

Participant Information Sheet

Type I Diabetes TrialNet Protocol TN-07

ORAL INSULIN FOR PREVENTION OF DIABETES IN RELATIVES AT RISK FOR TYPE 1 DIABETES MELLITUS

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You ('you' means you or your child) have been participating in the TrialNet Natural History study. You have had blood tests that show you have certain markers associated with an increased risk of developing type 1 diabetes. You have also had an **Oral Glucose Tolerance Test (OGTT)** that showed that your blood glucose levels are normal.

You are now being invited to take part in another TrialNet research study which is a diabetes prevention trial. Please take time to read the following information carefully. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please talk to others about the study if you wish.

What is the purpose of the study?

The purpose of this study is to see if giving oral insulin (that is insulin given by mouth) will delay or prevent type 1 diabetes.

TrialNet is an international research group dedicated to the study, prevention, and early treatment of type 1 diabetes. Type 1 diabetes is an autoimmune disease. This means that the immune system (the part of the body that helps fight infections) mistakenly attacks and destroys the cells that produce insulin (the islet cells found in your pancreas). The body's ability to produce insulin decreases as the immune system destroys islet cells.

Oral insulin has already been tested in a diabetes prevention trial. In the overall study, oral insulin did not delay or prevent diabetes. However, the

results suggest that oral insulin may delay diabetes in people with higher levels of insulin autoantibodies. This new study is being done to see if these findings are true in a similar group of people.

This booklet describes the tests and procedures you will have if you are in the TrialNet Oral Insulin Diabetes Prevention Study. If you choose not to be in the Oral Insulin study, you can remain in the Natural History Study to be monitored for the possible development of type 1 diabetes.

What is the drug that is being tested?

The medication is a capsule containing insulin crystals. One capsule should be taken every day. Insulin taken in this way is digested by your stomach and will not have any effect on your blood glucose level.

There is also a placebo (dummy drug) group in this study. This group will be given a capsule containing crystals, but these do not contain the active ingredient. This is a 'blinded' randomised trial, so that neither you nor the researchers will know which capsules you are taking until the study has been completed.

What will happen during the study?

Study visits

For this study, you will have an initial study visit, a three month follow-up visit, and then regular visits every six months while you are in the study.

At each study visit, we will ask you questions about your family history and medical history. You will have a brief physical examination and blood tests. The total amount of blood collected for tests done at each study visit will be safe for your age and weight, and for most people this will be about 4-7 tablespoons. You can learn more about specific blood tests in the Research Volunteer Handbook.

The exact duration of the study is not known. We hope that the study will take no longer than 7-8 years from its start in 2007.

Initial study visit

The initial study visit will take place within 7 weeks of you having an oral glucose tolerance test (OGTT) as part of the Natural History study. At this visit you will have a test called an **Intravenous Glucose Tolerance Test (IVGTT)**. The IVGTT tells us how well the pancreas makes insulin. After an overnight fast (not eating during the night), glucose is given through a vein in your arm (intravenously). To make the blood sampling easier, we will place an intravenous needle and plastic tube (IV cannula) in a vein in your arm. The needle will be removed but the IV cannula will stay in your arm until the

end of the test. Blood samples will be taken before you receive the glucose and then several times after the glucose is given. The entire test will take about 20 minutes.

Most people will only need one IVGTT. However, in some cases we will ask for a second IVGTT to confirm the results of the first test. This can be done at the time of your next study visit.

As in the Natural History study, we will also test your blood to see if you have diabetes related autoantibodies. Autoantibodies are proteins that are made by the body's immune system. In diabetes, they are a sign that the cells in the pancreas that produce insulin could be damaged. These proteins can be found in the blood years before a person develops type 1 diabetes.

At the end of the study the results of your antibody and IVGTT tests will be used to understand the effects of oral insulin in different groups of people.

