We would like you to consider participating in a research study which is exploring the mechanisms leading to the risk development Type 2 Diabetes. Before you decide whether you would like to participate or not, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others (for example family members or your GP) if you wish.

The information sheet is divided into 2 sections:

- **Part 1** gives details about the study: why the study is being run and what you would need to do if you decide to participate.
- **Part 2** gives you more detailed information about the conduct of the study.

Please ask us if there is anything that is not clear or if you would like more information and take as much time as you need to decide whether or not you wish to take part.

Part 1

What is the purpose of this study?

The purpose of this study is to find out whether reduced blood levels of the naturally occurring hormone Insulin-like Growth Factor-I (IGF-I), that regulates growth and metabolism, are associated with reduced insulin production and function.
This information would be useful in understanding the mechanisms that might lead to the development of type 2 diabetes, a chronic disease characterised by reduced insulin production and action.

Why have I been chosen?

You have been selected to participate in this study based on your initial recruitment into the Cambridge BioResource and the levels of IGF-I which have been measured in the blood sample you donated on joining the BioResource. We are inviting people whose IGF-I levels are either at the higher or lower ranges to join the study. We are inviting healthy volunteers aged between 18 and 50 years of age to take part.

Do I have to take part?

It is up to you to decide whether or not you wish to take part. If you decide to participate, you will be given an opportunity to discuss the study in more detail and you will be asked to sign a consent form. You are free to withdraw from the study at any time and without giving a reason.

What will happen to me if I take part?

If you agree to take part, we will be asked to visit the Clinical Research Facility at Addenbrooke's Hospital for a single overnight stay. You will be asked to arrive by 3 pm and will be free to leave by 2pm the following day.

You will be asked to eat a prescribed evening meal the night before and a prescribed breakfast before 8 am on the study day. These meals will be based on your usual choice of food, but the meal portion size may differ as it will be based on approximately a third of your daily energy needs. Following the breakfast you will need to fast until the study is completed on the next day. This corresponds to about 30 hours of fasting (from 8 am until 2 pm the next day). You will be provided with a meal before you leave.

On arrival at CRF your height and weight will be measured. Measurement of your body fat will also be made by determining the amount of fat in your liver and muscle using magnetic resonance spectroscopy (MRS) and in your abdomen by using magnetic resonance imaging (MRI). These scans will be performed in succession in the MRI machine at the Wolfson Brain Imaging Centre (WBIC) situated in Addenbrookes' campus. The scans will take approximately 60 minutes to complete. These scans will be repeated the following day just before you leave. In this way we will be able to measure the changes in the amount of fat in your liver and muscle after fasting. The scans use magnetic fields and radio signals to image the body, and do not involve X-rays or any ionising radiation. The scans are painless, but you will be asked to remove loose metal objects such as earrings or your watch. You should not have the scan if you have metal implants anywhere in your body (for example following surgery) or if you are claustrophobic (dislike enclosed spaces). Not being able to have the scans will exclude you from participating in the study. The scanner generates some noise, but you can listen to music through headphones if you wish.

Further measurements of your total body fat will be made using a "DXA" scan. This works much like an X-ray but the exposure to radiation is minimal (equivalent to the natural radiation received from the surroundings in one hour). The scan involves lying still on a flat couch while the scanner passes over the top of you and takes only a few minutes. It does not hurt and does not involve lying in an enclosed space.

A small drip (known as cannula) will then be placed into a vein, one in each of your arms. You may feel temporary mild discomfort whilst cannulas are inserted, but once in place, you will be able to relax and watch television etc. We will then use one of the cannulas to take small blood samples from you at regular intervals throughout your stay without

causing further discomfort. The total amount of blood we take will be less than 250 ml (about half of a normal blood donation).

In order to find out how much glucose your body is producing and the rate at which your body is breaking down fat, we will infuse 'non-radioactive' glucose and glycerol isotopes. These isotopes are heavier forms of glucose and glycerol (a body fat) which are normally present in small quantities in the body and in food. The infusion will start at 5 am and will continue until 11 am.

On the following morning, we will also perform a short procedure known as "calorimetry". This involves placing a transparent canopy over your head and shoulders so that we can measure how much oxygen and carbon dioxide you breathe in and out. Calorimetry will tell us the proportion of carbohydrate and fat your body utilises for energy production. This will be followed by a so called "intravenous glucose tolerance test" (IVGTT) in order to find out how much insulin your body produces in response to glucose. IVGTT involves giving you a dose of glucose followed by a dose of insulin both administered through one of the drips.

We would also like to invite you to consider undergoing to a muscle biopsy as an additional optional procedure for the study. The procedure is not a requisite to taking part in the study. Muscle biopsy will help us to study how insulin influences glucose metabolism in muscle. The procedure involves taking a very small sample from the muscles in the right thigh, using a special needle device. Before doing the biopsy we numb the area with local anaesthetic. The total amount of muscle tissue that we take is about the same size as the small eraser on the tip of a pencil. After the biopsy the thigh may feel bruised for about two days and then returns to normal. A bandage has to be worn on the thigh for 24 hours afterwards. Sometimes a small area of skin where the needle is inserted can feel numb for several weeks afterwards but this does not usually cause problems. You would still be able to participate in the study even if you decide not to undergo this procedure.

Before you leave we will perform MRS and MRI scans once more, to look for changes in the fat content in the liver, muscle and abdomen after the fasting period.

Once these tests are finished, you will be provided with a meal after which you will be free to go home.

Will I be reimbursed?

A payment of £100 will be made to the volunteers who complete the study to compensate them for their time and participation. We are able to cover travel or parking expenses, subject to the provision of receipts.

