PARENT/GUARDIAN RCT INFORMATION SHEET

INVITATION TO TAKE PART

We would like to invite your child 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 and your child 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, relatives or your child's doctor. At the back of this leaflet you will find a 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 your time to decide whether or not 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 ARE WE BEING ASKED TO TAKE PART?

We are inviting all children who have a positive screening test result to take part in the next part of the study which is designed to prevent the development of type 1 diabetes. If more than one child from the same family is eligible to take part in the study, both will be assigned to the same group.

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 now being invited to participate in Stages 1 and 2 of the treatment phase 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. Stage 2 will test 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 the participant will take either the trial medicine or the placebo (dummy) and will attend their local hospital clinic on three occasions for tests.

Stage 2 takes the trial to Month 36 but, because those recruited early will have entered Stage 2 before those recruited late have even entered Stage 1. Accordingly, you and your child's consent will be sought for Stages 1 and 2 together.

We will give you additional information before Stage 3 begins, to enable you and your child to decide whether or not to continue.

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. The Medicines & Healthcare Regulatory Authority (MHRA) has approved our use of metformin in this way.

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

Your child will be assigned either metformin or placebo randomly. Randomisation inevitably means that half the participants will be taking the placebo treatment, and half the metformin treatment. Blinding in this way means that nobody knows which treatment you are assigned to until the end of the study. This is essential scientifically to ensure that it is the metformin, and nothing else that has successfully prevents diabetes. Both groups will have all the same tests and measurements carried out.

While metformin lowers blood sugar levels it will do so only slightly, and your child will not be aware of the adjustment.

DOES MY CHILD HAVE TO TAKE PART?

No. Participation is entirely voluntary and you and your child 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 families make, which will help us develop the design of future studies.

The decision to participate in this study will not affect the medical care your children receive, or the relationship that you and your child have with the doctors or nurses.

If you, your child, the study doctor, or another health professional decides your child should withdraw from the study, we would like your and your child's consent to keep and analyse the data we have already collected.

If your child is female and becomes pregnant during the study, the study team will need to be informed. Your child 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 and your child decide to participate, you will both be asked to sign consent forms. You will be given a copy of these forms to keep along with this Participant Information Sheet. If your child decides to withdraw from the study, we will invite them to come for a withdrawal visit.

If your child turns 16y during their participation in the study, we will ask them to re-consent independently at their next scheduled visit.

If you or your child plan to relocate outside your local health board while participating in the study, please inform the study team, as every effort will be made for your child to continue in the study by attending one of our other study sites.

WHAT WILL THE STUDY INVOLVE?

Table 1 outlines what is involved in the study.

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

At each planned hospital visit we will ask your child to fast (but can drink water) from 10pm the night before their morning visit. They will be given a sweet drink as part of the study on the morning of the test, (see below) and a snack before they leave the hospital.

We will ask general questions about their health and medications. We have to ensure that the study will suit them on entry and document any side-effects, ill-health and new medicines as they continue.

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

Your child's height, weight and waist measurements will be taken. Their weight is used to calculate the volume of the drink they will be asked to consume (see below) and the dose of study medicine they 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 during the course of the test will be approximately 40mls (2½ tablespoons) which is within the clinical guidelines for children. If, for some reason, the research team is unable to obtain a blood sample, you and your child will be given the opportunity to return at another time that is convenient to you.

To test how much insulin your child's body produces, we will carry out what is called a Mixed Meal Tolerance Test (MMTT). This involves your child drinking a sweet tasting drink like a milk-shake. To prepare your child for this we will also insert a cannula (see blood samples below), which will allow us to take small volumes of blood, at scheduled time intervals, for up to two hours.

By the end of the first visit (Month 0) we will receive your child's blood results from the NHS laboratory and if eligible, your child will be randomised into the study (a computer programme randomly allocates your child to metformin or placebo). If, for some reason, there is a delay in the blood samples coming back, we will be able to randomise your child once we have reviewed the results. We can call and inform you of the results and, if they are not eligible, discuss the reasons. If eligible (almost every child will be at this stage), we can send the study medication by tracked mail, or if more convenient to you, you can collect it from the hospital. You and your child will be given both verbal and written instructions on how to take the study medication.

