HPS-4
TIMI 65
ORION-4

A double-blind randomized placebo-controlled trial assessing the effects of inclisiran on clinical outcomes among people with atherosclerotic cardiovascular disease

You are invited to join ORION-4 - a health research study

UNIVERSITY OF OXFORD

British Heart Foundation

TIMI Study Group

The Orion Project Orion-4

A new health research study - quick summary

- You are invited to join a health research study called ORION-4.
- You don't have to take part - it's up to you.
- ORION-4 is testing a new medication called inclisiran which helps to lower bad (LDL) cholesterol. The study scientists want to find out whether having an injection of inclisiran every 6 months prevents heart attacks and strokes.
- About 15,000 people will take part in this study. Half will get inclisiran injections and half will get dummy (inactive placebo) injections. Which treatment you get is decided by chance and you will not know which treatment you are given.
- Joining the study involves 3 clinic visits in the first 5 months and then a visit every 6-months.
- At each visit a trained researcher will ask some questions about your health, take a blood sample and give you an injection into your abdomen (tummy).
- You are asked to stay in the study for about 5 years.
- If you join the study, your GP will be informed. Your usual medical care will not be affected by taking part.
- This study is coordinated by the University of Oxford and co-sponsored by The University of Oxford and Novartis.
- If you'd like to find out more please read the rest of this leaflet carefully.

Cholesterol, heart attacks and strokes

If you have had a heart attack or stroke, or have had a procedure to unblock your arteries, you probably know about cholesterol and the need to keep its level low. It can be a struggle, but a good diet and statins can help. However, even with these treatments the 'bad' cholesterol can remain too high. For this reason there is a need for new drugs to help manage this 'bad' cholesterol more effectively.

What is this research study about?

ORION-4 is a research study coordinated by the University of Oxford and co-sponsored by The University of Oxford and Novartis. The study aims to find out if a new cholesterol-lowering injection safely lowers the risk of heart attacks and strokes in people who have already had one of these conditions, or who have had an operation or procedure to treat blocked-up arteries.

What is the treatment being tested?

This study is testing a medicine called inclisiran which helps to lower bad (LDL) cholesterol in the blood. Doctors hope that giving this injection every 6 months for several years will lower the number of heart attacks and strokes, but they do not know this for certain. Inclisiran is given as an injection into the tissue just under the skin every 6 months, with an extra injection 3 months after starting the treatment. Inclisiran has been approved by the UK Medicines and Healthcare Products Regulatory Agency to treat some patients.

'Did you know that there is a new injection to lower bad cholesterol?'

Why me?

Your medical records suggest you may have had a heart attack, stroke or an operation or procedure on your arteries and so might be able to take part in this study. In order to invite you to take part in this study your details (such as your name, sex, date of birth, NHS number, contact details and information about admissions to hospital) were sent securely to the ORION-4 researchers at the University of Oxford. For people in Scotland, these details were sent securely to the Health Informatics Centre (HIC), University of Dundee, from NHS Scotland Health Boards so that invitation letters could be mailed. Your details will not be used for any other purpose and will be removed from the database at the University of Oxford (or HIC in Scotland) before the end of scheduled study treatment period in 2024 if you decide not to take part. Some people in the Manchester area are invited to take part by their GP (see www.nweh.co.uk/get-involved/patients for more details).

To find out more about how information about you has been processed and your rights, see the "Data protection" section of the study website www.orion4trial.org or contact the ORION-4 team using the contact details at the back of this leaflet.

Do I need to take part?

No, you do not have to take part in this study. It is your decision. But if you did help, many millions of people from around the world might benefit from this research in years to come.

If you join this study, it will not affect any decisions about other medical treatment you might need or be receiving from your own doctors. If you agree to take part, we will tell your GP.

Travel expenses

The study can pay you back for reasonable costs for travelling to your study appointments. Make sure you ask at the clinic.

Who decides what treatment I get?

Half the people taking part in this study will get the inclisiran injections and half will get the dummy (inactive placebo) injections. Which treatment you get will be decided by chance (like tossing a coin). This is called Randomization. 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).

Are there any alternative treatments?

During the study you should continue any cholesterol lowering treatment prescribed by your own doctor such as a statin.

Inclisiran is recommended within the NHS for some patients who already have heart and circulatory problems (such as heart attacks and strokes) and continue to have high bad (LDL) cholesterol levels despite trying tablet cholesterol lowering treatments such as statins. You can discuss with your GP or other doctors if you would like to know more about getting inclisiran through the NHS.

There are other new treatments to lower bad (LDL) cholesterol which work in a similar way to inclisiran. These include evolocumab (Repatha®) and alirocumab (Praluent®). However, the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), which produce guidance for UK doctors, recommends these drugs only for a small number of people with particular cholesterol problems. If you are taking one of these medicines you will not be able to take part in ORION-4.

