DIRECT: Variation in response to GLP-1 Receptor Agonists **Patient Information Sheet Group A full study** ***<site name>***	
Version 5 February 07, 2013	

As you and your doctor have agreed that you should start a new injection treatment (GLP-1 Receptor Agonists (GLP-1RA)) for your diabetes, we would like to invite you to participate in a research project relating to this treatment. However, before you decide whether or not you wish to participate, we need to be sure that you understand firstly why we are doing it, and secondly what it would involve if you agreed. We are therefore providing you with the following information. Please read it carefully, and feel free to ask any questions you may have and, if you want, discuss it further with your doctor, friends or family. We will do our best to provide further information and answer any questions you may ask for now or at a later date. You do not have to make an immediate decision.

Who is conducting this research?
The research is being funded by the European Union, in conjunction with funding from some leading pharmaceutical companies. This group of researchers and scientists within Europe is called the DIRECT consortium and it is interested in how people with diabetes present or respond to treatment. The day-to-day organisation of the research in <*region*> is being co-ordinated by <*local PI*>. A number of centres are involved in the UK, and the University of Dundee with NHS Tayside is the co-ordinating centre and legal sponsor of the study (taking legal responsibility for it).

What is the purpose of this Research?
You are being started on an injection to help treat your diabetes. These injections are a type of drug called a GLP-1 Receptor Agonist (GLP-1RA), and currently there are two available types of this drug called Exenatide (Byetta), Liraglutide (Victoza) and Lixisenatide (Lyxumia). This type of treatment has been used around the world for the last few years and can have some dramatic results both in terms of stabilising blood sugar levels and helping with weight loss. This is why this treatment is becoming increasingly popular with patients and their doctors. However, some patients' blood sugar levels do not improve very much with these injections.

The purpose of this study is to try to find out why people respond differently to treatment with GLP-1RA. This raises a number of potential issues. If, as a result of this research, we could predict in advance that someone is not likely to respond to treatment it would save them the inconvenience of having to inject the treatment for at least 6 months and put up with potential unnecessary side effects. Conversely, if we understand why some people respond very well to this sort of drug, we may be able to develop better drugs that work in more people.

Why have you been asked?
You have been asked as you are about to start one of the GLP-1RA injections (Exenatide, Liraglutide or Lixisenatide).

What does the study involve?
In this study, we would like to carry out some tests before you start the injection treatment

that your doctor has prescribed, and again after 6 months of treatment. If you turn out to be in the group of people who respond particularly well, or the group of people who don't respond well, we would then like you to take part in some slightly more involved tests. We anticipate that one in four people will have a particularly good response and one in four will have a poor response to the GLP-1RA injection.

In more detail, there will be 3 visits that everyone will be asked to attend (two 30 minute visits and one 3 hour visit). We plan to do an MRI scan at one of these visits, however, we may need to organise this at a separate mutually convenient time. If you are in the group whose diabetes control responds very well or poorly to the treatment we would like you to attend for 2 further visits lasting 4-5 hours each to try to work out more about why your diabetes responded as it did.

All participants will be asked to take part in visits 1-3 (see flow chart)

Visit 1.

In this visit we will seek your consent to take part and ask you some details about your diabetes and treatment. All participants will have an MRI scan either at this visit (visit 1) or between visits 1 and 2 or at visit 2 or shortly thereafter according to the availability of the MRI machine (see section on MRI scan). If you are female we may ask you to have a urine based pregnancy test to check that you are not pregnant. If you've not had a diabetes blood test (HbA1c) within the last 2 weeks we will ask you to undergo one. Without the MRI scan this visit will take less than 30 minutes. The MRI scan will add a further 30 to 40 minutes.

Visit 2.

- Unless you take insulin, you will be asked to stop your diabetes treatment, except for metformin if you take this, for 3 days prior to this visit. This is so that the tests we do are not affected by your diabetes treatment. It is common practice in research studies to stop some diabetes treatment for this short period of time, and we would not anticipate this causing you any difficulty, but we will ask you to measure your blood sugar once a day during this time to make sure the sugar levels remain satisfactory.

