DIRECT

DIABETES RESEARCH ON PATIENT STRATIFICATION



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Behind the scenes: a research nurse's point of view

Nicky Mcrobert is a Senior Diabetes Research Nurse who works at the Churchill Hospital in Oxford which in partnership with the University of Oxford is one of the DIRECT institutions. She gave us a run-down on the area of the DIRECT study that she has been involved with.

Nicky says that it's one of the more complex projects she has been involved with as there were several complicated tests to carry out. Not only that but scheduling five appointments over six months takes a lot of planning. Add in arranging MRI scans to coincide with appointments, calls to check participants have stopped taking certain medicines before an appointment, calls to make sure they aren't having side-effects from the drugs and it becomes quite a logistical challenge.

There's a surprising amount of paperwork and administration that happens 'behind the scenes' with forms to be filled in and timings to juggle. At some of the more complex visits, there is also equipment to prepare and doses of medicines to calculate – each patient's is worked out according to their weight.

At some appointments participants had to have a cannula put in; this is a thin tube that is inserted into a vein in the arm using a fine needle. This meant that a meal test could be carried out, which involved taking blood samples at various time points before and after they had a carbohydrate drink. At the final appointment participants had to have a cannula in both arms in order to have blood taken at the same time as being given doses of medication and a glucose solution.

There's no denying the altruism shown by the participants who are willing to do these tests which aren't very pleasant, and also take up a lot of time – up to five or six hours for the appointments with the meal tests. Nicky is very admiring of these people who do all this for no personal gain but because they want to do something to help advance knowledge and understanding about diabetes, and hopefully improve diagnosis and treatment of the disease in the future. And that's true of everyone taking part in the DIRECT study.

For Nicky and the other research nurses the work is really only just starting when the participants leave. All the blood samples that have been taken need to be put in a machine called a centrifuge which spins them at very high speeds so that the blood separates into different layers. The layer of plasma (the colourless part of blood) is removed and put into a small tube called an aliquot – there can be up to eight from each blood sample. Aliquots are stored in large freezers so each one has to be labelled with a unique barcode that determines which participant it belongs to, in which freezer it will be kept and where in that freezer. Every barcode is scanned – like it would be in a supermarket – and this information goes into an electronic database so that when researchers need a particular sample, they can look on this database and easily find the aliquot they want.

Finally, all the clinical information gathered at the visit needs to be added to the database using a unique identification number. This links participants' information with their samples but keeps the details anonymous so the individual can't be identified by researchers analysing the data.

Eventually the samples are transported to the main research centres in Dundee and Exeter. Nicky and her team also organise this – 'dry ice' to keep the samples frozen while they are moved, a courier and someone to receive them at the destination.

All in all a great deal goes on that is unseen but essential to the smooth running of the DIRECT study. But as Nicky pointed out, it's the participants who are the crucial part and without you none of it would be possible.

DIRECT participants and researchers at the plenum in Gentofte in May 2016

Thanks to the Innovative Medicines Initiative (IMI) DIRECT has funding for another two years.

You can also receive updates or talk to us directly using our Facebook page: 'The Direct Project', via twitter: @DIRECTdiabetes or the participant section of our website: www.direct-diabetes.org/information

THANK YOU VERY MUCH!

Research is more relevant and valuable if it involves people who have first-hand experience of the subject being investigated. This means that for the DIRECT project, your continued support is vitally important. Without you and the data you provide, by answering questionnaires and giving samples, the studies wouldn't happen. We recognise that you give up a lot of time coming for appointments and sometimes the things you're asked to do aren't very nice!

So everyone working on the DIRECT project wants to thank you and encourage you to keep up your participation.

We realise that it may be frustrating if you were expecting your final follow-up appointment soon, but we ask you to please stay involved. Your contributions are essential to the continuing success of the project, and in finding out more about diabetes and treatments for it.

Have your say – the participant survey

So far, a total of 7,264 people have joined the DIRECT study – thank you! This is a fantastic number of people and will give the researchers a huge amount of valuable medical and genetic information. This will be used for research into new tests that will eventually help patients get the most suitable treatment as quickly as possible.

DIRECT researchers are also very interested in hearing your views and experiences of taking part, so some of the Oxford team have designed a survey to find out more. Professor Jane Kaye, Dr Harriet Teare and Dr Victoria Coathup worked on this and participants in Denmark, France, the Netherlands, Sweden and the UK have been invited to complete it. Hopefully you will have received your copy through the post or when you went for a follow-up appointment. If not, please do ask for one.

The survey asks about a number of things related to the DIRECT project including your:

- reasons for taking part
- experience so far of taking part
- views on the data that is collected from DIRECT being shared with other researchers after the study ends
- views on the types of researchers who may be able to use your data after the study ends
- thoughts on the risks and benefits of sharing data for medical research
- opinions about what needs to be considered if data is shared with other researchers

The completed surveys are anonymous although the researchers ask for some general information about you, including your age and gender. This won't be used to identify you – it's to help researchers understand differences in people's views. All answers are confidential and nobody apart from the researchers carrying out the survey will see them.

To date, the researchers have received a total of 635 completed questionnaires from the Danish, Dutch, Swedish and UK centres taking part in DIRECT. But they still hope to receive many more and will continue collecting them into the new year. So if you have a survey but haven't yet filled it in, it's not too late.

The next steps will be for the researchers to analyse the survey results and write them up. A summary will be made available for all participants and the full findings will be published in a scientific journal. We will let you know when this happens. In the meantime if you'd like to find out more or haven't had a copy of the survey and would like one, please get in touch with Dr Victoria Coathup at the University of Oxford (victoria.coathup@dph.ox.ac.uk).

