ASCENDPLUS

A STUDY OF CARDIOVASCULAR EVENTS IN DIABETES

Participant Information Leaflet

You are invited to join ASCEND PLUS, a clinical trial in people with type 2 diabetes.

How can we protect people with type 2 diabetes from heart attacks, strokes and other health problems?

A guide to this leaflet

A quick summary of ASCEND PLUS

- You are invited to join a health research study called ASCEND PLUS. **You don’t have to take part – it’s up to you.**
- The aim of the study is to find out whether a treatment called oral semaglutide can prevent heart and circulatory problems (such as heart attacks and strokes) and other complications in people living with type 2 diabetes.
- Oral semaglutide helps to control blood sugar levels and lower body weight, and is already approved for use in the UK as a treatment for some patients with type 2 diabetes.
- The study is coordinated and sponsored by the University of Oxford, in partnership with the National Institute for Health and Care Research.
- The study will involve 20,000 volunteers with type 2 diabetes. The results of this trial could help improve the lives of the millions of people worldwide with type 2 diabetes, and prevent thousands of deaths from heart and circulatory disease each year.
- If you join the study, you will be asked to take one study tablet each day for about five years, in addition to your existing treatment, and to complete a total of about 12 questionnaires during this time.
- Half of the study participants will get tablets containing semaglutide and half will get inactive placebo tablets (which look like the oral semaglutide but have no active drug in them). Which treatment you get is decided by chance and you will not know if you are taking the active tablet.
- No additional clinic visits are required as part of this study. The study medication will be sent to your address by post.
- If you join the study, your GP will be informed. Your access to medical care will not be affected, whether or not you take part.
- This leaflet tells you about the study so you can decide whether to take part.

> “Despite good treatment, some people with type 2 diabetes will unfortunately still go on to develop complications. We want to find out if taking oral semaglutide can help to reduce the risk of these problems.”
>
> - Dr Marion Mafham, Co-Principal Investigator

Having type 2 diabetes increases your risk of other major health conditions

Around one in 11 adults worldwide has diabetes: a long-term condition where a person's blood sugar levels are too high.

There are two main types of diabetes:

- **Type 1 diabetes** – where the body's immune system attacks and destroys the cells that produce the hormone insulin so that no insulin is produced. This is treated with insulin injections.
- **Type 2 diabetes** – where the body does not produce enough insulin, or the body's cells do not react to insulin. This usually occurs later in life and is often treated with tablets. Some patients eventually need to be treated with insulin.

People with diabetes are more likely to suffer from other major health problems. These include heart and circulatory problems (including heart attacks and strokes), high blood pressure and dementia. Diabetes can cause kidney disease, problems with feeling in the feet, and eye problems that may affect vision.

What is this research study about?

ASCEND PLUS is a clinical trial led by Dr David Preiss and Dr Marion Mafham at the University of Oxford. The study aims to find out if regularly taking oral semaglutide, a once-daily tablet medication for type 2 diabetes, can help to prevent heart attacks, strokes or mini-strokes, the need for heart artery 'balloon' and bypass procedures, and death from heart and circulatory conditions.

Semaglutide is similar to a hormone called Glucagon Like Peptide 1 (GLP-1) in the body. It acts like the hormone to:

- Help the body make more insulin
- Help the liver make less sugar (glucose)
- Reduce hunger and lower energy intake

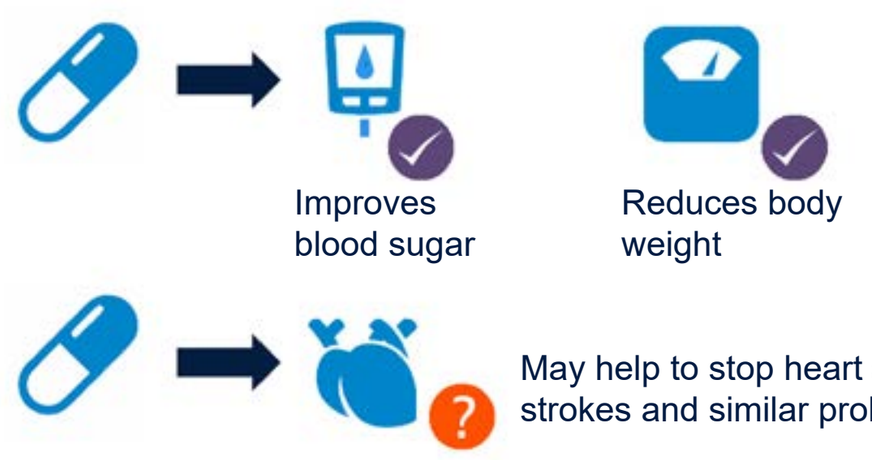
All of these help to control blood sugar levels. You can find out more about GLP-1 and how oral semaglutide works on the study website (**www.ascend-plus-trial.org**).