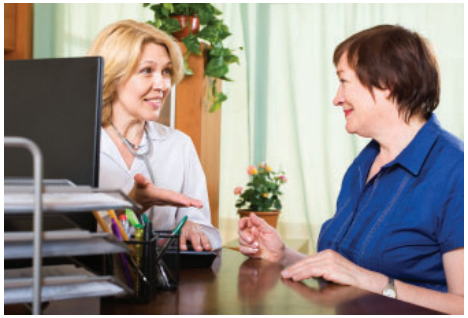
What will I have to do?

For ORION-4 to produce the best results, it is important that people stay in the study for about 5 years, if possible. You will need to attend the study clinic 3 times in the first 5 months and every 6 months after that. At each visit, a trained researcher (usually a nurse) will ask you about your health, take a blood sample and give you an injection of either inclisiran or placebo.

What happens at the first visit?

At your first study visit (called your Screening visit), the study nurse will explain the study to you. You will have plenty of time to ask questions. If you want to continue, you will be asked to sign a Consent Form agreeing to take part.

The nurse will ask you about your medical history and will take a finger-prick blood sample to measure your cholesterol while you are in the clinic. If this finger-prick cholesterol level is below a certain level, you will not be able to take part in this study.



If you are able to take part in ORION-4, the nurse will then give you an injection into the tissue just under the skin of your tummy (abdomen). The research team will then write and inform your GP to let them know that you are planning to join the study.

'You will not need to fast before your study visits.'

What happens at the second visit?

After about 2 months, you will have your second appointment (called your Randomization visit) to see if you are willing to commit to the study for about 5 years. If you are happy to continue, the nurse will take a blood sample (from a vein in your arm or hand) and will give you your next injection.

What happens at the Follow-up visits?

Your next appointment (called your Follow-up visit) will be 3 months later. After that, the study nurse will see you every 6 months for about 5 years. At each Follow-up visit, the nurse will ask you about any new medical problems since your last appointment, take a blood sample (from a vein in your arm or hand) and will give you an injection.

Your blood samples will be sent to the laboratory in Oxford for tests and, if you agree, for long-term storage for future research (see later section).

You will not need to fast before your study visits. Each Follow-up appointment will usually take less than half an hour.

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

We hope you will be able to continue getting the injections for the full course of the study. But, if you do choose to stop them, it would be helpful if you would allow the study scientists to stay in touch with you, to see how you get on. Ideally, this means still coming to the study clinic.

If this is not possible then it would be very helpful if we could keep in contact by phone.

It helps the study to produce reliable results if we can get complete information about the health of as many participants as possible. However, during the study you may decide you no longer wish to, or are no longer able to, stay in contact with the study team.

With your permission, the study scientists can also get information about your health from NHS bodies such as NHS Digital, or Health Registries (see next section).

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

How will information about me be collected and processed?

As well as the information you provide during your study visits, the coordinating centre in Oxford will ask for information about your health from your doctors, Health Registries or NHS bodies such as NHS Digital. The ORION-4 team will send your name, date of birth, NHS number (or CHI number in Scotland) and postcode to NHS Digital, or other NHS body, who can link this information to individual participants in the study. For participants living in England and Wales, NHS Digital provides information about any cancer on behalf of Public Health England. NHS Digital also provides information about any admissions to hospital (called Hospital Episode Statistics). In addition, NHS Digital provides information about people who may have passed away in order that the study does not make contact and cause any distress to relatives. This information includes date and cause of death. Similar information will be requested from the relevant bodies for participants living in Scotland.

At any time you can contact the study team to withdraw permission for the study to get this information about you (see back page for contact details).