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

For the first month your child will be on half the normal dose of study medication. For the first two weeks they will take it once a day, followed by twice a day for two weeks. They will receive instructions from research nurse when to start taking it taking it twice a day. This is to reduce the chance of side-effects (see below.) You will be given measuring droppers, specific instructions and guidance. The medication will be taken with/after food.

After taking the medicine for one month at half-dose, we will increase it to full-dose, and you or your child will receive a follow up telephone call one week later. It may be necessary in a few cases to reduce the dose to its previous level.

The dose will be recalculated according to body weight at each study visit, and adjustments made as necessary.

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

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

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 and your child agree.

We can provide appointment letters for you and your child to present to school and employers if required.

ARE THERE ANY DISCOMFORTS OR RISKS TO TAKING PART?

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

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, abdominal pain and loss of appetite. All children will start on half dose for one month to reduce the chances of these symptoms. In addition, it helps 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 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 (affects more than 1 in 100 people)
Changes in how things taste

Very rare (affects 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 be not 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 never been described in healthy children. We will be monitoring your child 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 may be a problem

Blood Samples
Anaesthetic spray or cream is used in children, so that they feel 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. We will use a needle to 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 working with children.

IS THERE ANYTHING ELSE TO BE WORRIED ABOUT IF WE TAKE PART?

General
If your child is seen by another doctor or health professional during the study they 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. 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.

Vomiting or diarrhoea can reduce the effectiveness of oral contraception. The usual instructions about alternative methods of contraception should be followed. Such information will be supplied with their contraceptive or available from the GP or pharmacy.

It is common practice in clinical trials using a medicine to ask menstruating females to take a pregnancy test before and during the study. Therefore, all female participants in adAPT who have started menstruating will undergo 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.

Any female planning a pregnancy during the study should 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 OF TAKING PART?

Your child has tested positive with two or more antibodies. Four out of every ten youngsters 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 CHILD'S INFORMATION BE STORED?

All the information which we collect about your child during the study will be kept confidential. There will be two sets of information. One will be your child's routine blood tests, which will be analysed in NHS laboratories, held on NHS Clinical Systems and stored in their medical records. The second set will be the non-identifiable (anonymised) information collected during the study. Your child 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 be sent to the University of Dundee hospital laboratory for preparation before distribution to the specialist laboratories for analysis. The specialist laboratories are located in Bristol and in Leiden (Netherlands).

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

Your and your child's contact details and date of birth will be stored during the trial to enable the study team to manage appointments and to send you relevant study information. This information will be held on password protected secure study databases to which access will be limited to the research team.

All study information will be kept for 15 years to record any diagnoses of diabetes or 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 child's personal details will remain anonymous in any publications or presentation of the data.

FURTHER CONTACT

We will ask you and your child's 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 your child applies for health insurance, questions may be asked about their 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 such biomarkers in the absence of disease. Your child's data will remain confidential unless we are legally required to disclose information by Court order or by statute.

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

Your child will not be given metformin by the study team after their 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 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 and your child agree we can provide a summary of the study results and which medication they took during the trial, but this information will only be made available once all participants have completed the study.

WHAT IF THERE IS A PROBLEM OR SOMETHING GOES WRONG?

If you or your child has 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 or your child 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 you 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 IS CONDUCTING AND FUNDING THIS 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 Juvenile Diabetes Research Foundation (JDFR) 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 child's research records, 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 are adequately protected.

WILL I RECEIVE PAYMENT FOR TAKING PART?

No, you will not receive payment for taking part in the study but we can cover reasonable travel expenses for all your study visits.
We will also give your child 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 online 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 YOUR CHILD IS UNWELL DURING THE STUDY

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

You can find out more information about this study 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