ASCEND PLUS is testing **oral** semaglutide (taken 'by mouth' as a tablet). Semaglutide is also available as an injection but ASCEND PLUS is only testing the oral version of this treatment.

Oral semaglutide (and other medications which work in a similar way) reduces the risk of heart and circulatory problems, such as heart attacks and strokes, in people who already have one of these conditions or are at very high risk because of other health problems. However, currently few UK patients with diabetes are prescribed these medications as they are only recommended for people with specific other medical conditions as well as diabetes.

Because heart attacks and strokes often result in disability and reduced quality of life, we need treatments that can reduce the risk of these happening in the first place. The aim of ASCEND PLUS, therefore, is to find out whether regularly taking oral semaglutide can prevent heart attacks, strokes, and other heart and circulatory problems from developing in a broad range of people with type 2 diabetes **who have never had a heart attack or a stroke before.** This would allow the treatment to be used in many more patients than is currently the case.

Oral semaglutide



Oral semaglutide could also potentially reduce the risk of people with type 2 diabetes from developing other health problems related to diabetes, such as kidney disease and long-term memory problems including dementia. The ASCEND PLUS research team will also investigate this.

Why me?

People are potentially able to take part in ASCEND PLUS if they are at least 55 years old, have type 2 diabetes and have not had a heart attack or stroke in the past.

A computer search of your electronic medical record held by NHS Digital suggested you might be able to take part. The study invitation letter was produced, printed and mailed by Paragon Customer Communications Ltd who also handle patient letters for the NHS. Your name, address and post-code were passed securely to Paragon Customer Communications Ltd who will not use this personal data for any other purpose and will delete the data within 30 days of sending this invitation letter. This process has approval from the South Central - Oxford B Research Ethics Committee, called a “favourable opinion”, and support from the Health Research Authority (HRA) following advice from the Confidentiality Advisory Group (an independent body which provides expert advice on the use of confidential patient information).

You can find out more about your rights and how the ASCEND PLUS team processed data about you by visiting the study website or reading the leaflet ‘Data protection information for participants’ sent with this leaflet and available on the study website.

Do I need to take part?

No, you do not have to take part in this study. **It is your decision.** But we hope you will because, if you do, many people might benefit from this research in years to come.

Your access to medical care will not be affected, whether or not you take part. If you agree to take part, we will tell your GP.

What will I be asked to do if I take part?

The ASCEND PLUS researchers will recruit 20,000 people to take part in the study. Half will get tablets containing semaglutide and half will get inactive placebo tablets (which look like the semaglutide tablets but have no active drug in them). Which treatment you get will be decided by chance by a computer (like tossing a coin). This process is called randomisation. You, and your doctors, will not know which treatment you are given and the study staff will not know either (although they can find this out if needed).

If you join the study, you will be asked to take **one study tablet each day** for about five years in addition to any other medications that you usually take. You will also be asked to complete a questionnaire four times in the first six months, and then once every six months. In total, this will be about 12 questionnaires spread over five years. You can choose whether you complete the questionnaires online yourself or with a research nurse by telephone or video call.

No additional clinic visits or travel are required to take part. Everything happens from your own home, and the study medication will be posted to your address, **so it won't interfere with your daily routine.**

During the five-year scheduled treatment period, and for up to 20 years after that (unless you contact us to opt out), we will collect health data about you from NHS Digital, other NHS organisations and national registries.

What happens to my usual diabetes treatment?

During the study you should continue any diabetes treatments prescribed by your own doctor, such as tablet medications or insulin. If you develop low blood sugar, the study team may suggest an adjustment to your diabetes medication. This would be discussed with your GP.

Are there any alternative treatments?

ASCEND PLUS is testing whether **adding** oral semaglutide to patients' usual diabetes treatment helps to protect against complications of type 2 diabetes.

