adAPT autoimmune diabetes ACCELERATOR PREVENTION TRIAL

PARTICIPANT 16y INFORMATION SHEET

INVITATION TO TAKE PART

We would like to invite you to take part in the second part of the adAPT study, which we believe may be of value to you and your family.

Before you decide whether or not you wish to participate, we would like you to understand why we are doing it, and what it would involve if you agreed. Please take time to read the information below, and to discuss it with friends and family and your doctor. At the back of this leaflet you will find space to write down questions you may wish to ask the study doctor or research nurse. We will do our best to explain and provide any further information you may ask now or later. Take you time to decide if you wish to take part.

WHY ARE WE CONDUCTING THIS STUDY?

At present, there is no treatment that can prevent type 1 diabetes. We know that more children each year are developing the disorder, and want to find a way to stop this trend.

WHY AM I BEING ASKED TO TAKE PART?

Your screening test was positive, and around 4 out of every 10 youngsters who have a positive screening test will become diabetic within five years. We are inviting all who have a positive test to take part in the next part of the study, which aims to prevent the development of type 1 diabetes.

WHAT DOES THE TREATMENT PHASE OF THE RESEARCH HOPE TO ACHIEVE?

In the adAPT study we want to find out if we can prevent children at high risk of developing type 1 diabetes from needing insulin, by treating them with a medicine called metformin. We think metformin will help children at risk of developing type 1 diabetes because it will stop their insulin cells from working too hard, which could then protect them from the damage that would eventually lead to the children needing to inject insulin.

You are being invited to take part in the treatment stages of the study which will test whether the medicine metformin can lower demand for insulin. If it can, we believe

there is a good chance it can also reduce the risk of developing type 1 diabetes. There are three treatment stages, and we are concerned with Stages 1 and 2 here. Stage 1 aims to find out whether metformin can reduce the workload, Stage 2 whether the treatment can slow the changes that are known to lead to diabetes, and Stage 3 whether it reduces the number of cases of diabetes.

Stage 1 lasts four months during which time you will be asked to take the trial medicine, and attend your local hospital clinic on three occasions for tests. You will then continue stage into Stage 2.

Stage 2 takes the trial to Month 36. Your consent will be sought for Stages 1 and 2 together.

Before Stage 3 begins, we will give you additional information about the study before you decide if you want to take part.

WHAT IS THE MEDICINE BEING TESTED?

This study is a clinical trial of a medicine called metformin. Metformin has been around for 50 years and is known to be safe in healthy people. It can prevent type 2 diabetes in adults, but has never been tested before in children at risk of type 1 diabetes.

If you are eligible to take part, you will asked to take either metformin or placebo (dummy) twice a day. Both active and placebo medicines are liquids taken with an oral syringe, the dose will be adjusted according to your body weight at each study visit. The medicine is suitable for vegans, vegetarians and is gluten free and kosher but not halal.

You will be assigned either metformin or placebo randomly (a bit like tossing a coin, but done by computer). Randomisation inevitably means that half the participants will be taking the placebo treatment and half the metformin treatment. Blinding means that nobody knows which treatment you are assigned to until the end of the study. This is essential to scientifically test if metformin prevents diabetes.

Both groups will have all the same tests and measurements carried out. This means the outcome between the groups, once decoded, can only be attributable to the active treatment.

While metformin lowers blood sugar levels it will do so within normal limits therefore you will not be aware of the adjustment.

If more than one child from the same family is eligible to take part in the study, both of you will both be assigned to the same group.

DO I HAVE TO TAKE PART?

No. Participation is entirely voluntary and you are free to turn down this invitation or withdraw from the study at any time, without giving us a reason. If you decide not to participate, and only if you agree, we would like to ask why you made that choice. This will help us understand the decisions people make, which may help us develop the design of this study and future studies.

The decision to participate in this study will not affect the medical care you or any members of your family children receive, nor the relationship that you have with the doctors or nurses. If you, the study doctor, or another health professional decides you should withdraw from the study, we would like your consent to keep and analyse the data we have already collected.

If you are female and become pregnant during the study, the study team will need to be informed. You will be withdrawn from the study and may be asked to give consent to be followed-up until then end of the pregnancy.

If you decide to participate, you will be asked to sign a consent forms. You will be given a copy of these forms to keep along with this Participant Information Sheet. If you decide to withdraw from the study, we will invite you to come for a withdrawal visit.

If you plan to relocate during your participation in the study, for example go to another city for work or University, please inform the study team as every effort will be made for you to continue in the study by attending one of our other study sites.