  If you do take insulin, this will be continued until the morning of the visit, when we will ask you to omit your insulin treatment. If you take long acting insulin you will not inject this both on the morning of the study visit and the evening before the study visit.

  You will continue on all your other medication (drugs that are not for diabetes treatment) unaltered.
- You will be asked to attend for this visit in the morning, fasted. "Fasted" means nothing to eat or drink except water from midnight. At this visit you will have some body measurements taken, including height, weight and waist and hip circumference, along with your blood pressure.
- We will ask you to bring a urine sample along which we will test (with a dipstick) and then store frozen.
- We will then ask you to have a 'meal' in the form of an energy/build up drink called *Fortisip*. This allows us to assess how well your pancreas, the organ in your body that produces the hormone insulin, is able to produce insulin in response to this 'meal'. This meal test will involve the following:
  - A cannula will be inserted into one of your forearms. A cannula is a fine plastic tube that is inserted into a vein using a fine needle. The needle is then

removed leaving the plastic tube in place so that we can take blood samples without having to keep using a needle. Because this procedure requires a small pinprick, you may request local anaesthetic to numb the skin if you wish.

  - Blood will be taken before the 'meal'. Some of the blood will be analysed for your DNA and RNA (this is what holds your genetic code).
  - We will ask you to drink 250mls (one glass) of the liquid meal over a 3-5 minute period. Following this we will take 4 blood samples from the cannula over a 2 hour period after starting the drink.
  - In total we will take approximately 50ml (quarter of a cup) of blood at this visit.

- You will be given a light breakfast before leaving.
- After this meal test is over, you will be asked to restart your usual diabetes treatment, and to start on the new injection (exenatide, liraglutide or lixisenatide).
- If you have not had the MRI scan before this visit, this will either be carried out following the meal test or within 2 weeks. Without the MRI scan this visit will take 3 ½ hours. The MRI scan will add a further 30-40 minutes to the test time.

MRI scan. This is a 30 minute scan. As the MRI scanner uses a strong magnet we will need to check with you before this scan that you do not have any metal inside your body, such as joint replacements or surgical clips. We will ask you to lie on the scanning table for the scan and keep still during this time. The scan takes place inside an enclosed space, which some people find claustrophobic. You are able to talk to the radiographers (people who do the scan) during this time and you can listen to relaxing music. If you have a history of a penetrating metal injury to the eye you may be required to have an X-ray of the orbit (eye) prior to the MRI scan.

Between Visit 2 and 3

- You will now be injecting your new diabetes treatment. All advice and input regarding this, including whether to increase or decrease the dose, will be made by your medical team (specialist nurse, hospital doctor or GP). We would, however, ask you to keep all the empty injection 'pens' and bring these along to visit 3 so we can work out how many injections you've given yourself over the 6 months. We will provide you with a container (box or bag) for these pens. You should discard the needles in the usual way.
- If you stop your GLP-1RA treatment before 3 months, please let us know. If this happens we won't need you to come for any further study visits. If you stop or plan to stop your GLP-1RA after 3 months but before 6 months please let us know so that we can ask you to come for Visit 3 sooner (less than 6 months after visit 2).

Visit 3. This will normally be 6 months after visit 2.

- You will be asked to not take your diabetes treatment, except for metformin if you take this, on the morning of the study visit. If you do take insulin, this will be continued until the morning of the visit, when we will ask you to omit your insulin treatment. If you take long acting insulin you will not inject this both on the morning of the study visit and the evening before the study visit. You will attend this visit fasted (as for visit 2). At this visit we will simply repeat the measures of your height, weight, waist, hip and blood pressure, collect a sample of urine, and take a further blood sample (10ml equivalent to a tablespoon full). Importantly we will test your

diabetes control (HbA1c blood test) and this result will be made available to you and your clinical team. This result will tell us how well you have responded to the new GLP-1RA injectable treatment.

