to participate in. You will be asked to indicate your preference on the Consent Form at the end of this document:

Optional electronic Patient Reported Outcome Measures (ePROMs) Substudy:
What are ePROMs?
Electronic Patient Reported Outcome Measures (ePROMs) are electronic questionnaires that help patients report on outcomes relating to their health. Rather than a member of the research team phoning the patient to ask them questions about their current health, the patient would complete the questionnaire online by themselves. A patient would normally be

sent the questionnaire electronically several times over the life of the study so comparisons could be made about their current health at different timepoints.

What is the ePROMs substudy?
We want to find out if using ePROMs is an easier way to collect health information from patients and also if patients prefer to be followed up via phone or by an electronic survey in the hope of including additional ways for patients to be involved in research for future studies. If you consent to take part in this substudy, we would ask you to complete the 1 year follow up via telephone by a member of the research team. We would also ask you to complete a small subset of the same questions which should take no longer than five minutes to complete via an online survey. A link to the Patient Reported Measures System (PRMS) would be sent to you via SMS or email to complete the survey online.

Why are we collecting the same information from you twice for the 1 year follow up?
We are collecting the same information from you twice to see if using an online system is as reliable and collects the same information as talking to a member of the research team on the phone. We understand that you may answer these same questions differently and that is completely fine.

What personal information will you need to collect from me?
Your name and phone number would normally be collected from you as part of clinical research so that the research team at the hospital you had your surgery can contact you to ask follow up questions. This data would be kept secure locally by the research team. As part of the ePROMS substudy we are recording identifiable information in the PRMS so that you can be contacted through this system. Your name, date of birth, email address and telephone number will be collected and stored in the PRMS database which is separate to the health related coded data that is held in the Clinical Trial Management System CTMS (or study database). The PRMS needs to store your identifiable information so that the system can contact you to complete the online follow up survey at 1 year. The PRMS system will hold your identifiable information, and this information will only be accessible by the research team at the site where you had your surgery, as well as the Research Path PTY Ltd team who manage the PRMS. The research team at the site you had your surgery at will not be able to view your answers in the PRMS system, and this is why they will also phone you, but they will be able to view if you have received and completed the survey electronically. The LOLIPOP trial management team will not have access to your identifying information, or the PRMS system.

Who are Research Path Pty Ltd and what is their involvement in the trial?
Research Path Pty Ltd is the commercial company that provides the LOLIPOP Trial with a Clinical Trial Management System (CTMS) and the Patient Reported Measures System (PRMS). The team are experts in data management. The CTMS they provide assists the LOLIPOP Trial team with the randomisation of patients and management of the data and patient follow up and management of the clinical trial drug. The Research Path team are paid for their services for the CTMS. The Research Path team have developed the PRMS which is a new system that allows patients to electronically report their clinical trial outcomes. They are providing the LOLIPOP trial team with the use of their system for free to generate more research on the use of their new system in clinical trials with the aim to provide further knowledge in this area and to publish this research together.

Optional Genetic Biobank Substudy:
If you consent to take part in this substudy, you will be asked to provide an additional blood sample (one tablespoon) that would be taken before your operation. This would be taken from the intravenous line at the time of insertion, during the preparation for anaesthesia, and then stored in a study specific biobank. Your blood sample will be used for genetic research

at the end of the study to examine multiple genes that are associated with lidocaine and pain.

Genes are made of DNA – the chemical structure carrying your genetic information that determines many human characteristics such as the colour of your eyes or hair. Researchers study genes in order to understand why some people have a certain condition and why some people do not. Understanding a person's genes also may be able to explain why some people respond to a treatment, while others do not, or why some people experience a side effect and others do not.

"Banking" is storing health information and/or blood or tissue for future research studies. A "bank" is the place where the health information and or/blood or tissue is stored.

Where will my samples be stored and how will my privacy be protected?
If you agree to participate in this substudy, we would like to store your blood for use at the end of this study. Your sample will be stored as part of the LOLIPOP Trial Biobank, which will be located at Monash University and will be overseen by Professor Tomás Corcoran and Professor Paul Myles, as an anonymised sample. This means the sample will only be identified by a specific study number that your data will be given at the outset of the study, that is stored against your data and not your personal details. The sample can be re-identified as yours even though the biobank does not know your identity.