Blood samples

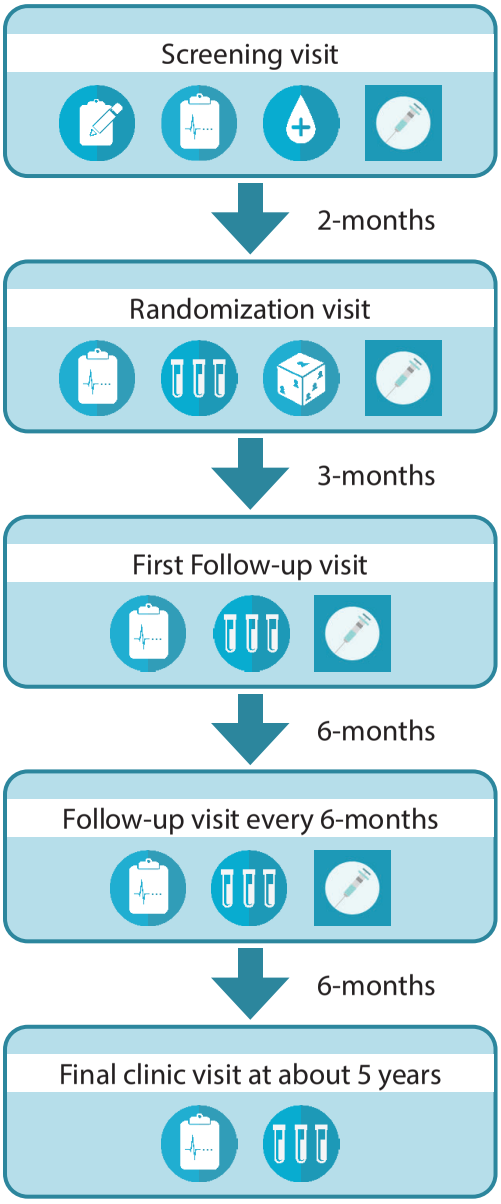
The blood samples you provide will be used to measure things which we know affect the risk of circulatory problems. This allows us to see whether the effects of inclisiran are different in different groups of people (for example people with higher or lower levels of certain risk factors). The results of your blood tests will not be routinely provided to you or your GP. However, the ORION-4 team may write to your GP about your blood results if there is a particular concern.

The study nurse will also ask you if you are happy for these blood samples to be stored long-term to help investigate the effects of inclisiran and the causes of heart disease, strokes and other conditions. However, you can still take part in the study even if you do not give permission for this long-term storage.

Stored samples and future research

Doctors already know about causes of heart attacks and strokes such as high blood pressure and high cholesterol, and are able to treat these with drugs. Scientists also think that other factors might play a part in circulatory problems, but there is limited understanding of how these work. In particular, we have limited knowledge about the effect of genes on risk of heart disease, strokes, diabetes or other important diseases. If we have your permission to keep your blood samples in a very cold freezer, then in the future we might be able to test new scientific discoveries by defrosting and analysing your samples.

ORION-4 Visit Schedule



What might happen at a visit?			
	Consent form		Randomization to inclisiran or placebo
	Questions about your health		Blood sample (from vein)
	Finger-prick blood test		Injection

How much blood will be taken?

About 4 teaspoons of blood will be taken each time. Numbered samples (without your name on) would be stored indefinitely at a secure location in the University of Oxford. Samples may be transferred to other collaborating scientists but would not be sent with any information identifying you.

What are the benefits of taking part in this study?

You will be helping doctors and scientists improve treatment for people who have had heart attacks or strokes, or who may be at risk of having one. If successful, results from this study might help to prevent many thousands of heart attacks, strokes and bypass procedures around the world.

'Results from the study may help improve the treatment of heart attacks and strokes.'

Are there any risks?

Most treatments have side effects, which some people may experience, and others may not. If you do experience any side effects during the study, they will be recorded, so that scientists can learn from you. You can stop receiving the study injections any time if you want.

ORION-4 is testing inclisiran, a drug approved for use in the UK. In a previous study including about 350 people treated with inclisiran for 6 months, about 1 in 20 people noticed some redness or soreness where the injection was given, but no other side effects were found. Inclisiran has also been given to over 1500 people in other completed studies and no additional side effects were noted. However, at this stage, scientists cannot rule out the possibility of there being side effects. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening.

Throughout the study, the research team will carefully monitor you for possible side effects. At every visit, the study nurse will discuss any new information about the drug with you.

If you do experience unexpected symptoms after joining the study you can contact your ORION-4 nurse, or a study doctor on Freephone **0800 585323**.

If you have private medical insurance or require travel insurance, your policy may be affected. You should check this with your insurance provider.

What will happen at the end of the study?

The results will be published in health or scientific journals and be discussed at major conferences. Others will learn from the results, which we hope will show that more lives can be saved by using inclisiran. No individual participant will be identified in any report or publication. We will try our best to inform participants and their GPs of the study results, and any related publicity.

The trial results will be available on the study website (www.orion4trial.org) and a description of this clinical trial will be available on https://www.clinicaltrialsregister.eu and http://www.clinicaltrials.gov.

After the end of the study, inclisiran will not be provided by the ORION-4 team. If the results of ORION-4 show that inclisiran helps to protect against heart attacks and strokes then we hope that it will become widely available for patients.

Your contribution to the study could be even more valuable if we can continue to get information about your health after your final Follow-up visit. This way we can learn a lot more about the possible longer-term health effects of this new treatment.

With your permission, the study team may like to stay in touch after your final Follow-up visit, probably with a simple questionnaire or phone call once or twice a year. Also, the study scientists would like to continue to get information about your health, such as details of any admissions to hospital from NHS Digital or other central registries after the end of the scheduled study follow-up period. This may include health information recorded throughout your lifetime. You can opt out of this at any time by contacting the study team (see back page for contact details).

