Participant Information Sheet/Consent Form – Parent/Guardian

Interventional Study - *Parent/Guardian consenting on behalf of participant*

Joondalup Health Campus

Title	*A Randomised controlled trial: Effect of probiotics on gut microbiome and vaccine responses in newborns with antibiotic-induced dysbiosis*
Short Title	ADAPTS: Antibiotic Dysbiosis and Probiotics Trial in infantS
Protocol Number	*Protocol Version 3.0*
Project Sponsor	*Joondalup Health Campus*
Coordinating Principal Investigator	*Dr Jason Tan and Dr Ravisha Srinivas Jois*
Location	*Joondalup Health Campus*

Part 1 What does the child's participation involve?

1 Introduction

This is an invitation for your baby to take part in this research project because they have needed antibiotics early in their life. The research project is testing to see if probiotics can improve the health of babies that have received antibiotics.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want your baby 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.

Participation in this research is voluntary. If you do not wish your baby to take part, they do not have to. Your baby will receive the best possible care whether or not they take part.

If you decide you want your baby 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 your baby taking part in the research project

• Consent for your baby to have the tests and treatments that are described

• Consent to the use of your baby's 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?

Antibiotics are one of the most prescribed medicines in newborn infants. Exposure to antibiotics early in life causes changes to the normal gut bacteria (microflora). This may increase the risk of childhood problems such as allergic disease, asthma and obesity. Some studies have suggested that antibiotic exposure may reduce the response to routine childhood vaccines.

Probiotics contain one or more 'friendly' bacteria that are usually part of the healthy microbial community that live inside of us. Probiotics have been used widely in Australia for adults to improve their gut microflora. Probiotics have been used to reduce the risk of serious gut infections in preterm infants, but they are not routinely used to improve the health of full-term infants, particularly those that have received antibiotics. This means that we must first test the use of probiotics in this way to see if it is an effective and safe treatment in term infants that have received antibiotics.

This study will be one of the first studies to look at using probiotics in newborn infants that have received antibiotics. The probiotic we will be testing is called Labinic™; it is a combination of three different friendly bacteria that has been used safely around the world with no reported safety issues. This novel study aims to:

1. See if probiotics can restore the changes in the gut flora because of antibiotic use,
2. See if this will help improve the response to routine childhood vaccines, and
3. See if probiotics might help to reduce gut problems such as colic.

The study doctors leading this study are Dr Jason Tan and Dr Ravisha Srinivas Jois.

3 What does participation in this research involve?

Your infant will be participating in a double-blind randomised controlled study. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put infants into groups and give each group a different treatment. The results are compared to see if one is better.

This study will be looking at term infants less than a week old who are receiving antibiotics from the neonatal unit at Joondalup Health Campus. Infants will be excluded if there is a suspected or known immune deficiency, or if parents have chosen to exclusively formula feed.

To see if the probiotics are effective in restoring the good bacteria in the gut, we will test your infant's stool to find out the different types and amounts of bacteria. We will collect your infant's stool just after stopping antibiotics and prior to starting probiotics (baseline), then again at 4-6 weeks, 6-8 months and 12 months. Your baby will be reviewed by the medical team at 4-6 weeks and 6-8 months and 12 months to collect stool and blood samples.

To see if probiotics can improve vaccine responses, a blood test will be taken just before you and your baby go home and a second blood test at 8 months. We will take approximately ½ a teaspoon of blood (2 mL) each time. This blood sample will be used to measure the degree of immune response your baby has to the vaccines.

We will ask you to complete questionnaires at around 1 month, 3 months and 6 months to ask about diet, use of medications, whether you're infant has needed any further antibiotics and about common issues such as colic and vomiting/reflux.

The total study time from start to the last blood and stool sample will be about 12 months.

Infants will be divided into two groups: one will receive a probiotic and the other will receive a placebo. A placebo is a medication with no active ingredients; it looks like the real thing but is not.

To try to make sure the groups are the same, each participant is put into a group by chance (random). Your infant will have an equal chance of being placed in the probiotic group or placebo group.

This study will be a double-blind study. This means that you will not know which of the treatments your baby is receiving and neither will the study doctor. However, in certain circumstances the study doctor can find out which treatment your infant is receiving. To ensure proper blinding, both placebo and probiotic will be mixed with oil and kept in the same type of container. The trial pharmacist will randomise and supply the trial intervention.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to false conclusions.

There are no additional costs associated with participation in this research project, nor will you or the participant be paid. All medication, tests and medical care required as part of the research project will be provided to free-of-charge.

It is desirable that the child's local doctor be advised of your decision for the child to participate in this research project. If the child has a local doctor, we recommend that you inform them of the child's participation in this research project at your next visit.

4 What does the child have to do?

Your child will be given the investigational product (probiotic) regularly (once daily) for four weeks, they will need to receive their routine childhood immunisations; and they are not given any over the counter probiotics.

We will try to contact you by phone to complete the questionnaires at 1, 3 and 6 months. During these conversations we will ask about your baby's health, well-being and whether they have received any medications.

5 Other relevant information about the research project

This study will try to recruit approximately 70 infants born at Joondalup Health Campus. It has been funded by the Ramsay research foundation.

6 Does the child have to take part in this research project?

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

If you do decide that the child can 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 that the child can or cannot take part, or that they can take part and then be withdrawn, will not affect their routine treatment, relationship with those treating them, or their relationship with Joondalup health campus.