Randomisation

After your initial study visit you will be randomly put into one of two groups. One group will receive oral insulin and the other group will receive a placebo or 'dummy drug'. A placebo looks like medicine, but has no medicine in it. Neither you nor the researchers can choose what group you will be in. Neither you nor the researchers will know who is getting oral insulin and who is getting the placebo.

Follow-up visits

Your 3 month follow-up visit will consist of a brief medical history, a limited physical examination, blood testing, and pregnancy testing for all female participants of child-bearing age (i.e. after puberty).

You will be asked to come in for study visits every 6 months. Every time we will ask questions about your health, do a limited physical examination, draw some blood, and perform a pregnancy test for female participants. Every 6 months we will just check your height, weight, blood pressure, and waist size. At the annual visit (i.e. 12 months, 24 months etc) we will do a fuller physical examination (not internal). This will involve listening to your chest and examining your abdomen, as well as testing your reflexes etc.

We will also draw some blood for testing autoantibodies and HbA1c (this is a test that measures a person's average blood glucose level for the last 2-3 months). An OGTT will be done in the morning after an overnight fast (not eating during the night). Your blood glucose (sugar) will be measured after you drink a sweet liquid that contains glucose over a 5-minute period. To make the blood sampling easier, we will place an intravenous needle and

plastic tube (IV cannula) in a vein in your arm. This IV cannula will stay in your arm until the end of the test. Blood samples will be drawn through the IV cannula before you drink the liquid and then at several times after you have finished drinking it. A total of about 1 tablespoon of blood will be drawn for the OGTT. The entire test will take about 2 hours.

If any of the tests suggest that you have diabetes, we will need to confirm this result. This may require an additional OGTT.

We will provide you with the study medication you will need to take until your next visit.

Phone calls

A member of the research study team will contact you every three months to ask about your health and to check that you are still taking your study medication.

Study Treatment

You (or your child) will be asked to take a capsule every day. This should be swallowed as a capsule, if possible. If you (or your child) cannot swallow capsules, you can mix the contents into juice or sprinkle on to a soft food, such as yoghurt. The capsule should be taken before breakfast. If you forget you can take it before lunch or dinner.

What are the risks?

There are some risks to having your blood drawn. These risks are discomfort and/or a bruise at the needle puncture site. Once in a while, some people may faint. It is rare, but some people may get an infection, form a small blood clot, get swelling of the vein and surrounding tissue or bleeding at the needle puncture site.

There are also some risks to the OGTT and IVGTT. Some people may feel sick when they have the OGTT. Some people may feel flushed when they have the IVGTT.

There is a small possibility that, instead of delaying or preventing the development of disease, oral insulin could increase the destruction of beta cells in the pancreas. This would cause type 1 diabetes to develop more quickly. However, previous studies using the same dose of oral insulin that we will use in this study have not shown any increase in the risk of developing diabetes.

If you are pregnant or breast-feeding you cannot take part in the study. All women of childbearing age will be asked to use a reliable form of

contraception. Pregnancy tests will be carried out at regular intervals.

Are there any benefits?

No specific benefit can be promised you from your (or your child's) participation in this study. However, since you (or your child) are at risk of developing diabetes, the close observation and frequent testing for diabetes may allow earlier detection and treatment of type 1 diabetes than would otherwise be the case. The TrialNet research program might increase knowledge about the prevention of type 1 diabetes in the future

What will happen to my blood samples?

If you agree, we would also like to store samples of your blood. Your blood samples will be used to help us learn more about how the immune system might cause type 1 diabetes and about new ways of identifying people at risk for type 1 diabetes. They also could help us learn more about type 1 diabetes, its complications (such as eye, nerve and kidney problems) and other conditions for which patients with type 1 diabetes may be at increased risk. There is more information about this in Part 2 of the form.

Are there any alternative treatments?

Before you decide to take part in this study, we will discuss with you the other options available to you. You may choose not to participate in this study. At present, there is no established treatment for persons found to be at risk of developing type 1 diabetes. There may be other research studies that you can choose to be in.

Will I receive anything for taking part?