Scientists are not sure how oral semaglutide might protect against heart and circulatory problems. Research suggests that it is not all through better blood sugar control (although blood sugar control is very important for maintaining health in people with type 2 diabetes). This is why people with type 2 diabetes are being invited to take part in ASCEND PLUS even if their blood sugar control is good.

Currently in the UK, oral semaglutide and similar medications are recommended only for people who have particular medical conditions since studies have not assessed the effects of these treatments in a broad range of people with type 2 diabetes.

However, if your doctor has already prescribed, or is planning to prescribe, oral semaglutide (Rybelsus ®) or similar drugs given by injection, you will not be able to take part in ASCEND PLUS. This includes the following treatments:

- Semaglutide injections (Ozempic ® or Wegovy ®)
- Dulaglutide (Trulicity ®)
- Exenatide (Byetta ®)
- Liraglutide (Victoza ® or Saxenda®)
- Lixisenatide (Lyxumia ®)

If you have been intolerant or allergic to one of these medications in the past, then you will not be able to join the study. Please do check these details with your doctor, if necessary.

What are the benefits of taking part in this study?

Taking part in this trial might not help you. However, you will be helping doctors and scientists improve treatment for people with type 2 diabetes. If successful, results from this study might help to prevent many thousands of heart attacks, strokes and heart artery stenting (‘balloon’) and bypass procedures around the world.

Are there any risks?

Oral semaglutide is already approved in the UK for treating type 2 diabetes. But, as with most treatments, it can cause side effects which some people may experience, and others may not. **You can stop taking the study medication at any time if you want.** Further information is provided in the ‘Possible side effects’ section on page 15 of this leaflet.

Will taking part affect my medical insurance or travelling?

If you have private medical insurance or require travel insurance, your policy may be affected by taking part in the trial. You should check this with your insurance provider. You can contact us for advice if you find taking part in ASCEND PLUS would cause problems with your insurance company.

How do I join the study?

If you decide to join the study, you will be asked to complete three steps:

Step one is called **‘Screening and consent’**. This is where you will:

- answer questions to find out if the study is safe and suitable for you
- get information about the study
- agree to join the study, if you still want to.

Step two is called **‘Run-in’.** This lasts about two months during which:

- you try out taking the semaglutide tablets
- your GP is told that you are planning to join the study
- you might choose to talk to your family or GP about the study.

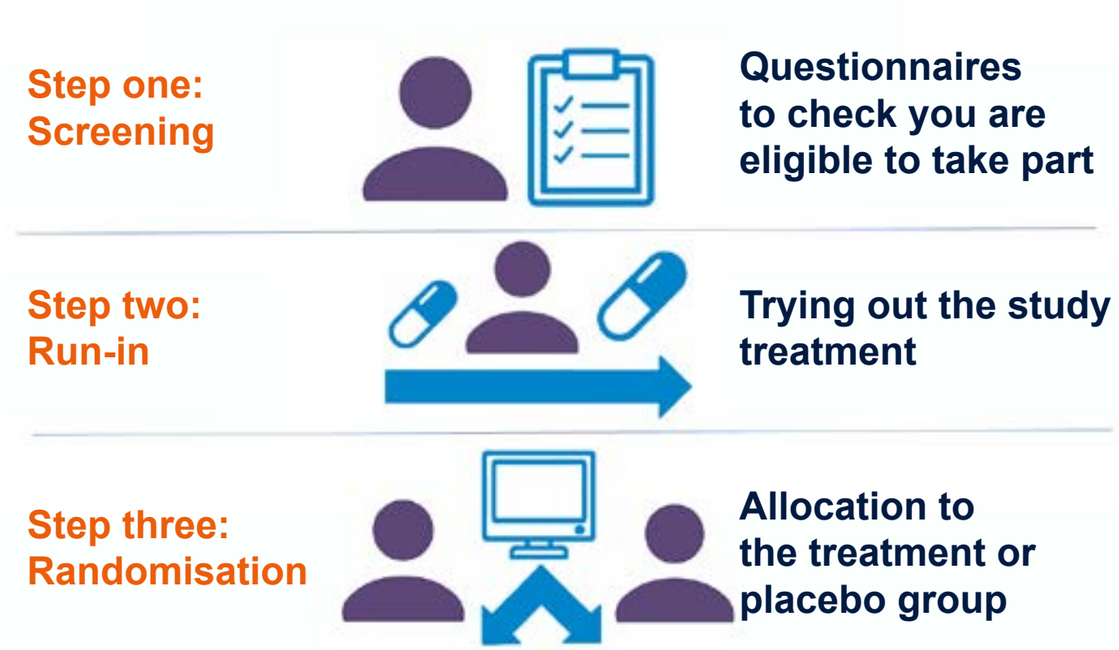
Step three is called **‘Randomisation’**. This is where you will:

- answer questions about any medical problems that happened during the ‘Run-in’, and how you found taking the ‘Run-in’ medication
- confirm that you still wish to join the study
- answer questions about smoking, and other risk factors for health problems
- be allocated to receive the active semaglutide tablets or the dummy (placebo) tablets (decided randomly by the study computer).

Your GP will be told that you have joined the study.

Further information about each step is provided below. Each step can be completed either online yourself or with a research nurse by telephone or video call. You decide which works best for you and you can change at any time.

Joining ASCEND PLUS: The three steps



Step one: Screening and consent

If you are completing this step online, you will be asked to complete an electronic questionnaire, which will ask questions about you, your medical history, and any treatments you take for diabetes.

You will then be asked to watch a video explaining the study and to complete some further questions to make sure that you have understood the information.

If the answers you have given suggest you are suitable to join the trial, you will be asked to give your informed consent to agree to take part in the study.

In total, it will take about 30-40 minutes to complete the whole screening and consent process online. This can all be done at your own home, at a time to suit you.

If you prefer, the screening and consent can be done by telephone or video call with a research nurse.

The study doctors will check your screening information to confirm that you are able to enter the study. The study team may call you, or contact your GP, if they need more detail about your answers to the screening questions. You will be sent a copy of your completed consent form. If you are able to take part, you will move to step two, the 'Run-in'.

Step two: The Run-in

You will receive a pack of study medication in the post containing two different types of study treatment: a smaller pack of **Type A Run-in Treatment** with a **blue** stripe on the label (containing one bottle of tablets) and a larger pack of **Type B Run-in Treatment** with an **orange** striped label (containing two bottles of tablets).

Both packs contain oral semaglutide, not placebo tablets.

You should take the medication as follows:

- Start with the bottle in the pack of **Type A Run-in Treatment** **(blue striped label)** and take **one** semaglutide 3 mg tablet **each day** until you finish the bottle.
- After four weeks, when the tablets in the Type A bottle are finished, switch to a bottle from the pack of **Type B Run-in Treatment** **(orange striped label)**.
- Take **one** semaglutide 7 mg tablet **each day** until you finish the tablets in the bottle and then switch to the next Type B bottle in the pack.

- Take the tablet when you wake up in the morning with up to half a glass of water.
- Wait at least half an hour after taking the tablet before eating or drinking anything else or taking any other oral medication.
- If you take another medicine which should also be taken on an empty stomach, it is important to leave half an hour between the study treatment and the other medicine.

We will be in touch about the next stage ('Step three: Randomisation') while you are taking the Type B Run-in tablets.
A letter will be sent to your GP to tell them that you are planning to join the study.
You can choose to stop the study treatment at any point and withdraw from the Run-in. If you do this, you will not be able to continue in the ASCEND PLUS study.

Step three: Randomisation

You will be asked to complete the randomisation questionnaire online or, if you prefer, by telephone or video call with a research nurse. You will be asked questions about any significant medical problems which might have happened during the 'Run-in', how regularly you have been taking the ASCEND PLUS medication since you received it and about risk factors for health conditions, such as high blood pressure and smoking.

It will take about 20 minutes to complete this questionnaire.The study team will check your answers and may call you if they need more detail.

If your answers show that you are able to continue in the study, the study computer system will then allocate you by chance to receive either the oral semaglutide or the inactive placebo tablets for the rest of the study. A six-month pack of study treatment (containing either 14 mg semaglutide or placebo tablets, six bottles) will be sent to you by post. You will be asked to **stop** taking your Run-in medication and **instead** to take one tablet each day from the new supply from then onwards. You should take the medication in exactly the same way as during the Run-in period.

A letter will be sent to your GP confirming that you have fully entered the trial.

What happens after I join the study?