- You will be given a light breakfast before leaving. This visit will take at most 30 minutes.

If your blood glucose response to the new GLP-1RA injection is average (not particularly good or not particularly poor) you will have completed the study at this stage and you will continue with the injections if advised to do so by your clinical team. The research nurse will telephone you to let you know.

Half of all participants will be asked to attend for visit 4 and 5 (see flow chart)

We anticipate that one in four people will have a particularly good response and one in four will have a poor response to the GLP-1RA injection. If you fall into one of these groups we would like you to proceed to visits 4 and 5 so we can work out why you responded well or poorly. The research nurse will telephone you to let you know that we'd like you to come in for these study visits.

Visit 4 (for those selected; within 1 month of visit 3)

- You will remain on all your usual medications up until the day of Visit 4, but you will need to avoid taking paracetamol the day before the visit.
- You will take your usual diabetes medications, including your GLP-1RA (exenatide/liraglutide/lixisenatide) injection, prior to coming in for the visit (or just as you arrive), and you will need to record the time you took the medications. If you take insulin, you will not inject this on the morning of the study visit. If you take long acting insulin you will not inject this both on the morning of the study visit and the evening before the study visit.
- You will be asked to attend the study centre, fasted, in the morning.
- If you are female you may be asked to have a urine pregnancy test just to check that you are not pregnant at this time.
- You will have a cannula (fine plastic tubes to draw blood from or inject into as detailed in visit 2) inserted into a forearm. Should you wish, you will be given topical anaesthetic prior to this.
- Two blood samples will be taken, 15 minutes apart. You will then be asked to drink 250 ml of *Fortisip* 'meal' just like at visit 2. Immediately afterwards you will be asked to take a liquid paracetamol drink.
- We will take blood samples from the cannula for 3 hours after the Fortisip meal and paracetamol. In total we will take approximately 50ml (approximately a quarter of a cup).
- After this visit is finished you will be given a light lunch, and your blood sugar will be checked. We may need to give you one or more injections of a small amount of insulin to bring the blood sugar down. We will need you to stay until your blood sugar is satisfactory.
- After visit 4 you will be asked to restart all your usual diabetes medication and you

may be asked to re-start your GLP-1RA (exenatide,liraglutide or lixisenatide).

