

**Participant Information Sheet and Consent Form**

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| **Title** | *PRE-assessment for the randomised Trial of URsodeoxycholic acid versus RIFampicin in severe early onset Intrahepatic Cholestasis of pregnancy: the PRE-TURRIFIC study* |
| **Short Title** | *PRE-TURRIFIC* |
| **Lay Title** | *Identifying potential participants with baseline studies for the Trial comparing URsodeoxycholic acid with RIFampicin in severe early onset Intrahepatic Cholestasis of pregnancy: the PRE-TURRIFIC study* |
| **Project Sponsor** | The University of Adelaide |
| **Principal Investigator** | Professor Bill Hague |
| **Associate Investigator(s)** | Professor Maria FullerStudy Coordinator: Suzette Coat |
| **Location**  | Women’s and Children’s Hospital, Adelaide |

**“PRE-TURRIFIC”**

**Part 1 What does my participation involve?**

1. **Introduction**

You are invited to take part in this research project. This is because you have had Intrahepatic Cholestasis of Pregnancy (ICP) in a previous pregnancy. We wish to identify women at high risk of ICP because of having previously experienced the disorder, and to perform tests that might help us to understand how ICP develops.

This Participant Information Sheet/Consent Form tells you about the research project PRE-TURRIFIC. It explains the tests 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 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 (PICF) to keep.

**2 What is the purpose of this research?**

Intrahepatic cholestasis of pregnancy (ICP), an uncommon disease of pregnancy that occurs in 6-7 per thousand Australian pregnant women, is associated with stillbirth, preterm birth and medical problems in newborn babies. The best way to treat and manage women who are diagnosed with this condition is not known. Evidence from carefully designed clinical trials is urgently needed. We also need to understand better what causes the disease, what changes happen and when, in women with ICP. We need to know if there are biochemical and other changes that occur before the onset of itch, which is the main symptom that accompanies the rise in bile acids in the blood, which help to establish the diagnosis. The current study represents a unique opportunity to establish evidence that will help to inform doctors and healthcare professionals around the world caring for women with ICP. We have assembled an international team of clinical researchers to investigate which treatment is the most effective.

Studies at this and other hospitals have shown that 70% of women who experience ICP will develop the condition again in a subsequent pregnancy. It also runs very strongly, but not 100%, in families, with genetic contributions that are not yet well established.

There have been some recent advances in knowledge about how better to diagnose and monitor ICP, using tests that are not yet standard practice. These include measurements of compounds in the blood, including progesterone metabolites and autotaxin, which may help to differentiate ICP from the common itching found in normal pregnancy (“pruritus gravidarum”), and which may be reduced by treatment.

The usual role of bile acids is to help in the uptake of fat in the diet from the small bowel. Bile acids in the blood are excreted into the urine and stools, and can be measured as bile acid metabolites, which may reflect the degree of ICP better than the amount of bile acids in the blood.

Women with ICP may have reduced fat uptake, which may also be altered by the bacteria and other micro-organisms in the bowel (the gut “microbiome”). Treatments, such as antibiotics, may also impact on the presence of micro-organisms in the bowel of both the mother and the newborn baby. We wish to measure the relationships between the amounts of bile acids in the blood, the amount of fat in the stools, and the proportions of micro-organisms in stool samples from women at risk of ICP prior to their developing symptoms and, in those women who develop ICP again, also after they have been diagnosed.

Our colleagues in the UK and Sweden have also established that pregnant women with established ICP have differences in the composition of the bacteria in their gut (the gut microbiome). But it is not known when these changes happen or why. We also know that a few women presenting with ICP improve without treatment. This may sometimes be because of an unrecognised transient viral or autoimmune disorder.

People with the genetic disorder cystic fibrosis, that particularly affects the lungs, may have worsening of symptoms that are associated primarily with intermittent viral infections, rather than with bacterial infections as thought in the past. It is possible that viral infections could worsen the symptoms of ICP as well. We wish to test if viral infections might underlie any of the presentations in pregnancy with ICP-associated itching. So, we would like to look for evidence of viral genetic material and associated inflammatory markers in your blood, both before and after the development of any symptoms.