Once you have completed randomisation, you enter the 'follow-up' part of the study. As long as it remains appropriate for you to continue taking the study treatment, packs of study treatment will be posted to you about once every six months.

You will be prompted by e-mail or text to complete an online follow-up questionnaire about three months after your randomisation questionnaire and again three months after that, and then about once every six months. These follow-up questionnaires will only take a few minutes to complete each time.

If you prefer to complete the follow-up questionnaires by telephone or video call then the study team will arrange to contact you (or, where appropriate, your relative or carer) when your next questionnaire is due.

You will be asked about your diabetes medications (including the ASCEND PLUS study treatment). If you stop taking the ASCEND PLUS study treatment at any point, you will be asked about what led you to stop. Some follow-up questionnaires will also ask about quality of life and the impact of diabetes on your daily activities.

As well as the information you provide in the online questionnaires, or telephone or video calls, the study team will receive information about your health from your doctors, health registries and NHS bodies such as NHS Digital. The ASCEND PLUS team will send your details (such as name, date of birth, postcode and NHS number) to NHS Digital, or another NHS body, who can link this information to individual participants in the study.

At any time you can contact the study team to withdraw permission for the study to get this health data about you (see back page for contact details). However, you won't be able to continue with the study medication if we are not able to get this health data about you.

If your health worsens and you are no longer able to make your own decisions but you have not contacted us to withdraw consent, we will continue to collect this health data about you.

Possible side effects

Oral semaglutide is approved in the UK for treating type 2 diabetes. Most people treated with oral semaglutide do not have any side effects, but about one in ten people who take the tablets experience nausea (feeling sick), vomiting, or diarrhoea. If severe, these symptoms can lead to dehydration. These problems usually happen soon after starting the medication (or when the dose is increased) and go away with time. Most people who develop these symptoms do manage to continue taking oral semaglutide.

If you do feel sick or develop diarrhoea, small changes to your diet can help. These include stopping eating as soon as you start to feel full, and cutting down on fatty foods. You can contact the ASCEND PLUS team (see back page for contact details) or download the 'ASCEND PLUS tips to help with side effects' sheet from the study website (**www.ascend-plus-trial.org**).

Your study medicine may rapidly improve your blood sugar. Good blood sugar control helps to protect against eye disease caused by diabetes in the longer term, but fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disease in some patients. It is therefore important that you attend your NHS retinal screening appointments as part of your regular diabetes treatment.

Women who are pregnant, planning a pregnancy or breastfeeding, should not take part in the trial because oral semaglutide is not recommended during pregnancy or breastfeeding.

If you do experience unexpected symptoms after joining the study you can contact a study nurse or doctor on freephone **0808 164 5090.**

Hypoglycaemia (low blood sugar)

If you also take insulin, gliclazide or another 'sulphonylurea' tablet then you might experience hypoglycaemia (low blood sugar or 'hypo') when you start taking semaglutide.

'Sulphonylurea' tablets include:

- Gliclazide (Diamicron®, Dacadis®, Vamju®, Ziclaseg® or Zicron®)
- Glipizide (Minodiab®)
- Glimepiride (Amaryl®)
- Glibenclamide (Amglidia®)
- Tolbutamide (Orinase®).

If you already monitor your blood sugar levels at home, you should ensure that you continue to do this regularly. This is particularly important for the first few months after starting the study medication.

You can contact the study team if you have any questions.

What should I do if I get symptoms of low blood sugar?

Symptoms of low blood sugar include:

- excessive sweating
- feeling very tired
- feeling dizzy or faint
- feeling shaky or trembling
- becoming easily irritated, tearful, anxious or moody
- turning pale.

If you get any of these symptoms, test your blood sugar if you can do this at home.

If you can't test your own blood sugar, or if your blood sugar is less than 4 mmol/l, have a sugary drink or snack. After about 10 or 15 minutes, you should test your blood sugar again (if you can). If your blood sugar is still less than 4 mmol/l, or you still have symptoms of low blood sugar, then have another sugary drink or snack.

After having a hypo you may need to eat or drink a bit more to stop your blood sugar going down again. Try to eat or drink a slow-acting carbohydrate, such as a:

- sandwich
- piece of fruit
- bowl of cereal
- glass of milk.

You do not usually need to get urgent medical help if your symptoms and blood sugar get better. **However, you should contact the ASCEND PLUS study team or your own GP as your medications may need to be adjusted.**

What happens if I stop the study treatment?