WHAT WILL THE STUDY INVOLVE?

Table 1 (page 4) outlines what is involved in the study.

We will ask you to visit the research team three times in the next four months, then every four months until Month 12, and every six months thereafter to the end of Stage 2. However, depending on the results from Stage 1, the study may stop before you have reached the end of Stage 2.

At each planned hospital visit we will ask you to fast from 10pm the night before your morning visit. You can however drink water. You will have a sweet drink as part of one of the tests (see below) during your hospital visit but we will also provide other snacks before you leave your appointment.

We will ask general questions about your health and any medications you may take. On entry into the study we have to ensure that the study is suitable for you and as you continue in the study that any side-effects, ill-health and new medicines are documented.

To assist you, you will be given a diary you to record any changes between each study visit.

Your height, weight and waist measurements will be taken. Your weight measurement is used to calculate the volume of the sugar drink (see below) and the dose of study medicine you will take.

We will also obtain blood samples. Some of the samples are to check routine blood chemistry and the others are for the study. The total blood taken will be approximately 40mls (2½ tablespoons) which is within the clinical guidelines. If for some reason the research team are unable to obtain a blood sample, you will be given the opportunity to return at another time that is convenient to you.

Activity	Month 0[1]	Month 1	Months 1[1], 2 & 3 (phone)	Months 4, 8, 12, 18, 24, 30, 36[2]	Withdrawal Visit [3]
General Health & Medication Questions	X	X	X	X	X
Blood samples	X	X		X	X
Urine Pregnancy Test (if required)	x	x		X	X
Measure height, weight and waist	X			X	X
Sweet drink test (MMTT) – 5 small blood samples over 2 hours	X	X		X	X
Medicine Group Allocation	X				
Collect study medication	X	X		X	
Return all study medication bottles (use/unused)				X	X

Table 1. TREATMENT PROTOCOL STAGES 1 and 2

1. Telephone calls to discuss medication. Dose change instructions will be given.
2. The study nurse will call you every 3 months or so to check on how you are feeling. You can call the study team at any time during the study.
3. Withdrawal visit will be performed if you agree.
   We can provide appointment letters for you to present to school/college or and employers if required.

To test how much insulin your body produces, we will carry out what is called a Mixed Meal Tolerance Test (MMTT). This involves you drinking a sweet tasting drink like a milk-shake. To make things easier for you, we will also anaesthetise the skin and insert a cannula into the arm, which will allow us to take small volumes of blood at scheduled time intervals for up to 2 hours.

We will receive your blood results from the NHS laboratory by the end of the first visit (Month 0) when, if all is well, you will be randomised into the study. If for some reason

there is a delay in the blood samples, we will inform you of the results by phone and, if you are not eligible, discuss the reasons why. We can send the study medication by tracked mail or, if more convenient, you can collect it from the hospital. You will be given both verbal and written instructions on how to take the study medication.

If we randomise you on the day of your first visit, we will send you home with the study medicine, specific instructions on how to take it and how to contact the study team if you have any questions.

You will be on half the normal study medication dose for the first month. You will be asked to take it once a day for the first two weeks, followed by twice a day. You will receive a call from the research, nurse who will give you instructions when to start taking it twice a day. This is to reduce the chances of possible side-effects .In addition, it may help to spread the two doses over the day and to take the medicine with food. We will give you instructions about how to give the study medication at the visit.

You will be given a dropper, specific instructions and guidance. The medication is best taken with food. After taking the medicine for one month at half-dose, we will increase it to full-dose, and you will receive a follow up phone call one week later The dose will be recalculated according to body weight at each study visit, and adjustments made as necessary.

If you withdraw, or are withdrawn from the study, we will invite you to attend a withdrawal visit to collect final test information (see Table 1.)

ARE THERE ANY DISCOMFORTS OR RISKS TO TAKING PART?

All medicines have some risks and side-effects. Most children and young adults will have no problems with the medication, but there may be side effects for a few:

Very common (affects more than 1 in 10 people)
The following are dose-related, and most often occur temporarily and at the beginning of the treatment with metformin: feeling sick (nausea), vomiting, diarrhoea, stomach ache (abdominal pain) and loss of appetite. The half dose for one month aims to reduce the chances of these symptoms. You will be given a telephone number to contact the study team if any of the symptoms are troublesome. In addition, the study nurse will call you a week after starting the medication to check on progress.

Common (affect more than 1 in 100 people)
Changes in how things taste

Very rare (affect fewer than 1 in 10,000 people)
Skin reactions such as redness of the skin (erythema), itching or an itchy rash (urticaria). Low vitamin B12 levels in the blood (only described in adults, and may not be a true side effect). As part of the study we will take regular blood samples to test for Vitamin B12 levels.