RESEARCH ROUND-UP

The DIRECT research programme is split up into a number of different studies (called work packages) all of which have been making good progress – here are some updates.

The answer could be in your genes

One area of research being carried out in a joint effort from groups from Denmark, Germany, the Netherlands and the UK is investigating if particular genes affect the secretion of insulin. Different substances that are known to stimulate insulin secretion were injected into people's bloodstreams. Researchers found that the effects of one of these – a hormone (chemical produced by your body) called GLP-1 – are linked to variations in more than 50 genes. Some drugs that reduce glucose levels work on GLP-1 so it's useful to know more about how genes influence this hormone and may affect insulin secretion.

The researchers have also been looking at biomarkers in the blood to see if they provide information about insulin secretion in people who don't have type 2 diabetes. They found that the difference in the amounts of two markers is linked to insulin secretion. This difference is greater in people who have type 2 diabetes than in people who don't. The researchers also found that the level of these two markers in healthy people can predict who will go on to develop type 2 diabetes in later life. This might be useful for early identification of people who are at an increased risk of diabetes.

Responder or non-responder?

Another study aims to find out more about why some people with type 2 diabetes seem to benefit from treatment with a type of drug known as 'GLP-1 receptor agonists' whereas other people don't respond so well. This drug has several different forms including exenatide (Byetta, Bydureon), liraglutide (Victoza, Saxenda) and lixisenatide (Lyxumia), is given by injection and is designed to improve blood sugar levels.

Participants in this study were people who had just started taking one of these drugs, or who had been taking it for a few months. They made one or more visits over a few months to their local research centre where various blood samples for an assortment of tests were collected. The samples were taken before and during a period when they were treated with the drug while also having a 'meal' (in the form of a high energy drink). One of the research nurses from Oxford told us about working on this – see *'Behind the scenes: a research nurse's point of view'* overleaf.

Analysis of the samples and the data collected from these participants is ongoing. However, it has been possible to group them into people who have shown a clear response to the drug and those who have not. From this we hope to identify any differences between the two groups ('responders' and 'non-responders') in terms of their genetic make-up or their metabolism (the chemical processes going on in their body) that may help explain why they fall into one group or the other.

In the future this may enable doctors to predict who should be offered this type of drug to help treat their diabetes, and who would not benefit and so perhaps need an alternative treatment.

The faces behind the names

They mainly keep themselves hidden away but here are the academic lead for DIRECT, Professor Ewan Pearson (on the left), and Professor Hartmutt Ruetten (industry lead/coordinator), and below them you can see some of the DIRECT analysts hard at work at a recent meeting.

Why do only some people get type 2 diabetes?

One study within the DIRECT project is looking at how and why type 2 diabetes develops differently in different people. We know that certain things like being overweight or other people in your family having the condition can make you more likely to develop it. But there is much more that researchers want to find out about why only some people go on to a diagnosis of type 2 diabetes.

Professor Paul Franks (Lund, Sweden – pictured) and Professor Ewan Pearson (Dundee, UK) lead research which follows participants who don't currently have an official diabetes diagnosis but are in a possible 'pre-diabetic' state. This means that their blood sugar level is higher than normal, but not high enough to be classed as having type 2 diabetes. If you have 'pre-diabetes', you may be more at risk of developing type 2 diabetes in the future – but importantly, you may never develop it.

Professor Franks' team are looking at why this is and whether there are 'biomarkers' that show who will and who won't go on to get type 2 diabetes. By understanding more about the reasons for this, researchers will be better able to try to find ways of helping to prevent type 2 diabetes in the first place.

This team are also looking at why people who already have type 2 diabetes don't all progress in the same way. They want to find out why type 2 diabetes in some people doesn't change too much over time and is straightforward to manage (ie by watching what you eat or taking just one type of medication) but in others the condition gets worse much more quickly and needs lots of different treatments.

Currently there is no way of knowing how type 2 diabetes will develop when someone is first diagnosed. Researchers believe that by understanding more about type 2 diabetes when it's in its early stages, they will be in a better position to tell how it will progress in future in different people. In particular, they are investigating how well someone's pancreas produces insulin after eating, and if how much fat there is in the pancreas and liver could affect this.

As you will know if you've been involved with either of these areas of research, a number of measurements have been taken and samples collected. These helped establish what is known as a 'baseline measure' when you first joined the study; the tests were then repeated 18 months later. Over 2,000 people provided information at baseline in the pre-diabetes study and of these, over nine out of 10 had follow-up measurements taken at 18 months. In the other study, over 800 people gave baseline information and just over eight in 10 of these have had second measurements taken.

The plan had been to then take measurements again at 36 months from the group with pre-diabetes. However, in most people the condition had not progressed as fast as the researchers had expected. So they have extended the time to 48 months from the date of first appointment and in early 2017 a sub-group of these people will be asked to attend another appointment to follow up their progress. Similarly, the study of people with early stage type 2 diabetes had to be extended so participants were followed up after 36 months. These visits are now almost complete and soon the samples will be ready for scientific analysis.

If you're one of these participants, it's good news that your type 2 diabetes hasn't become as serious as researchers had previously thought it might. However, it does present some challenges for researchers, not least that as time goes on, it's more difficult for them to maintain contact with everyone who is taking part and keep them involved in the study. Participants are so valuable to DIRECT – in fact all research projects! – and we don't want to lose you.

What exactly is a biomarker anyway?

A biomarker is something that can be identified or measured to give an indication of a biological state. For example, detecting a particular antibody in someone's blood may mean that they have an infection. Biomarkers can show many things, such as how a disease is developing or how well a treatment is working.

The DIRECT study is looking for biomarkers that show how diabetes develops differently from person to person and how well certain treatments work in different people.