We would like to invite you to take part in a research study to evaluate the performance of the IONA® test which is a non-invasive prenatal test (NIPT) for Down’s syndrome and other chromosomal abnormalities in twin pregnancies, from a maternal blood sample. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Please take as much time as you feel you need to decide whether or not you wish to take part. Please feel free to talk to your own doctor, another healthcare professional, or anyone else about the study if you wish.

1.1 What is the purpose of the study?
This study aims to evaluate the performance of the IONA® test, which is a screening test that helps in the diagnosis of unborn babies with Down’s syndrome (and other chromosomal abnormalities) in twin pregnancies from a simple maternal blood test. Currently, the only method to make an absolute diagnosis of Down’s syndrome involves either taking a sample from the placenta (known as chorion villus sampling (CVS)) or obtaining a sample of amniotic fluid which surrounds the baby (known as amniocentesis) - see Figure 1 below. Both of these tests carry a 2-3% potential risk of miscarriage in twin pregnancies. The use of a screening test like the IONA® test could avoid having to perform as many amniocentesis/chorionic villus sampling tests in the future.

Figure 1: Summary of the NHS Care Pathway for Twin Pregnancies

1.2 Why have I been invited?
You have been invited to take part in this study because you have been identified as having twins and are at a stage of pregnancy in which pre-natal screening for Down’s syndrome is usually performed. You are attending the hospital because your pregnancy has:

1. been identified as ‘low-risk’ by conventional screening test, (combined or quadruple test or ultrasound scan), or you are about to have pre-natal screening
2. been reported as ‘high-risk’ for a chromosomal problem such as Down’s syndrome and you have decided to undergo prenatal invasive diagnosis, or
3. you are undergoing invasive prenatal therapy, such as laser treatment for twin to twin transfusion syndrome (TTTS) where a sample of the amniotic fluid is taken.
You are being invited to join the study along with all of the other eligible women in similar position. Over the full course of the study, about 500 women will be participating.

1.3 Do I have to take part?

No. It is entirely up to you to decide whether or not you would like to take part. We will describe the study and go through this information sheet, which we will then give to you. If you are interested, we will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This will not affect the normal standard of care you receive for your pregnancy from your healthcare provider.

If you choose to withdraw from the study, we will destroy all your identifiable samples, but would ordinarily need to use the data collected up to the time you withdrew.

1.4 What will happen to me if I take part?

If you are happy to take part in this study, the step-by-step procedure will be as follows. One of the healthcare professionals (i.e. fetal medicine specialist) looking after you will take you through a consent form for you to sign, confirming that you agree to take part. You should take as long as you need to feel comfortable with your decision, even if it means coming back on another day to provide your blood sample.

Your GP/family doctor may be informed of your participation in this study where appropriate and the hospital consultant in charge of your care will be aware of your inclusion.

After giving your written consent you will be asked some questions about your pregnancy and then a blood sample (two standard-sized tubes, maximum 20ml/four teaspoons equivalent) will be taken from a vein in your arm, in the normal way. This may take up to 30 minutes to complete.

Rarely, the pregnancy may start as twins but one twin dies and is absorbed by the body, or a reduction may be performed to remove excess embryos (e.g. with IVF); any remaining materials are referred to as a vanishing twin and whilst being absorbed they shed DNA fragments into the maternal blood for several weeks. If a vanishing twin is identified after you have been recruited to the study and a blood sample has been taken, we would require another blood sample (20ml) at around the 18-20 week anomaly ultrasound scan (at least 8 weeks after the first blood sample). These would be the only procedures that would be over and above your standard care. Otherwise, the care you receive will be identical to that if you were not participating in the study, and no normal treatments will be withheld.

Your blood sample will then be taken to the laboratory and the fetal DNA from the sample will be tested to see how well the IONA® test works in twin pregnancies.

We will aim to provide the results within three to four weeks of the sample being received in the laboratory for testing, providing plenty of time for you to be counselled by your fetal medicine specialist and go forward on the normal NHS care pathway dependent on the results of this test and your other screening tests (e.g. for the next step you would have an 18-20 week scan to look for any abnormalities, or if you get high risk results from your screening tests (normally a combined test which is a blood test and ultrasound performed at 10-12 weeks) you will be offered a diagnostic test such as a CVS or amniocentesis.

We will look at your pregnancy notes, to record the results of your screening tests and to follow the outcome of your pregnancy. If the pregnancy outcome is not available from your medical notes the fetal medicine unit responsible for your pregnancy may contact your GP, or you if necessary, by telephone for this information. At no point would you be contacted by the Sponsor company.

No confidential information that could personally identify you will be moved from the hospital site looking after you, nor be made available to any research team members not employed by either Premaitha Health, or the University of Oxford or Oxford University Hospitals NHS Trust.

1.5 What will happen to the samples and data I give?

The blood sample(s) taken will be taken solely for the study. On the consent form you will be asked to initial a box giving permission for us to use any left over sample for future quality control and development purposes. The samples, and any data generated from them, will not be identifiable as yours outside the
hospital. The only link to your identity will be by way of a unique, anonymous number. All identifiable data will be retained securely at the hospital site. No researchers other than health professionals working at University of Oxford or Oxford University Hospitals NHS Trust, or Premaitha Health will have access to your personal data. The research health professional acting as your liaison with the study will enter the information in to a folder held for the purposes of the study. This folder will be kept in a secure room in the hospital. Data may also be entered in to a file on a secure computer. Samples will not be transported outside the UK. The samples themselves will be kept until the end of the study. If you have given us permission to keep any of the remaining genetic material isolated from your blood sample, this will be stored in our laboratory for potential use in future studies, subject to appropriate ethical approvals. Otherwise, we will destroy any material isolated from your blood sample.