This study is designed to assess the status of the microbiome and its associated biochemistry, in pre-symptomatic pregnant women at their initial antenatal assessment together with a baseline assessment of their viral status, with which to compare subsequent changes in pregnancy, with and without symptoms.

**3 What does participation in this research involve?**

You will be eligible for this study if you have a viable pregnancy of 12 or more weeks gestation and have previously had ICP.

You will be participating in an observational study. We wish to collect samples of your blood, urine and stool, when you first present in pregnancy, when you attend after the morphology scan at approximately 20 weeks, then later at the time of your 28-week glucose tolerance test, at 36 weeks when you come for a routine check or earlier if you develop symptoms in the meantime, and finally at around 6 weeks after the delivery of your baby.

If you agree to take part, you will be asked to collect urine and stool samples and to have blood drawn (usually at a time when routine tests are being performed), both at the first pregnancy visit, at two subsequent pregnancy visits and at a final visit after pregnancy. Please see the bottom of page 8 for a cartoon depiction of study visits and samples.

The blood samples will be collected by trained staff in a pathology collection centre. The stool samples can be collected by you at home immediately before your visit, while the urine samples can be collected while you are at the hospital for your visit.

Should you develop ICP at any stage, you will be offered standard treatment. If you develop ICP early (before 34 weeks) and have blood bile acid numbers that would define you as having severe disease (at least 40 µmol/L off treatment), you will be eligible for the TURRIFIC trial, a randomised trial of rifampicin, a drug commonly used to treat infections, such as tuberculosis (TB) against the standard treatment, ursodeoxycholic acid (UDCA).

You will not be able to take part in the PRE-TURRIFIC study if:

* You have an active Hepatitis A or Hepatitis B infection, or are a Hepatitis B or C carrier
* You are known to have α-1-antitrypsin deficiency, autoimmune hepatitis, or other known active liver disorder
* You are already taking medication that can cause changes in your liver tests

If you agree to take part, you will be invited to attend an appointment of approximately one hour duration at the Women’s and Children’s Hospital. At this appointment we will:

* Discuss the study and any questions you have about it.
* If you are willing to participate, ask you to sign the consent form. No study assessments will be conducted before you have signed the consent form.
* Collect “baseline data”: we will collect some basic demographic information about you, such as your age and where you live, and ask questions about your health and pregnancy history, including how bad any itch has been in the last 24 hours.
* Invite you to collect the baseline bio-samples for the study (blood, urine and stool). Where possible, we will arrange to collect these on the same day as any routine blood tests are being collected.
* Invite you to complete a brief dietary questionnaire, which will give us an insight into the nutrients you consume in your diet.

We will also ask about the health of your family members. We will enter information about you into our study database where your information will be identified with only a unique study number, not your name.

**Subsequent study visits:**

At approximately 20 weeks when you attend to review the morphology scan, at 28 weeks gestation, around the time of your standard glucose tolerance test, and at 36 weeks, you will be invited to collect the extra bio-samples for the study. Where possible, we will arrange to collect these on the same day as your glucose tolerance test visit or when other clinical samples are being collected. At each visit we will:

* Discuss the study and any questions you have about it.
* Ask you to indicate if you have had any itch in the last 24 hours.
* Record your routine blood test results for glucose tolerance and blood count, together with measurements of bile acids, and liver chemistry tests.
* Ask you about any illnesses you have had since we last saw you, and any medication you may have been prescribed in the meantime.

Should you develop symptoms at any stage, we will liaise with the clinical team looking after you and discuss with you the various possibilities of standard or trial treatments as appropriate.

Additionally, we will also be recording whether you develop complications, such as gestational diabetes, and how they are being treated.