Who is running and who is funding the study?

ORION-4 is coordinated by Oxford University's Clinical Trial Service Unit (CTSU) and is co-sponsored by The University of Oxford and Novartis. The study is led by Professor Louise Bowman and Professor Martin Landray at CTSU and many heart doctors and nurses around the UK and other parts of the world will be taking part. We are collaborating with investigators at the TIMI Study Group at Brigham and Women's Hospital in Boston, USA.

The ORION-4 team has permission from an ethics committee to do the study in the UK (Oxfordshire C Research Ethics Committee, Ref. No 18/SC/0243). These committees check whether the health question being asked is important enough to warrant a study, and that the study is being carried out in an honest and professional manner.

An independent committee of experts monitor the results while the study is ongoing. This committee could stop the study early if there was important new information from this, or other studies, which affected whether ORION-4 should continue.

Studies such as ORION-4 are costly to run. Treatment for the study is provided free by Novartis, which also helps with the cost of running of the study, by a grant given to the University from Novartis.

Will my taking part be kept confidential?

Yes. If you join the study, information about you will be entered onto a computer, processed and stored securely. The University of Oxford is the "Data Controller" for this information. This means that the University of Oxford is responsible for looking after your information and using it properly. The University of Oxford plans to keep the information collected about you for least 25 years after the "end of the study", and perhaps longer if required by the law or other research needs to undertake the ORION-4 study. The "end of the study" is when the last health information is collected about study participants, which may be many years after the end of the scheduled treatment period when everyone stops the study injections and the main results are analysed (see "What happens at the end of the study?" section).

In this study, personal data that directly identifies you such as your name, address, and date of birth can be accessed by the ORION-4 doctors and nurses who are running the study at your local site and by the ORION-4 coordinating team at the University of Oxford. The ORION-4 team at North West eHealth www.nweh.co.uk/get-involved/patients will be able to access details of people taking part in ORION-4 at local General Practices in Manchester so they can help with enquiries about appointments and questions about the trial.

No information identifying you is given to Novartis. The only people in the ORION-4 coordinating team who will have access to information that identifies you will be people who need to contact you (for example to arrange your ORION-4 clinic appointment or discuss any questions you or your doctors have about the study) or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Your rights to access, change or move your information are limited as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you decide that you do not want any more information to be collected about you, The University of Oxford may be obliged by law to keep your information already collected about you to ensure consistency and reproducibility of the study results.

You can find out more about how the information collected about you is stored and processed on the data protection section of the study website www.orion4trial.org or by contacting the ORION-4 team (see back page for details).

Nurse monitoring staff from the coordinating centre may occasionally ask your permission to be present during your clinic visit to make sure the study procedures are being followed. Relevant sections of your medical notes, and information collected about you during the study, may be looked at in confidence by authorised individuals from your local study site, the University of Oxford, Novartis, and regulatory authorities to check that the study is being carried out correctly.

Blood samples are sent to a laboratory at the University of Oxford for analysis. They are identified by a unique number linked in the computer to other study information. In the laboratory they are not linked to your name.

Neither you, or your doctors will be given any information from stored blood samples, including details of your genes. In particular, having these samples stored and tested would not affect your ability to get insurance.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer, data.protection@admin.ox.ac.uk, who will investigate the matter. You also have the right to complain to the Information Commissioner's Office (ICO) https://ico.org.uk/concerns/handling/.

What if there is a problem?

You have all the usual rights of an NHS patient. The University has arrangements in place to provide for harm arising from participation in the study. In the unlikely event of you being harmed by taking part, insurance cover is provided by Novartis. Any compensation would be paid in accordance with the guidelines of the Association of British Pharmaceutical Industry.

If you have a concern about any aspect of the study you can speak with the ORION-4 team by calling a 24-hour Freephone number: **0800 585323**. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. You can get details from the hospital.

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 had, or who may have, a heart attack or stroke.

ORION-4 Visit Schedule

About 5 years

	Consent Fom	Questions about your health	Finger-prick blood test	Randomization to inclisiran or placebo	Blood sample (from vein)	Injection
Screening visit	✓	✓	✓			✓
Randomization Visit		✓		✓	✓	✓
First Follow-up		✓			✓	✓
Second Follow-up		✓			✓	✓
Every 6-months		✓			✓	✓
Final Follow-up		✓			✓	

If you have any questions you can contact the ORION-4 team:

By phone:
24-hour Freephone number:
0800 585323

By post:
ORION-4
Clinical Trial Service Unit (CTSU)
Richard Doll Building
University of Oxford
Roosevelt Drive
OXFORD, OX3 7LF

By email:
orion4@ndph.ox.ac.uk

Or visit our website:
www.orion4trial.org

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