If you decide to be in this study you will receive a small amount of money to cover your expenses for each study visit that you complete. By signing this consent form, you understand and agree that, if this research project results in the development of any product that can be sold, you will not receive a share of any money that is made.

Do I have to take part in the study?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. If you chose to withdraw you can stay in the Natural History Study.

Your doctor may also choose to take you out of the study at any time if he/she feels that staying in the study may hurt you. This may happen if the side effects are too great, or if you do not follow the study instructions. You will be told of any new findings that affect your being in this study.

What happens when the research stops?

The treatment will not be available after the research finishes. If you develop diabetes during the course of the study or after the study has ended you may be eligible to take part in other TrialNet studies.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

What will happen to my data?

All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Where can I get more information?

You will receive a copy of this information sheet. Please ask questions about this study or consent at any time. You are welcome to discuss this study or consent with your family, doctor, or anyone else. The staff of the research study will be happy to discuss any questions with you. You may direct your questions to the TrialNet team on 0117 323 6188

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 to my data?

Your consent to be in this study includes consent for the TrialNet researchers to review all your health records as may be needed for the purposes of this study. Your consent gives TrialNet researchers permission to collect study information (data) related to this study and to use it for research purposes. Your consent also includes permission for the sponsor of this study (NIDDK) and the UK and US regulatory authorities (the Medicines and Healthcare products Regulatory Agency (MHRA) and the Food and Drug Administration (FDA)) to review your study records.

Information from your research records will be sent to our central coordinating centre at The University of South Florida, USA for statistical analysis. No personal information that directly identifies you will be included with these data. Personal information is information such as your name. Instead you will be assigned a unique study code. The key to the code, linking your personal information to you, will be kept in a locked file here at the University of Bristol. Only Prof. Polly Bingley and her research staff will have access to the key to the code. The data obtained from this study will be combined with your Natural History data. After the study is completed, the study data may be placed in a US government information bank and may become available to researchers under the supervision of the NIDDK/NIH. Your privacy will be protected whenever this information is used.

TrialNet researchers will consider your records private. Rarely, representatives of the MHRA, U.S. Department of Health and Human Services (DHHS) or TrialNet may review or ask for a copy of your study records. If this happens, we will provide your records. Also, employees of the University of Bristol, the NHS Trusts' R&D group or its agents could be allowed to see your study records to make sure that the study is being done properly.

The results of this study may be published for scientific purposes. By signing this form you are agreeing to this. Your records and results will not be identified as belonging to you in any publication.

Our procedures for handling, processing, storage and destruction of their data are compliant with the Data Protection Act 1998

Who else will be informed that I am taking part in the study?

With your permission we will contact your GP to inform him that you are

taking part in a research study. He or she will be sent some information about the study. We will not routinely send results of the study investigations. We may need to contact your GP if we find you have developed diabetes during the course of the study. We may also need to talk to other healthcare professionals about your care during the study. With your permission we will inform the diabetes consultant who cares for the person in your family with diabetes.

What will happen to my stored blood samples?

Your blood samples will be stored without your name or any other identifying information on them. You will not routinely be provided with test results from stored samples. Your blood samples could be stored for a number of years, but we can't say for how long. Even if you do not want to have your samples stored, you can still participate in the rest of the study.

As long as TrialNet continues, your stored blood samples could be used by TrialNet researchers and researchers from outside of TrialNet. However, if researchers from outside of TrialNet want to use your samples, they must first get permission from TrialNet researchers and the sponsor of this study, the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK).

When TrialNet is over, your blood samples will continue to be stored under the supervision of the NIDDK. Researchers would not be able to use your blood samples without the permission of the NIDDK.

Your blood sample will be treated as a gift to the custodian of the NIDDK sample repository. They will assume responsibility for your sample's use, storage and disposal.

What if something goes wrong?

Taking part in this research study may hurt you. If you need to get medical care right away, you should go to your GP or to the nearest Accident and Emergency. Be sure to explain that you are in a research study. If you do not need emergency care, the TrialNet researchers will help you get the care you need.