At birth, with your consent, we will examine the placenta, as is usually done at this hospital for women with ICP, using a standardised procedure to report on its apparent health. We will also collect a very small sample, a “slide”, to be examined by a Placental Pathologist at the Women’s and Children’s Hospital, to examine the micro-structure of the sample, which, if there are any problems experienced by the baby, will help to interpret them.

At birth, we will also ask for a swab from inside your baby’s cheek and for samples of amniotic fluid, of cord blood and of the baby’s meconium to be collected, and for further stool samples and cheek swabs to be collected from the baby at one week and six weeks after birth.

After your baby is born, we will collect information about your health and your baby’s health at birth from the hospital medical record. This will ensure that all appropriate factors that might impact on the outcome of your pregnancy can be reviewed and taken into account.

You will be asked to return for a follow-up visit at 6-8 weeks after the birth of your baby to collect a further set of samples, if possible and appropriate at the same time as any routine bloods, such as a repeat glucose tolerance test. We will provide any initial results from the study that are available. We will write to you with a summary of results, once the study has been completed, and offer an appointment for a face-to-face discussion of the outcome. This may not be for a year or more after the completion of your pregnancy.

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

You may be reimbursed for any reasonable travel, parking, meals and other expenses associated with a research project visit not associated with your standard care.

If you decide to participate in this research project, with your permission the study doctor will inform your local doctor. With your permission also, information about your condition will be provided to your local doctor at the end of the pregnancy, and advice given about management in any future pregnancy, should this occur.

**4 What do I have to do?**

If you agree to participate in the study, we will need to have an appointment with you. At this appointment, we will go through the study information and procedures with you. If, after answering any questions you may have about the study, you are willing to participate, we will ask you to sign the consent form. After the consent form is signed, we will ask you questions to enable us to enter you into the study. We will also organise subsequent visits with you over the course of your pregnancy.

You should continue with any other medications, including dietary supplements, which you are currently taking as advised. In general, there are no restrictions on other medications that might be necessary. It is important, however, that you let us know should any of your medications change, especially if new ones are added, particularly any antibiotic.

If you develop ICP, and go on to take UDCA, we will ask you, on the days when you need to have your blood tests, to delay taking the medication until after the morning blood sample has been drawn. This is to avoid measuring UDCA, itself a bile acid, in the blood test. Fasting is, however, not necessary for collection of blood to measure bile acids.

**5 Other relevant information about the research project**

ICP is an uncommon disorder of pregnancy, which in Australia only affects six to seven in every thousand pregnant women each year. We are hoping to recruit a total of 40 women to the study in Adelaide, Brisbane and London. We expect to recruit 15-20 women to the study at each site.

**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 the Women’s and Children’s Hospital.

**7 What are the alternatives to participation?**

You do not have to take part in this research project to receive pregnancy care and treatment at this hospital.

**8 What are the possible benefits of taking part?**

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include informing future patients of the factors that may impact on the development of ICP.

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

Collection of bio-samples, such as blood, urine and stool, can seem unhygienic and care needs to be taken to avoid contamination, and to take the usual precautions of handling such body fluids.

Having a 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?**

We would like to collect serum, urine and stool samples alongside routine blood and urine samples collected for any testing your doctor might order to monitor your health. We would also like to collect some of the placenta for routine examination when your baby is born.

All non-routine study samples collected will be identified by your study identification number, date of collection and a unique lab number. Details such as your name and date of birth will NOT be applied to any samples. Your samples will be re-identifiable. This means that we will be able to link information about you to your samples. It also means that we will be able to advise you of any findings that the study doctor thinks may be of relevance to your health.

Your samples will be stored on site under appropriate conditions until the end of the study, when the samples will be analysed. At the Women’s and Children’s Hospital, your samples will be stored at the Robinson Research Institute, University of Adelaide. At the end of the study your samples may be sent interstate or overseas to the laboratory of a study partner. The specific location to which each sample will be sent will depend upon the test being done.

The progesterone and bile acid metabolites and serum autotaxin will be measured in the laboratories of our European colleagues.

All the microorganism studies, the fat metabolism studies and the various associated viral tests will be performed in laboratories within Australia.