You can have your sample removed, destroyed or returned to you by contacting the study doctor, Professor Tomás Corcoran, in writing at the Royal Perth Hospital, Dept of Anaesthesia and Pain Medicine, Wellington St, Perth 6000.

What are the possible benefits from participating in the Genetic Biobank Substudy?
The results of this research project will not provide you with any direct benefit. However, other people might benefit if researchers learn more about how genes are associated with lidocaine and pain.

You will not be given any research results from participation in this Optional Genetic Biobank Substudy.

What are the possible risks and discomforts from being in this Optional Genetic Biobank Substudy?
In general there are minimal risks and discomforts of being involved in the Optional Genetic Biobank Substudy. As a blood sample is taken occasionally there may be some small pain or discomfort, and a small bruise may form. Where possible the blood will be taken from a dedicated study cannula (that is inserted during your surgery) and will involve no further needle insertions. There is no extra physical risk to you as part of the research.

You will not be given any research results of the genetic testing from the optional genetic biobank substudy; therefore you will not be informed if you have an increased risk of developing disease or disorders related to lidocaine and pain.

Genetic research involves the study of genetic material (typically DNA) that is shared with your blood relatives. Genetic research is undertaken for many reasons, including discovering more accurate ways of predicting disease within a group of people, or in people where there is strong family history or predisposition of disease.

Will there be future research using my information and samples?
If you agree to participate in this optional substudy, we may continue to use your data and samples for future research related to this substudy unless you withdraw from the study. We

will not use your personal health information for a different research project without the permission of a Human Research Ethics Committee. Once all personal identification is removed, the information might be used or released for other purposes without asking you. Results of the research project may be presented in public talks or written articles but information will not be presented that identifies you.

Optional Drug Concentration Substudy:
If you consent to take part in the drug concentration substudy, we will take up to two additional blood samples (approximately a tablespoon each), one from 6-12 hours after the start of the study drug and another between 12-24 hours from the start of the study drug. Where possible these will be taken from a dedicated study cannula (that is inserted during your surgery) and will involve no further needle insertions.

These blood samples are taken for researchers to look at the concentrations of lidocaine in the bloodstream to make sure it is at a suitable level.

The blood samples will be anonymised. This means the sample will only be identified by a specific study number that you will be given at the outset of the study that is stored against your data and not your personal details. The samples will also be frozen, stored and analysed by a laboratory. At the end of the study, any remaining frozen samples will be destroyed.

4 What do I have to do?

If you are staying overnight after your surgery, you will be required to wear a mobile syringe pump placed in a small pouch and carried over your shoulder for up to 24 hours after your surgery, which will deliver the study drug via the cannula placed just under the skin in your stomach (this is the cannula that was inserted during your surgery).

5 Other relevant information about the research project

The LOLIPOP Trial is a large international study of 4300 patients from hospitals around Australia, New Zealand, Hong Kong and the United Kingdom.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with your institution.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. As lidocaine infusions are not currently part of routine practice it is unlikely you will be offered this option by your anaesthetist. There are no treatments currently proven to reduce the development of chronic pain after breast surgery.

8 What are the possible benefits of taking part?

We cannot guarantee that you will receive any benefits from this research. However, possible benefits may include a reduction in acute (early and usually temporary) and chronic (late and sometimes persistent) pain after surgery and a reduction in side effects relating to the use of strong painkillers. It is also possible that lidocaine infusions could lead to a better quality of recovery. As a result of the follow up process, all patients may benefit from research team members and clinical staff paying closer attention to detail during the recovery period, especially as both the research team and/or clinical staff will be asking you questions every four hours while the study drug infusion is running to ensure no side-effects are developing.

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

Medical treatments 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. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Lidocaine infusions are given under the skin, close to nerves and into veins in everyday anaesthesia practice.

In previous clinical trials targeting the reduction of acute pain only, lidocaine infusions into veins for up to 24 hours after surgery have been extensively investigated in over 2,500 patients. Although side-effects have not always been specifically collected, very few significant problems have been reported with such infusions.