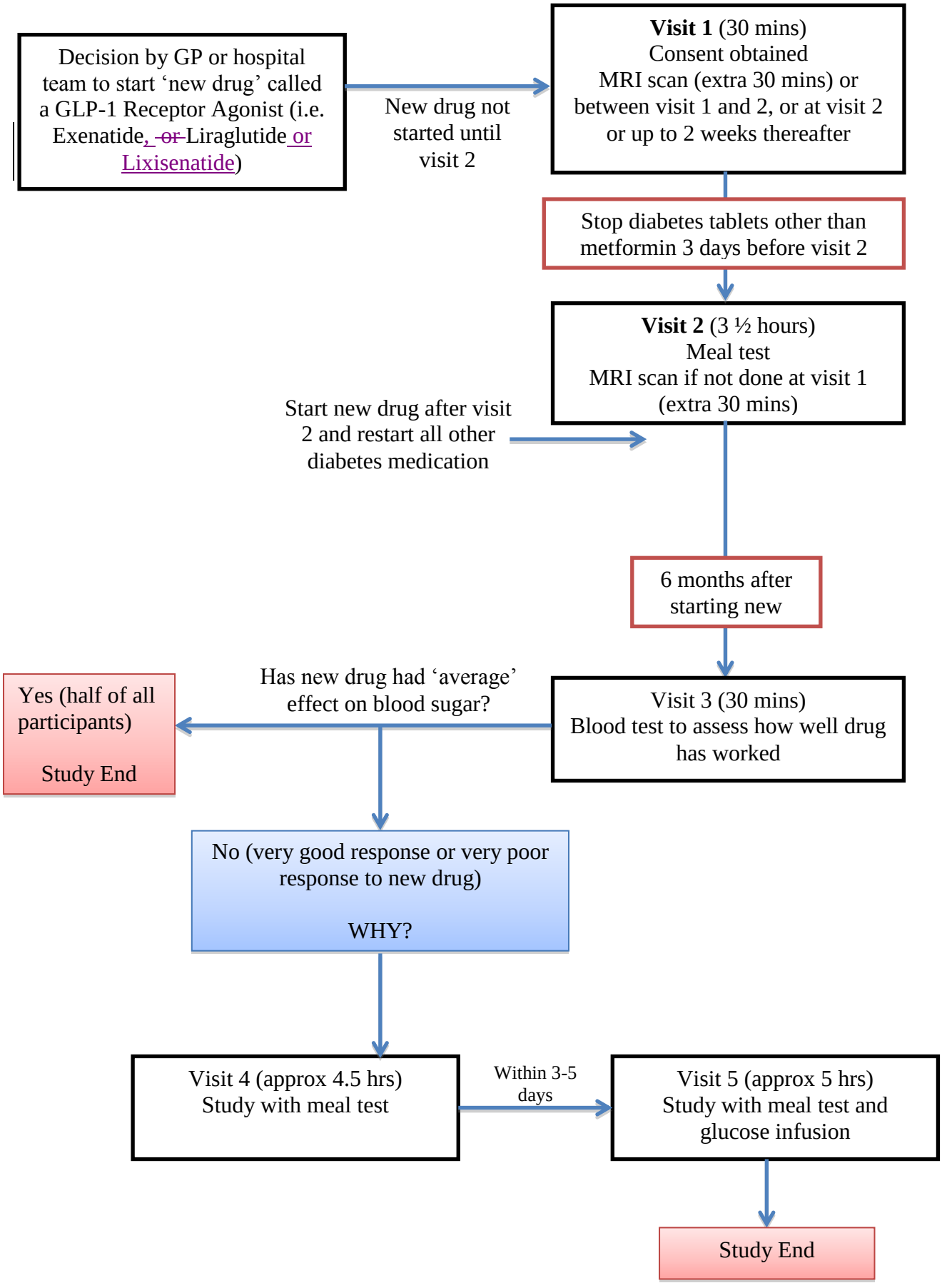
- This visit will last approximately between 4 and 6 ½ hours depending on your blood sugar level at the end of the test.

Visit 5 (for those selected; within 3-5 days of visit 4)

- You will remain on all your usual medications up until 3 days before Visit 5, when you will stop injecting your GLP-1RA (exenatide,liraglutide or lixisenatide). You will need to avoid taking paracetamol the day before the visit.
- You will take your usual diabetes medications, excluding your GLP-1RA (exenatide/liraglutide) injection, prior to coming in for the visit (or just as you arrive), and you will need to record the time you took the medications. If you take insulin, you will not inject this on the morning of the study visit. If you take long acting insulin you will not inject this both on the morning of the study visit and the evening before the study visit.
- You will be asked to attend the study centre fasted in the morning.
- You will then have a cannula inserted into each forearm. Should you wish, you will be given topical anaesthetic prior to this.
- Two blood samples will be taken. You will then be asked to drink 250 ml of *Fortisip* 'meal' just like at visit 4. Immediately afterwards you will be asked to take a liquid paracetamol drink.
- We will take blood samples from the cannula for 2 hours after the Fortisip meal and paracetamol.
- A solution of glucose will be attached to one of the cannula in your arm. Blood samples will be taken every 10 minutes for the next hour.
- After one hour the glucose solution will be swapped for a solution of GLP-1 and blood samples will be taken every 10 minutes for the next hour.
- On this visit day, we will take approximately 100ml (approximately a half of a cup) of blood.
- After this visit is finished you will be given a light lunch, and your blood sugar will be checked. We may need to give you one or more injections of a small amount of insulin to bring the blood sugar down. We will need you to stay until your blood sugar is satisfactory.
- This visit will last approximately between 5 and 6 ½ hours depending on your blood sugar level at the end of the test.