Extremely rare
Lactic acidosis which incurs severe vomiting and abdominal pain. It has not been described in children with healthy kidney function. We will be monitoring your kidney function throughout the study.

Interactions with Metformin
The effect of oral contraceptives can be reduced if vomiting or diarrhoea occur. Additional contraception will be required.

Metformin can interact with alcohol. Please discuss this with your study doctor if alcohol could be a problem.

Blood Samples
Anaesthetic spray (or cream) can be used so that only a small scratch and light pressure is felt when a cannula is inserted

The Mixed Meal Tolerance Test (MMTT) involves blood samples at 30 minute intervals over two hours, and we will place a small flexible plastic tube (a cannula) in the arm vein to minimise discomfort. This is not felt once it is in place. The cannula can be used for every sample needed during the visit. The tube will be removed after the last sample has been taken.

After the blood samples have been taken, we will place a small plaster or dressing over the spot where the blood was taken. There may sometimes be a small bruise for a day or two afterwards.

All of the study nurses and doctors are highly experienced in taking blood samples.

IS THERE ANYTHING ELSE TO BE CONSIDER IF I TAKE PART?

General
If you are seen by another doctor or health professional during the study you should inform them that they may be taking metformin. You will be given a card to show that you are taking part in the adAPT study.

X-rays using contrast
Metformin should be stopped temporarily in the event of specialist x-rays and scans using a contrast medium. You should inform the clinical team requesting this type of test and they will provide you with any specific instructions.

Pregnancy & Contraception
There is currently no evidence of harmful effects of metformin in pregnancy, but there is no specific evidence in the age group taking part in the adAPT study. For that reason, we will ask all female participants who are sexually active to use an effective method of contraception until the end of the study. Suitable contraception is at least one of the following: true abstinence; combined hormone contraceptive pill, patch or ring; progesterone pill, injection or implanted rod; coil device or system. If you are taking a contraceptive pill and have vomiting or diarrhoea, it can reduce the effectiveness of oral contraception. The usual instructions about alternative methods

of contraception should be followed. Such information will be supplied with prescribed contraceptive or available from the GP or pharmacy. Please feel free to discuss this with the doctor or research nurse in confidence.

It is common practice in clinical trials using a medicine to ask menstruating females to take a pregnancy test before and during the study. All female participants in adAPT who have started menstruating will have a routine urine pregnancy test done before they start study medication, and at all study visits.

Any participant who becomes pregnant will be withdrawn from the study. Any pregnancy must be reported to the study team as soon as possible so that we can arrange any support and care needed. We will also ask to follow her up and to assess her health until the end of the pregnancy.

If any female is planning a pregnancy, please discuss this with the study doctor.

Contraceptive advice for those who seek it will be available from routine NHS services (clinical team or specialist contraceptive advisor).

WHAT ARE THE POTENTIAL BENEFITS TO ME OF TAKING PART?

You have tested positive with two or more antibodies. Four out of every ten people who have two or more antibodies may expect to become diabetic within five years. We cannot know the result of the trial in advance, but participation might prevent a second case of diabetes in your family. We also intend that the wider information learned from the study will help other children and young people who are at risk of developing diabetes in the future.

HOW WILL MY INFORMATION BE STORED?

All the information which we collect about you during the study will be kept confidential. There will be two sets of information. One will be your routine blood tests, which will be analysed in NHS laboratories and held on NHS Clinical Systems and in your medical records. The second set will be the non-identifiable (anonymised) information collected during the study. You will be identified using a study barcode, and all the research samples taken during the study will be labelled using these barcodes. All research blood samples will either be processed at the University of Dundee or hospital laboratory for preparation before sending onto the specialist laboratories for analysis. These laboratories are in England and the Netherlands.

There may be small volumes of blood left over. We will ask your permission to gift any residual blood to be stored anonymously for possible use in future medical research.

All information about you will either be stored in locked cupboards or password-protected networked computers, to which access will be limited to the research team.

Your name, address, date of birth and contact details will be stored during the trial to enable the study team to manage appointments and to send you relevant study information.

We will ask your permission to inform your GP that you have taken part in the study and inform them if any of your blood tests are clinically antibody test result for your medical records.

All study information will be kept for 15 years to record any diagnoses of diabetes and so we can make checks if there are any questions or queries at a later date.

We will publish and share our results with others in the field of diabetes. Your personal details will remain anonymous in any publications or presentation of the data.