It helps the study to produce reliable results if as many participants as possible continue to take the study medication throughout the full five years of the follow-up period. However, you may need to stop taking the study treatment on the instruction of your doctor or the study team. You may also simply choose to stop at any point. If this happens but you are then able and willing to restart treatment at a later date, the study team will arrange for this (provided it is safe for you to do so).

When restarting study treatment after a prolonged period off treatment, your dose will be increased gradually (using the same approach as in the original Run-in period). The study team will explain what to do if this is needed.

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

We hope you will be able to continue with the study treatment for the full course of the trial. But, if you do choose to stop taking it, it would be helpful if you would allow the study team to stay in touch with you, and for you to continue to complete the six-monthly questionnaires.

However, you may decide you no longer wish to, or are no longer able to, stay in contact with the study team. With your consent at the start of the study, the study scientists can also get information about your health from NHS bodies such as NHS Digital or other NHS bodies and health registries. You can read further information on this on the ASCEND PLUS website and in the leaflet 'ASCEND PLUS data protection information for participants'. If you would like us to stop collecting information about your health from these organisations you can contact the study team at any time (see contact details on the back page). However, data already received by the study would still be analysed to make sure that the study produces reliable results.

You are free to stop taking part in this study at any time without this having any effect on your future medical care.

What will happen at the end of the study?

Once the five-year scheduled treatment period is completed and all the participants have stopped their study treatment, we will analyse the main results of the trial.

We hope that the results will show that more heart attacks, strokes and other heart and circulatory problems can be prevented by using oral semaglutide, and that this medication can help protect the millions of people living with diabetes around the world. We will send a summary of the trial results to participants and their GPs. The trial results will be also available on the study website (**www.ascend-plus-trial.org**).

After the end of the scheduled treatment period, oral semaglutide will not be provided by the ASCEND PLUS team. We will tell you whether you were taking the oral semaglutide or placebo and your doctor can decide whether to prescribe oral semaglutide for you. If the results of ASCEND PLUS show that semaglutide helps to protect against heart and circulatory diseases then we hope that it will become widely used in patients with type 2 diabetes.

After the five-year scheduled treatment period we will continue to collect health data about you from NHS Digital and other NHS organisations and national registries for the next 20 years. This will allow the long-term effects of oral semaglutide to be assessed. If you change your mind, you can later opt out of this long-term follow-up if you wish.

Who is running and who is funding the study?

ASCEND PLUS is coordinated by the University of Oxford's Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), sponsored by the University of Oxford, and supported by the National Institute for Health and Care Research.

The ASCEND PLUS team has permission from the Medicines and Healthcare products Regulatory Agency (MHRA), the South Central - Oxford B Research Ethics Committee (Reference Number 22/SC/0116) and support from the Confidentiality Advisory Group to do the study in the UK.

Studies such as ASCEND PLUS are costly to run. Novo Nordisk produce oral semaglutide and are providing the treatment for the study for free. They have also given a grant to the University of Oxford to help with the cost of running of the study. However, they are not directly involved with either coordinating the study or analysing the results.

Will my taking part be kept confidential?

Yes. The University of Oxford is the 'Data Controller' for this information. This means that the University of Oxford is responsible for looking after the data collected about you for ASCEND PLUS and using it properly.

If you choose to take part, we will need to use information from you, from your medical records, your GP and from central NHS bodies such as NHS Digital and national health registries for this research project.

People running the study who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. Only study staff who do need to know who you are (for example study doctors and nurses who might need to speak to you, send letters to you or your doctor, or send you medication) will have access to this information.

We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that you may not be able to exercise all of your rights under the UK General Data Protection Regulation (UK GDPR).

To find out more about how the information collected about you is stored and processed, how we protect your data, and your rights, read the leaflet 'ASCEND PLUS data protection information for participants', or visit the data protection section of the study website **www.ascend-plus-trial.org**.

What if something goes wrong?