The study is now complete and you will resume all your usual diabetes medications.

FLOW CHART OF VISITS



Would there be any risks?
The insertion of cannulae into the forearms may cause discomfort and may result in bruising that may persist for a few days after the test.

You will be required to stop some of your diabetes medication prior to visit 2, 3, 4 and 5. This will only be up to a maximum of 3 days and should not cause you any health problems. Stopping medication temporarily is often done in diabetes research studies. There is a small chance that your blood sugar will rise enough to make you feel thirsty or to pass a lot of urine. If you feel unwell in any way during this time and if your blood sugar is high, we will ask you to start taking your pills again and you will be withdrawn from the study.

The MRI scan uses a strong magnet only, and does not use x-rays or other harmful radiation. Because the MRI uses a magnet we will need to make sure you do not have any metal inside your body that is magnetic, and you will be asked about this. There are no known safety concerns with MRI scanning. No contrast injections, which are sometimes used with other types of scan, will be given during the MRI scan.

Can I drive before and after these visits?
There will be no problem driving to or from each visit. We will ensure that your blood sugar levels are safe before you leave the research facility.

Are there any direct benefits to those taking part?
In general there is no major direct benefit to you as a participant in this study. The main benefit is that we hope to improve the care of patients with diabetes by better understanding why people get diabetes and how it can best be treated.

Will my GP be told of my participation in this study if I agree to take part?
Yes, with your permission we will write to your GP to let him/her know that you have agreed to take part. We will also let your GP know of any clinically important findings about your health.

What will happen if the MRI scan shows up something abnormal?
The MRI scan is being carried out to look at the liver and pancreas. In so doing we obtain images of the abdomen and chest. Occasionally abnormalities are seen. Often these have been there for years and are of no concern; rarely, a serious abnormality is seen that requires follow up by your doctor. The radiologist, involved in this study, who is an expert in MRI scans, will study any abnormality and decide on whether this needs to be followed up. In this circumstance we will tell you and your General Practitioner, and make your MRI images available to your clinical team.

What about confidentiality?
We regard the protection of your personal information (i.e., the security of any data we collect on you as part of this study) as being extremely important. We have special systems in place to make sure that once we obtain your consent and you have completed your study visits that we then separate your name, address and any CHI (health care) number from the rest of your data, which helps ensure third parties cannot link information about your health to your name, address or other information that identifies who you are.

When you have given consent to take part in the study we assign you a code known as a "study number". Your study number is then used in place of your name when keeping track of the remaining information or samples we collect from you. In general, we will not write

your name, address or health record number on any of your samples or on the forms that are used to collected information from you during the study. In this way, your study data and samples are anonymised. The only exception to this is when we send blood samples to the NHS lab, which your doctor and we will use to determine how well you have responded to treatment (HbA1c test), and the MRI images that are stored within the NHS clinical system and available to doctors looking after you in the future. When the information and samples we collect from you are exchanged amongst scientists working within our study, your samples and data will be identified using your study code and we will never pass on your name or address to scientists or third parties who are not directly involved in your clinical care, such as your GP. Your name will never appear in any report or publication that arises from this study.

<Towards the end of the study we store the file and consent form containing your name, address, health record number and study number in a special locked database held separately from the rest of the information. This is never shared with anyone outside of the research team in Dundee. The only reason for safely storing this information is to allow information from your past and future clinical/ NHS record to be extracted and linked anonymously to the study data for the next 10 years. >delete if not appropriate for site

What will be done with the information collected about me and blood and urine samples?
The anonymised data we collect from you directly and, with your permission, indirectly from your medical records relating to your diabetes will be linked to your anonymised MRI images and blood and urine samples. These data and samples will be stored indefinitely and used as part of this study to investigate different types of diabetes, why people get diabetes, why some people progress rapidly to insulin and why some people respond well or poorly to the diabetes drugs GLP-1RA (such as liraglutide and exenatide). The studies to be carried out will include genetic tests on your DNA and other genetic material as well as measuring other substances in the blood and urine.