FURTHER CONTACT

We will ask you for permission to contact you with information about any supplementary or future studies that may be of interest to you. You do not have to take part in these additional studies.

FUTURE HEALTH INSURANCE

You should be aware that if you apply for health insurance, questions may be asked about your health, including medical history, pre-existing medical conditions and genetic testing. Participation in this study does not constitute a *genetic test* and a positive diabetes antibody test is not a diagnosis of type 1 diabetes. Insurance companies are not currently permitted to seek information on biomarkers in the absence of disease. Your data will remain confidential unless we are legally required to disclose information by Court order or by statute.

WILL I CONTINUE TO RECEIVE THE MEDICATION USED IN THIS STUDY AFTER IT FINISHES?

No, you will not be given metformin by the study team after your participation has ended. If the trial is successful, appropriate consideration will be given by the authorities to licence metformin as a means of preventing diabetes in children at risk.

WILL I BE TOLD ABOUT THE STUDY FINDINGS?

adAPT will take more than five years to complete. The results will be made available on the study website, and through scientific publications. However, by taking part in Stage 1 and Stage 2 of the study, you will be informed of the results from Stage 1 as soon as they become available and you will be given the opportunity to take part in Stage 3 of the study.

If you agree we can provide a summary of the study results and which medication you took during the trial, but this information will only be can only be made available once all participants have completed the study.

WHAT IF THERE IS A PROBLEM OR SOMETHING GOES WRONG?

If you have a concern or a complaint about participating in the study, please speak firstly to your research nurse or the study doctor involved in your care. You can ask to speak to a senior member of the research team or the Complaints Officer at your local Health Board/Trust. To do so, the study team will provide the contact details of the local Complaints Team.

If something does go wrong, and you are harmed during the research due to someone's negligence, you may have grounds for legal action against the NHS Health Board/Trust involved in the research or may have the right to make a claim for compensation against the University of Exeter, which is sponsoring the trial. Where you wish to make a claim, you should consider seeking independent legal advice, but you may have to pay for your legal costs.

WHO ARE CONDUCTING AND FUNDING THE STUDY?

The study team is led by Professor Terry Wilkin from the University of Exeter and Professor Stephen Greene from the University of Dundee. The study is sponsored by the University of Exeter, funded by the Juvenile Diabetes Research Foundation (JDRF), and conducted by the Tayside Clinical Trials Unit at the University of Dundee.

WHO HAS REVIEWED THIS STUDY?

All research in the NHS is reviewed by an independent panel of people, called a Research Ethics Committee, to protect your interests. The East of Scotland Research Ethics Service REC 1, which has responsibility for scrutinising all proposals for medical research on humans in the United Kingdom has examined the proposal and has raised no objections from the point of view of medical ethics.

It is a requirement that your records in this research, together with any medical records, be made available for scrutiny by monitors from the University of Exeter or individuals appointed by the Sponsor whose role is to check that the research is properly conducted, and the interests of those taking part adequately protected.

WILL I RECEIVE PAYMENT FOR TAKING PART?

No, you will not receive payment for taking part in the study, but we will cover reasonable travel expenses for all your study visits.

We will also give you a choice of gift vouchers during the study to say thank you for assisting in the study from £10 to £15. These can be used on-line or in high-street shops. In addition, during the study we will provide small tokens of gratitude in the form of drinks bottles, mugs and a study bag to help you carry the study medication home.

CONTACT NUMBERS IF YOU ARE UNWELL DURING THE STUDY

If during the study you become unwell or are concerned, you can contact the study team using the number on the Study Participation Card (01382) 383115. If you become unwell and need urgent assistance, do not delay in seeking further advice through the NHS services such as NHS24 (Tel: 111) or by contacting your GP who (subject to your agreement) will have received details of your participation in the study.

WHERE CAN I FIND OUT MORE ABOUT RESEARCH?

If you wish to seek independent advice about taking part in the study you can contact Dr Michael Murphy, Clinical Reader at the Department of Biochemical Medicine, University of Dundee on 01382 383541 or m.j.murphy@dundee.ac.uk.

If you would like to find out more taking part in health research there are a number of organisations you can contact such as:
Scotland Children's Research Network CRN - www.scotcrn.org
Children's Research Network - www.crn.nihr.ac.uk/children
People in Research – www.peopleinresearch.org
INVOLVE – www.invo.org.uk

Further information

More information about this study is available on the website www.adaptdiabetes.org

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Thank you for taking the time to read this information sheet, and for thinking about taking part.

Any Questions