What are the possible risks of taking part?

The unusually long fast may cause some discomfort. We will try to make you as comfortable as possible and you will have the facilities to watch TV, movies or listen to music.

In order to find out how much glucose you produce and the rate of fat breakdown, we will use glucose and glycerol isotopes. These are non-radioactive heavier forms of the naturally occurring glucose and glycerol. They are normally present in small quantities in the body and in food and do not cause side effects.

The MRI scans of the abdomen will be reviewed by a consultant radiologist. There is a chance of less than 1:100 that your MRI scan may show an abnormality of which you are unaware. In such circumstances, you will be appropriately counselled by one of the study doctors. We will also inform your General Practitioner (GP) who will be able to arrange referral to appropriate specialists if necessary. Such early detection has the benefit of starting any treatment earlier but, in a small number of cases, may have implications for future employment and insurance.

What are the possible benefits of taking part?

Participating in this study is unlikely to benefit you directly, but the results will give us a greater understanding of the origin of type 2 diabetes, and ultimately help to improve care of people with this condition.

Who should I talk to if I have any questions or concerns?

If you have any questions regarding this study, please do not hesitate to ask any of the study nurses or the doctors listed below.

On behalf of the Study Team, we would like to thank you for taking the time to consider participating in this important research programme.

This completes part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What will happen if I don't want to carry on with the study?

If you agree to take part, please remember that you are free to withdraw at any time without giving any explanation. All you need to do is tell us. If you

withdraw from the study we will destroy all of your identifiable samples, but we will ask your permission to use the data collected up to your withdrawal for our later analyses.

What if there is a problem?

If you have a concern about any aspect of this study, you can speak to the researchers who will do their best to answer your questions (see contact details below). If you are unhappy about the conduct of the study and wish to complain, you can do this through the Addenbrooke's Hospital Patient Advice and Liaison Service (PALS). You can contact PALS by calling 01223216756 or by

Email: **pals@addenbrookes.nhs.uk**.

In the unlikely event that something does go wrong and you are harmed during the research study there are no special compensation arrangements unless this is deemed to be due to the negligence of one of the doctors or nurses. In this case, you may have grounds for legal action for compensation against the Addenbrooke's NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanism will still be available to you.

Will my taking part in the study be kept confidential?

Strict confidentiality will be maintained at all times. Only initials and a study number will identify those who participate in the study. Names and addresses will not be used. Only the researchers who are directly involved in the study will have access to the data. The study sponsors, Cambridge University Hospitals NHS Foundation Trust may also review the data for audit/monitoring purposes. The study files will be locked away in the Department of Paediatrics. The data will be stored for 5 years and will be disposed of securely.

The magnetic resonance imaging (MRI) data will be stored on a secure network to which only members of the Wolfson Brain Imaging Centre (WBIC) or relevant research team working in association with the WBIC will have access. Your MRI and magnetic resonance spectroscopy (MRS) scans will have your name and date of birth on them, but the scans are held securely on computer by the WBIC, with the Assistant Director of Imaging acting as custodian. In addition, in order to double check that there is nothing abnormal on any of the MRI scans, the imaging data will also be sent to and stored on the Addenbrooke's hospital system and will be checked by specialist radiology doctors in Addenbrooke's Hospital.

We may share some anonymous information gathered in the course of this study with other doctors and scientists but your name and address will be removed so that you cannot be recognised.

Will my GP be informed?

We will inform your GP about your participation in the study. Also, in the unlikely event of encountering any worrying results during the study, we will inform your GP who will be able to arrange referrals to appropriate specialists, if necessary.

What will happen to any samples I give?

The samples collected during the study will be labelled with a unique identification number. Names and addresses will not be used. The samples will be stored securely and locked away and only researchers directly involved in the study will have access to them. Once the measurements have been completed the samples will be disposed of securely.

What will happen to the study results?

Once the study is finished all data will be entered onto a computer and will be used to analyse the results. These study results may be presented at scientific meetings or published in a scientific journal but individuals will not be identifiable from any study data. If there is anything abnormal seen in the MRI scans, you would be contacted by the study doctors and referred to appropriate specialists in consultation with your GP.

Who is organising the research?

The research study has been organised by Cambridge University Department of Paediatrics, based at Addenbrooke's Hospital.

Who has reviewed the study?

Before any research goes ahead it has to be checked by an Ethics Committee. Your project has been reviewed by *Cambridgeshire* 2 Research *Ethics Committee*

If I agree to join the study

The study will be explained to you in more detail and you will be able to ask questions and voice any queries. Once you have agreed to take part we will ask you to sign a consent form. We will then arrange the date for your hospital visit.

Thank you for having taken the time to read this information sheet. If you have any

questions, please do not hesitate to contact a member of the research team:

Dr Ajay Thankamony (Research Fellow)
01223 768025
gna25@medschl.cam.ac.uk

Dr Daniela Elleri (Research Fellow)
01223 763405
de250@medschl.cam.ac.uk

Dr Päivi Tossavainen (Research Fellow)
01223 763405
pht27@medschl.cam.ac.uk

Dr Rachel Williams (Clinical Lecturer)
01223 763404
rmw33@cam.ac.uk

Professor David Dunger (Professor of Paediatrics)
01223 336886
dbd25@cam.ac.uk

UNIVERSITY OF CAMBRIDGE

Department of Paediatrics

Developmental Origins of Type 2 Diabetes: Tolerance of Fasting and IGF-I Levels

Information Sheet for Study Participants

Prof. David Dunger
dbd25@cam.ac.uk

Department of Paediatrics
University of Cambridge
Level 8, Addenbrooke's Hospital
Tel: 01223 336 886