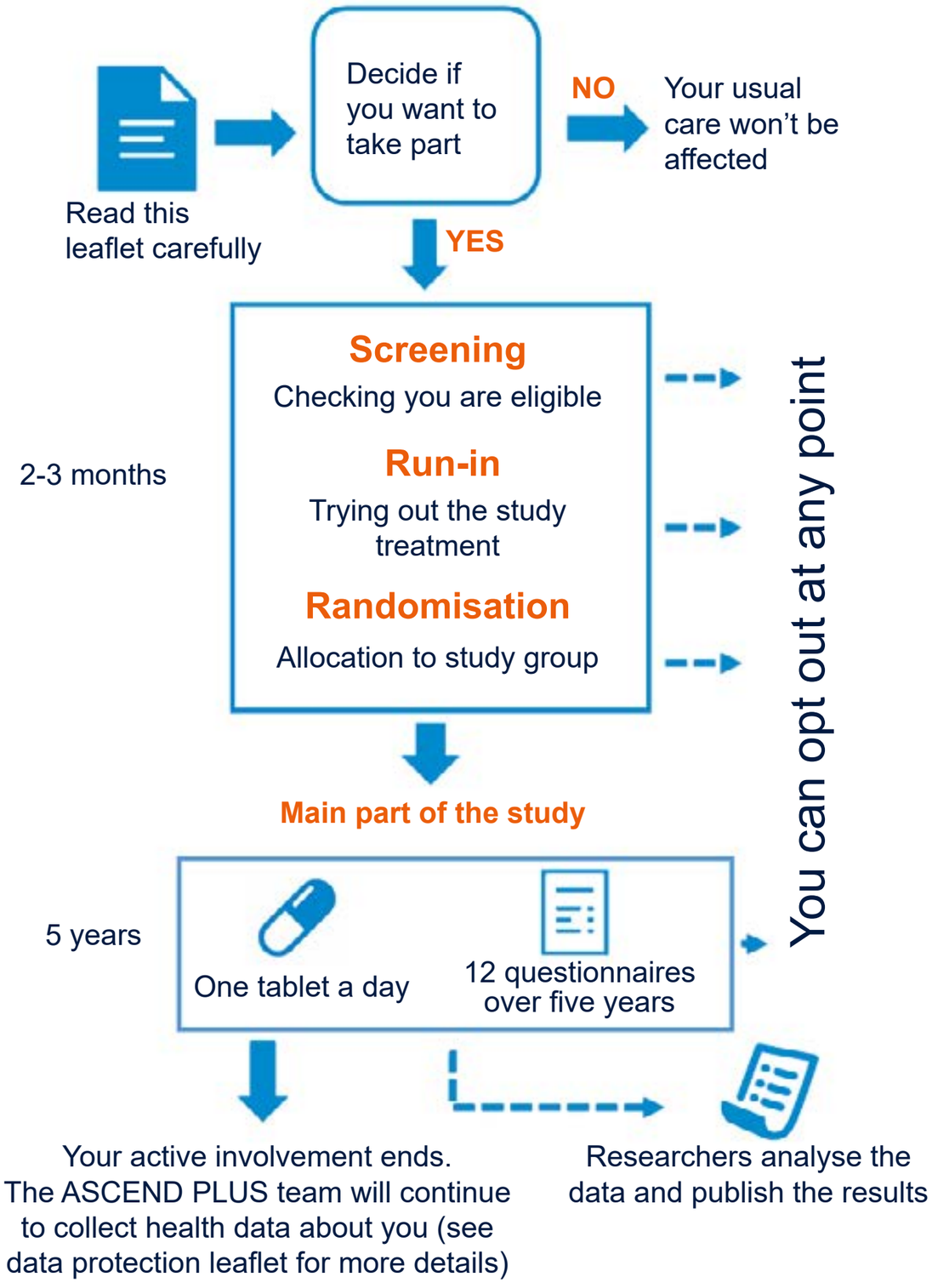
If you have a concern about any aspect of the study you can contact the ASCEND PLUS team using the contact details on the back of this leaflet. If you are not satisfied with the response you can contact the University of Oxford Research Governance, Ethics and Assurance Team (ctrg@admin.ox.ac.uk).

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect to any non-study treatment you receive.

Thank you

Thank you for your interest in this study. Our aim is to make your participation an interesting and worthwhile experience, while helping us and others to improve the treatment of people who have type 2 diabetes.

Overview of the ASCEND PLUS study



Contact Information

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Please contact the ASCEND PLUS office if you would like to receive this document in another format

IRAS: 1004252

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UNIVERSITY OF OXFORD

OXFORD POPULATION HEALTH CTSU