7 What are the alternatives to participation?

Your baby does not have to take part in this research project to receive treatment at this hospital. At present it is not clear whether or not we should provide probiotics to infants that have received intravenous antibiotics, so we do not routinely provide probiotics to term infants.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that the child will receive any benefits from this research; however, possible benefits of probiotics may include reduced intestinal problems, reduced colic and gastro-oesophageal reflux and improved vaccine effectiveness. This study will help us to understand the benefits of probiotics and will guide future research.

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

Medical treatments often cause side effects, although probiotics are usually very well tolerated and are unlikely to have side-effects. The participant may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If your baby has any of these side effects, or you are worried about them, talk with the study doctor. The study doctor will also be looking out for side effects.

Probiotics are a dietary supplement containing live bacteria that are usually found in the gut. They are used commonly in the preterm babies born more than 10 weeks early and are well tolerated. Some mild side effects include abdominal discomfort, vomiting and loose stools. A rare but serious possible side effect is a blood stream infection. This has been seen generally in preterm infants.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell the study doctor immediately about any new or unusual symptoms that the participant gets. 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, the study doctor may need to stop the child's treatment. The child's study doctor will discuss the best way of managing any side effects with you.

10 What will happen to the child's test samples?

The test samples that have been taken from your baby (blood and stool) will be transferred and stored securely at Joondalup Health Campus. The blood and stool samples will be primarily used and analysed for this study. The ORIGINS Project group at Joondalup Health Campus may request the results for use in the future. All the samples taken will be re-identifiable (coded). This means that the stored samples will have a unique code but no names or dates of birth. If needed we can link that code to you or your infant in case we have to inform you of an abnormal result.

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, the study doctor will tell you about it and discuss with you whether you want the participant to continue in the research project. If you decide to withdraw your baby from the study, their study doctor will make arrangements for their

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, the study doctor might consider it to be in the participant's best interests to withdraw them from the research project. If this happens, the doctor will explain the reasons and arrange for the participant's regular health care to continue.

12 Can the child have other treatments during this research project?

It is important to tell the study doctor and the study staff about any treatments or medications the participant may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the study doctor about any changes to these during the child's participation in the research project. If your baby is part of this trial, we would recommend that they do not receive other over the counter probiotics.

13 What if I withdraw the child from this research project?

If you decide to withdraw from the project, please notify a member of the research team of your wishes.

If you do withdraw the participant during the research project, the study doctor and relevant study staff will not collect additional personal information, 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 of withdrawal will usually form part of the research project results. If you do not want them to do this, you must tell them before the participant joins 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:

• Unacceptable side effects

• The treatment being shown not to be effective

• The treatment being shown to work and not need further testing

15 What happens when the research project ends?

Once the research project ends you will receive a letter to update you of the results of the trial. If the research team find any abnormal blood results, you will be informed and appropriate follow-up will be arranged.

16 Linkage with The ORIGINS Project?

The ORIGINS Project is another cohort study that is currently being run at Joondalup Health Campus. Your child may be eligible to be enrolled in both studies at the same time and will be informed of both studies. You may decide to enrol you child in one, both or neither of these studies.

There is an overlap of data that would be collected by both studies. If you are already enrolled in The ORIGINS Project or you decide to be part of both studies then we would like to share data between the two studies. All information and/or samples that is shared will remain confidential. They will only be used for health-related research that has received ethical approval from the Joondalup Health Campus Human Research Ethics Committee.

If you decide not to enrol you child into ORIGINS then no information or samples will be shared between the two studies.

Part 2 How is the research project being conducted?

16 What will happen to information about the child?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about the child for the research project. Any information obtained in connection with this research project that can identify the child will remain confidential. All electronic information that is stored will not contain your baby's name or date of birth. Your baby's 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 child may be obtained from their health records held at this 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 the child's participation in this research project.

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 the child cannot be identified, except with your permission.

Information about the child's participation in this research project may be recorded in their health records.

17 Complaints and Compensation

If the participant suffers 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 for the participant. If the participant is eligible for Medicare they can receive any medical treatment required to treat the injury or complication free of charge as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

Dr Jason Tan and Dr Ravisha Srinivas Jois, are consultant paediatricians at Joondalup Health Campus, and are conducting this research project. No member of the research team will receive a personal financial benefit from the child's involvement in this research project (other

than their ordinary wages). The research project is funded by the Ramsay Research Foundation.

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

The ethical aspects of this study have been approved by the Ramsay Health Care WA | SA Human Research Ethics Committee (RHC WA | SA HREC). If you have any complaints or reservations about any ethical aspect of your participation in a research project, please contact the Consumer Liaison Office at Joondalup Health Campus on (08) 9400-9404 who will direct your complaint to the most appropriate person. Any complaint you make will be investigated by an independent party, treated in confidence, and you will be informed of the outcome.

20 Further information and who to contact

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

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

Clinical contact person

Name	*Dr Jason Tan, Dr Ravisha Srinivas Jois or Elayne Downie*
Position	*Drs / NNU Research Nurse Co-Ordinator (Clinical Nurse)*
Telephone	*9400 9312 / 94083118*
Email	*tanj@ramsayhealth.com.au or srinivasjoisr@ramsayhealth.com.au or elayne.downie@telethonkids.org.au*

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

Complaints contact person

Name	*Jason Tan or Ravisha Srinivas Jois*
Position	*Drs*
Telephone	*9400 9312*
Email	*tanj@ramsayhealth.com.au or srinivasjoisr@ramsayhealth.com.au*

The ethical aspects of this study have been approved by the Joondalup Health Campus Human Research Ethics Committee. If you have any complaints or reservations about any ethical aspect of your participation in a research project, please contact JHC Executive Office on (08) 9400 9404. Any complaint you make will be investigated by an independent party, treated in confidence, and you will be informed of the outcome.