Who will have access to my anonymised data and samples and how will this be controlled?
This study is being conducted by a large group of European doctors and scientists at Universities and Hospitals as part of a consortium that includes a number of companies from the pharmaceutical industry. None of these groups will ever have access to your name, date of birth or address. Your anonymised data will be held on highly secure computers internationally, including Denmark. This data will be accessible by members of the consortium and by approved members of the scientific research community, but access to the data and your blood and urine samples will require approval by a data access committee who ensure that all use of the data and samples is for scientific research and who ensure that appropriate data security and confidentiality is safeguarded. When the DIRECT study has completed all analyses, the samples will continue to be stored securely at the Peninsula NIHR Clinical Research Facility at the Royal Devon & Exeter Foundation Trust where additional use will require appropriate ethics committee approval.

Where commercial companies conduct research or provide financial assistance to non-commercial researchers to do the research, they could require the commercial rights to benefits arising from the discoveries. To allow potential collaborators to proceed you are asked to waive any future claim to financial benefit through participation in the study. So for example, if a company discovered the basis of a new diabetes drug by using your blood sample (as one of thousands of blood samples), and went on to profit from this discovery, you would have no future claim on this profit.

Who has reviewed this study?

The East of Scotland Research Ethics Committee REC1, which has responsibility for scrutinising all proposals for medical research on humans in Tayside, 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 relevant records, be made available for scrutiny by monitors from University of Dundee and NHS Tayside, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Could you choose not to take part?
Yes, of course. Participation in this study is entirely voluntary. If you chose not to participate, you wouldn't have to give a reason why and it would not affect any future medical care you may receive. It is in your and our best interests that you only participate in this study if this is something you freely decide to do.

Could you withdraw from the study?
Yes. You would be free to withdraw from the study at any time by contacting your local diabetes study team (contact details are at the end of this document). You would then carry on with your diabetes treatment as planned by your health care team. We would still store and utilise your samples and data collected up until that point unless you specifically ask us not to by formally withdrawing your consent. If you decided to withdraw your consent, we would destroy any of your samples held by us and from then on any anonymised data collected from you would not be included in the analyses we perform as part of this study. Blood results and MRI images that had been placed on the NHS clinical system would not be destroyed. Importantly, if your anonymised data had already been included by researchers in an analysis from which results had been derived and reported, this could not be changed.

What about insurance companies?
Sometimes insurance companies ask people if they've ever had any genetic tests. However participation in this study does NOT constitute a "genetic test" as defined by insurance companies. The fact that you are taking part in this study will not affect your ability to get insurance. Data will never be released by us to a third party unless we are legally required to do so.

What about travel expenses?
Your travel expenses will be reimbursed in full.

Will there be any further contact?
At time of participation we will ask you to indicate if you are willing to be re-contacted by the study team in the future to be invited to participate in any ethically approved research related to this project.

Complaints?
If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and to seek compensation through the University of Dundee who are acting as the research sponsor. Details about this are available from the study manager at the coordinating centre at University of Dundee Tel: (01382) *<xxxxxx>* or you can contact your local research team on the contact number at the foot of this document.

Also, as a patient of the NHS, you have the right to pursue a complaint through the usual NHS process. To do so, you can submit a written complaint to the Patient Liaison Manager,

Complaints Office, at your participating site. Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this is due to someone's negligence, you may have grounds for a legal action against NHS Tayside but you may have to pay your legal costs.

<Patient Liaison Manager address at participating site>

Who should I talk to if I have any further questions or concerns?
If you have any questions regarding this study you can phone the study team.

<Contact details of study team>

Or if you wish to seek independent advice then please contact <details of local contact> who is a clinician with an interest in diabetes who is independent of the research team.

Thank you for considering our request to take part in this study. Your involvement may help the current generation of those who suffer from diabetes, and might help to offer new treatments for our children's generation and beyond