DIRECT: Metformin intolerance **Patient Information Sheet**	
Version 3.0 September 02, 2013	

You have been given this information sheet to read because you have previously had some severe gut related side effects when taking metformin. We would like to you to take part in this study so we can try to understand why people develop such problems. 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 Dundee is being co-ordinated by Dr Ewan Pearson. The University of Dundee with NHS Tayside is the legal sponsor of the study (taking legal responsibility for it).

What is the purpose of this Research?
On the Patient Information Leaflet provided with Metformin it is stated that gastrointestinal problems such as nausea, vomiting, diarrhoea, stomach pain or loss of appetite are very common side effects of metformin (affecting more than 1 in 10 people). For some people these side effects are more marked than for others.
We are trying to understand why some patients with diabetes develop side effects to metformin, whereas other people can take it in high doses without any side effects whatsoever. You have been selected as someone who has had gut related side effects to metformin previously.

What does the study involve?
This is a very simple study consisting one visit only where we take a few tubes of blood, collect a urine sample, take some basic body measurements and ask a few questions about your diabetes. You do not have to change your medication at all. The visit can be arranged to be somewhere local to you.

In more detail:

The visit will last 30 minutes.
We will initially obtain your consent and then ask you questions about your diabetes (when it was diagnosed, how it is treated and what happened to you when you took metformin for the first time or tried to increase the dose of metformin). We will ask you about any other health problems you may have. We will take a note of all of your medication.

We will then measure your height and weight.

At this visit will take 30 ml of blood (an eggcup full) and collect a urine sample. The blood will be used to store your DNA (genetic code) and some plasma (the fluid the blood cells float in). If you have not had your kidney or liver function checked for more than 1 year we would like to collect an additional 5 ml of blood to check this result. This result will be done 'clinically' and therefore will be available to your GP and other health care professionals.

We will also ask your permission to access your medical records to find out more about your diabetes, and in particular to find out more about the symptoms you had and doses of metformin you were treated with previously.

Would there be any risks?
The blood test may result in minor bruising but there are no other risks.

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. It is important to be aware that taking part in this study will not improve your side effects with metformin if you try this drug again in the future.

Will my GP be told of my participation in this study if I agree to take part?
Yes we will inform your GP of your participation in this study and let him or her know if there is any significant new abnormality in your kidney or liver function if we have needed to check that.

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 if we need to send blood to the NHS labs to measure your kidney and liver function. 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.

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 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 and why some people have bad side effects to metformin. The studies to be carried out will include genetic tests on your DNA 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. After your anonymised data has been logged into the database, it will be held on highly secure computers internationally, including Denmark. We will require no further information from you once this is completed. The completed 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 REC2, which has responsibility for scrutinising 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. 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 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 reasonable travel expenses will be reimbursed in full.

Will I receive payment for taking part?
Patients who respond to the mailshot placed after September 2013 will receive a £10 shopping voucher (such as M&S) if they complete the study successfully.

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) 740561 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.

Mrs Hazel Scofield

Complaints and Claims Manager

Complaints and Advice Team

Level 9

Ninewells Hospital

Dundee

DD2 2DZ

Free phone: 0800 027 5507

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.

Dr Anna Barnett Tel: (01382) 383455 or Prof Ewan Pearson Tel: (01382) 383387

Or if you wish to seek independent advice then please contact Prof Rory McCrimmon, Tel:

(01382)383444, 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.