Similarly, the samples from your baby will be analysed for the presence of micro-organisms both in the stool specimens and within the mouth in the cheek swabs to see how this might be affected by the disease in you, the mother, and by your treatment and by your dietary intake.

ICP is a rare disease and your samples are a valuable research resource. In the consent form, we ask your specific agreement for the use of your samples in this and in future, as yet unplanned, studies. You will have a say in how widely or narrowly your samples may be used and you are allowed to change your mind on this at any time.

All samples will be retained until used up or for up to twenty years. At twenty years (or earlier upon your request), samples will be destroyed safely following local laboratory protocols. Your samples will not be sold by The University of Adelaide.

**11 What if new information arises during this research project?**

Sometimes during the course of a research project, new information becomes available about the disease 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?**

Whilst you are participating in this research project, it is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project.

It may also be necessary for you to take medication during or after the research project to address side effects or symptoms that you may have. You may need to pay for these medications and so it is important that you ask your doctor about this possibility.

**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 for that person or the research supervisor to discuss any health risks or special requirements that may be 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, The University of Adelaide, 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.

**Part 2 How is the research project being conducted?**

**14 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. Identifiable information will be held in a secure, password protected database at the site where you join the study. Any paper forms with your name and other identifiable details will be stored in locked filing cabinets on the site. Re-identifiable information collected for the study, “study data”, will be entered and stored on a password-protected research database. Only research personnel at this site will have access to your data. Your information will 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.

As ICP is an uncommon condition, any information we have collected about you, including any treatment you receive, and the results of the pregnancy and birth, is valuable, in a research sense. Therefore, with your permission, we would like to keep de-identified information about you and this pregnancy in a database. This will be used as a research resource and “pooled” with information about women with ICP in the future. The information will be stored in a password-protected database on a secure network at The University of Adelaide. Any future uses of this information would need to be approved by a certified Human Research Ethics Committee.

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, The University of Adelaide, the institution relevant to this Participant Information Sheet, Women’s and Children’sHospital, 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 may be recorded in your health records.

In accordance with relevant Australian andSouth Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

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.

We will retain the data that we have collected about you and your baby for 30 years as required by Government of South Australia data retention policies.

**15 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.

In the event of loss or injury, the parties involved in this research project have agreed to abide by the standard Medicines Australia Indemnity and Compensation Guidelines (<https://medicinesaustralia.com.au/policy/clinical-trials/indemnity-and-compensation-guidelines/>)

**16 Who is organising and funding the research?**

This research has been initiated by the senior study doctor, Professor Bill Hague, and is to be funded by the National Health and Medical Research Council (NHMRC) of the Australian government. The study is being coordinated by the Robinson Research Institute at The University of Adelaide, the Australian sponsor of the study. The study is being conducted at hospitals in Adelaide and Brisbane.

The study is being conducted at Women’s and Children’s Hospital by Professor Bill Hague.

By taking part in the sub-studies of this research project, you agree that samples of your blood or tissue (or data generated from analysis of these materials) may be provided to The University of Adelaide.

You will not benefit financially from your involvement in this research project.

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

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

**17 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 the Women’s and Children’s Health Network. Approval for the project has been given by both The University of Adelaide as sponsor and Women’s and Children’s Hospital.

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.

**18 Further information and who to contact**

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

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 0411 114 575 or the study coordinator: 0401 055 150.