1.6 Will any genetic tests be done?

This study aims to try to determine the ability to make accurate pre-natal testing for Down's, Edwards' and Patau's syndrome safer for twin pregnancies, using measurements of the fetal DNA obtainable from maternal blood samples in twin pregnancies. As such, all of the samples provided will be subject to tests involving fetal DNA assessments. These will not take the form of what is usually considered ‘genetic’ testing, and will not be aimed at identifying participants themselves, or genetic disease predisposition in participants themselves.

1.7 What are the alternatives for diagnosis or treatment?

The blood test involved in the study is an additional procedure, rather than an alternative. The normal standard NHS care you receive does not change whether you agree to take part in this study or not.

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

The important thing is that whether you participate or not, you will receive the currently available standard of prenatal care from your healthcare provider.

The specific risks involved in this study are simply those of having a standard blood sample taken. Giving a blood sample is a generally safe procedure; however there are some risks of giving a blood sample. This is called an invasive test because a needle will be put in your arm to draw a blood sample, it is the same procedure as for any other blood samples you may have had taken. Possible adverse events include bruising and pain at the site and less commonly: nerve damage, re-bleed, allergy (e.g. to the nurse’s gloves), inflammation of the vein, blood pressure change and arterial puncture.

Since participating in the study will not otherwise change the course of standard prenatal care, there should not be any other disadvantages involved in taking part. The volume of blood taken in the sample is small (i.e. 20ml/ about four teaspoons), and is not thought to represent any health risk.

All results produced using the IONA® screening test, whether low or high risk, will be considered along with all the other results from your standard screening tests. You will receive counselling by your fetal medicine specialist for the next steps appropriate to your results. There is a slight chance that this test could give a high risk result and some screening results be low risk. If a high risk result is present you will be counselled and recommended to have a diagnostic test to confirm these results.

1.9 What are the possible benefits of taking part?

The only direct benefit to you from taking part is access to an extra non-invasive screening test (the IONA® test). However, as a participant in this study we cannot provide the usual result turnaround time of three to five days but will endeavour to provide results within three to four weeks. It is hoped that this screening test could make prenatal diagnosis safer and less stressful for women who are pregnant with twins in the future by reducing the number of women who are recommended to undergo CVS or amniocentesis which carry a small (2-3%) risk of miscarriage in twin pregnancies.

1.10 What happens when the research study stops?

Most of the DNA we extract from your blood sample will be used up in assessing the performance of and further developing the IONA® test. We would like your permission to keep any of the remaining genetic material isolated (e.g. unused plasma) from your sample to be used to validate future, hopefully cheaper
and better technologies for the same purpose (detection of chromosomal abnormalities/reassurance and confirmation of health). If you prefer this did not happen, we will destroy any material isolated from your blood sample.

1.11 What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact the study Research Midwife on 01865 223211 or Dr Brenda Kelly, the Research Doctor, on 01865 741166).

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the Patient Advice and Liaison Service (PALS), Oxford University Hospitals Trust: Telephone number: 01865 221473 or email PALSJR@ouh.nhs.uk.

1.12 Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

The research team has a duty of confidentiality. The research team running the study are Premaitha Health (the Sponsor), and University of Oxford or Oxford University Hospitals NHS Trust employees (the healthcare providers from the fetal medicine unit) and they will be the only people with access to your personal data.

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you that leaves the hospital will be anonymised (i.e. it will have your name and address/any other identifying features removed so that you cannot be recognised). Participants have the right to check the accuracy of data held about them and correct any errors. Your anonymised data will only be used for the purposes of future scientific publication on the technology being developed and features that are academically noteworthy.

1.13 What will happen to the results of the study?

The study aims to test early-stage/cutting-edge technology for screening of chromosomal abnormalities. The laboratory method has been shown to be accurate in a small number of twins (eleven sets of twins) and now needs to be used in this larger study to evaluate how good it will be in large numbers of twin pregnancies and the information used to improve the test where necessary. When complete, the data from the study may be used in research papers published in scientific/medical journals. Participants’ identity will always be kept confidential and data used in any form of publication would be entirely anonymous. No participant in this research will ever be identified, or identifiable, in any publication or other report arising from the study.

1.14 Who is organising, funding and providing insurance for the research?

This study is being organised as a collaboration between Premaitha Health and University of Oxford or Oxford University Hospitals NHS Trust. Premaitha Health is the “sponsoring” organisation that is funding and providing the appropriate insurance/indemnity for the research. The research midwife helping to conduct the research is being paid for the time she devotes to the study.

1.15 Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. The study has been reviewed and given a favourable opinion by the South Central Berkshire Ethics Committee.

1.16 Further information and contact details

If you would like further information about the study, please consult the following:

1. General information about research and antenatal testing
   a. NPSA (National Patient Safety Agency) site offering advice on clinical research
      http://www.npsa.nhs.uk
b. Department of Health webpage dealing with confidentiality and Patients’ rights

c. NHS information resource detailing Down’s Syndrome prenatal screening procedures
   http://www.screening.nhs.uk/downs/procedures.htm

2. Specific information about this research project

   The health professional administering this information sheet and undertaking your informed consent should be able to answer most of your questions:

   Alternatively, the Study Co-ordinator  Rosalyn Mazey
   Rosalyn.mazey@premaitha.com
   0161 667 6867

   Or the Principal Investigator  Dr Brenda Kelly
   Brenda.kelly@obs-gyn.ox.ac.uk
   01865 741166