However, if lidocaine reaches a high enough concentration in the blood it can cause the following side-effects:

<u>Common Side Effects (in more than 1% of (1 in 100) patients)</u>
Tingling or numbness (most often experienced around the mouth)
Ringing in the ears
Mild changes in your vision
Dizziness
Strange taste in the mouth

<u>Rare Side Effects (in less than 1% of (less than 1 in 100) patients)</u>
Feeling faint
Twitching in the muscles
Confusion
Short Seizures
Abnormal Heart Rhythms
Unconsciousness

We have designed the dose of the lidocaine infusions in this study to make it very unlikely that such side-effects will occur. In addition, a member of the research team or nurse will check with you every 4 hours while the study drug infusion is running to ensure no side-effects are developing. In the unlikely event that they do occur, the infusion will be stopped, and you will be closely monitored while the levels of lidocaine in your bloodstream fall over 1-2 hours. There is also a drug called Intralipid which can be used to reverse some of the side effects of lidocaine. This drug will be available on the ward and will be given to you if the medical staff feel that it is required.

Having a drug injected or blood sample taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

10 What will happen to my test samples?

There are no extra samples taken as part of this study, unless you decide to take part in the optional substudies. However, some of the results of your routine clinical tests may be viewed by the research team.

Optional Genetic Biobank Substudy:
Your sample will be stored as part of the LOLIPOP Trial Biobank, which will be located at Monash University and will be overseen by Professor Tomás Corcoran and Professor Paul Myles, and will be labelled as a re-identifiable sample. This means the sample will only be identified by a specific study number that your data will be given at the outset of the study, that is stored against your data and not your personal details. The sample can be re-identified as yours even though the biobank does not know your identity. The sample will be kept for at least 15 years once the last participant has been recruited.

Optional Drug Concentration Substudy:
The blood samples will be frozen and stored at your site until they will be sent to a central laboratory at Pathology Queensland to be analysed at the end of the study. The blood samples will be anonymised. This means the sample will only be identified by a specific study number that you will be given at the outset of the study that is stored against your data and not your personal details. At the end of the study, any remaining frozen samples will be destroyed.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment 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, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Yes. This project has very few restrictions relating to other treatments. If any of these restrictions apply they will be explained by your study doctor.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study 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 sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• The drug being shown to cause unacceptable side effects
• The drug being shown to work and not need further testing

15 What happens when the research project ends?

The results of the study will be published in a medical journal with international readership. These studies will be available to mainstream media who may wish to report them. A plain language summary will be available to study participants on request, by contacting the study team.

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. Any information obtained in connection with this research project that can identify you will remain confidential.

All of the data collected will be coded with an id number. This means that anybody looking at the data will be unable to work out that it has come from you. At the outset of the study you will be assigned a specific study number which will be stored against your data in the online database and any paper copies of your data at the local site. When looking at the database or paper copies of the data, nobody will be able to identify that the specific study number is you thus maintaining your confidentiality. The data will be stored in a password protected online database which can only be accessed by research staff, including those at your site, and at Monash University and the lead trial site Royal Perth Hospital. The data will be kept for at least 15 years once the last participant has been recruited. 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.

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.

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) by the relevant authorities and authorised representatives of the Sponsor, Monash University, the institution relevant to this Participant Information Sheet, the Human Research Ethics Committee that reviewed this project, the Therapeutic Goods Administration (TGA), or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted 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.

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

In accordance with relevant Australian and/or your state/territory 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 which you disagree with will be corrected. Please contact the study 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, and any future research, 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.

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.

No provisions have been made in this trial to offer patients who suffer an adverse event financial compensation, but the absence of such a provision does not remove your rights to seek compensation under common law.

18 Who is organising and funding the research?

This research project is being led by Professor Tomás Corcoran, Royal Perth Hospital and is being funded by the Medical Research Future Fund in Australia. The project is being funded by the National Institute for Health and Care Research in the United Kingdom. Study costs will be covered locally with no external sources of funding or influence.

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 Alfred Health – the Alfred Hospital Ethics Committee.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research 2007 (updated 2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you would like any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor Professor Tomás Corcoran, on +61 0438 931 818.

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 name	Alfred Hospital Ethics Committee
Position	HREC Executive Officer
Telephone	03 9076 3619
Email	research@alfred.org.au

Reviewing HREC approving this research and HREC Executive Officer details