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then the University of Bristol will provide compensation for an injury caused due, on the balance of probabilities, to taking part in this research study.

The University will pay compensation where the injury probably resulted from the drug (oral insulin) or any test or procedure you receive as part of the research study.

The University would not be bound to pay compensation where the injury results from some cause outside the scope of the research study.

Any payment would be without legal commitment.

Please ask if you would like to receive more information about this.

How is the study funded?

The National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) is providing major support for this study. The study is also paid for by National Institute for Allergy and Infectious Diseases (NIAID), the National Institute for Child Health and Human Development (NICHD), the National Center for Research Resources (NCRR), the Juvenile Diabetes Research Foundation (JDRF), and the American Diabetes Association (ADA).

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by the North Somerset and South Bristol Research Ethics Committee

Thank you for taking time to read this information.

Type 1 Diabetes TrialNet Protocol TN-07

ORAL INSULIN FOR PREVENTION OF DIABETES IN RELATIVES AT RISK FOR TYPE 1 DIABETES MELLITUS

Name of Researcher: Prof Polly Bingley, Diabetes & Metabolism, Medical School Unit, Southmead Hospital, Bristol, BS10 5NB

Please read the Information sheet before you complete this form.

This form is for you to let us know if you agree to take part in this study ('consent'). After you have read all the information and asked any questions you have the investigator will go through this form with you and ask you to sign it if you wish to take part.

The following checkbox gives you the choice of whether to take part in the study or not.

I have read the information sheet about the study or it was read to me. I know what will happen, both the possible good and bad (benefits and risks). I choose to be (or to have my child) in this study: I know I can stop being in the study at any time and I will still get the usual medical care. I will get a copy of this consent form and the information sheet.

YES **NO** **INITIALS** _____

With your permission, we will also draw up to an additional 3 tablespoons of blood for future studies. The amount of blood will be adjusted according to your body weight. Please indicate whether you are willing to provide blood samples for storage. Your samples could be used to help us learn more about how the immune system might cause type 1 diabetes and about new ways of identifying people at risk for type 1 diabetes. They also could be used to help us learn more about type 1 diabetes, its complications (such as eye, nerve and kidney problems) and other conditions for which patients with type 1 diabetes may be at increased risk. Even if you decide not to have your blood samples stored, you can still participate in this study.

*I give permission for my blood samples to be stored for further testing as indicated in this form (mark **one** of the options below).*

- **Yes, store all samples including the genetic samples** **INITIALS** _____
- **Yes, store all samples, but not the genetic samples** **INITIALS** _____
- **No, I do not give permission to have any samples stored** **INITIALS** _____

I agree to my GP being informed of my participation in the study.

YES **NO** **INITIALS** _____

If YES please complete the GP contact form

I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Bristol, from regulatory authorities, U.S. Department of Health and Human Services (DHHS), TrialNet or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

YES

NO

INITIALS _____

SIGNATURES: By signing this consent form, you agree that you have read the information sheet and consent form and that the study has been explained to you. You also agree that your questions have been answered and that you agree to be in this study. You do not give up any of your legal rights by signing this informed consent form. You will receive a copy of this consent form and the information sheet.

CONSENT FOR SUBJECTS 18 YEARS OF AGE AND OLDER:			
Signature of Subject		Date	
Date of Birth			
Print Name of Subject			
Signature of Person Obtaining Consent		Date	
Print Name of Person Obtaining Consent			
Role of Person Obtaining Consent	Research Nurse / Investigator / Co-Investigator		

CONSENT FOR CHILDREN UNDER 18 YEARS OF AGE:			
Print Name of Subject			
Date of Birth			
Signature of Mother/Guardian			
Print Name of Mother/Guardian		Date	
OR			
Signature of Father/Guardian		Date	
Print Name of Father/Guardian			
Signature of Person Obtaining Consent		Date	
Print Name of Person Obtaining Consent			
Role of Person Obtaining Consent	Research Nurse / Investigator / Co-Investigator		