 **Clinical contact person**

|  |  |
| --- | --- |
| Name | Professor Bill Hague |
| Position | Senior Consultant in Obstetric Medicine |
| Telephone | 0411 114 575 |
| Email | bill.hague@adelaide.edu.au |

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

 **Complaints contact person**

|  |  |
| --- | --- |
| Name | *Luke Fraser* |
| Position | *Research Information officer* |
| Telephone | *+61 (0)8 8161 6521* |
| Email | *luke.fraser2@sa.gov.au* |

If you have any complaints about any aspect of the project and 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**

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| --- | --- |
| Reviewing HREC name | *Women’s and Children’s Hospital Network HREC* |
| Research Information officer | *Luke Fraser* |
| Telephone | *+61 (0)8 8161 6521* |
| Email | *luke.fraser2@sa.gov.au* |





**Consent Form**

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| --- | --- |
| **Title** | *PRE-assessment for the randomised Trial of URsodeoxycholic acid versus RIFampicin in severe early-onset Intrahepatic Cholestasis of pregnancy: the PRE-TURRIFIC study.* |
| **Short Title** | *PRE-TURRIFIC*  |
| **Lay Title** | *Identifying potential participants with baseline studies for the Trial comparing URsodeoxycholic acid with RIFampicin in severe early onset Intrahepatic Cholestasis of pregnancy: the TURRIFIC study* |
| **Project Sponsor** | *The University of Adelaide* |
| **Principal Investigator** | Professor Bill Hague |
| **Associate Investigator(s)** | Professor Maria FullerStudy Coordinator: Suzette Coat |
| **Location**  | Women’s and Children’s Hospital, Adelaide |

**Declaration by Participant**

***CONSENT FORM***

***I***

hereby consent to my involvement in the research project entitled:

***PRE-assessment for the randomised Trial of URsodeoxycholic acid versus RIFampicin in severe early-onset Intrahepatic Cholestasis of pregnancy: the PRE-TURRIFIC study.***

1. I understand the nature and purpose of the research project described on the attached Information Sheet and agree to taking part.

2. I understand that I may not directly benefit by taking part in this study.

3. I acknowledge that the possible risks and/or side effects, discomforts and inconveniences, as outlined in the Information Sheet, have been detailed in the attached Information Sheet.

4. I understand that I can withdraw from the study at any stage and that this will not affect medical care or any other aspects of my relationship with my doctor or this healthcare service.

5. I understand that there will be no payment to me for taking part in this study.

6. I have had the opportunity to discuss taking part in this research project with a family member or friend.

7. I am aware that I should retain a copy of the Consent Form, when completed, and the Information Sheet.

8. I agree to the accessing of my medical records and of my baby for the purpose of this study.

9. I understand that my information will be kept confidential as explained in the information sheet except where there is a requirement by law for it to be divulged.

10.Specific consents:

1. I agree to the collection of my placenta for laboratory examination, for a de-identified copy of the pathology report and de-identified microscopic sections to be sent for central review in Adelaide and subsequent storage of the microscope slide in a dedicated biobank.

 □ YES □ NO

1. I agree to the collection of samples of blood and urine from myself and from the cord blood of my baby at birth, and for these to be initially stored in a dedicated biobank and then sent to locations in Australia and in Europe/UK (as appropriate) for examination

 □ YES □ NO

1. I agree to the collection of amniotic fluid, from myself and from my baby at birth, and for this to be initially stored in a dedicated biobank and then sent to locations in Australia and in Europe/UK (as appropriate) for examination

 □ YES □ NO

1. I agree to the collection of stool samples from myself, as well as collection of a meconium sample and a cheek swab from my baby at birth, and further cheek swabs and stool samples from my baby at 1 and 6 weeks of life, and for these to be initially stored in a dedicated biobank and then sent to locations in Australia and in Europe/UK (as appropriate) for examination

 □ YES □ NO

1. Where I have agreed to the collection of additional samples above, I agree to their use in other studies into liver conditions in pregnancy, provided the study has the approval of a certified Human Research Ethics Committee

 □ YES □ NO

1. I consent to be contacted after this pregnancy to be invited into follow up studies about myself and my child

 □ YES □ NO

1. I consent to non-identifiable data being used for future research and childhood development research that is approved by a certified Human Research Ethics Committee

□ YES □ NO

Signed: .........................................................

Full name of participant: ......................................................................................

Dated:.............................

*I certify that I have explained the study to the participant and consider that she understands what is involved.*

*Signed: .................................................... Title: .......................................................*

*Dated: ...............................*