



Questions about the study should be directed to the coordinating centre in Oxford

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REVEAL

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REVEAL

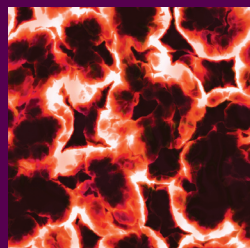
**Randomized
EValuation of
the Effects of
Anacetrapib through
Lipid-modification**



**...an invitation
to join a health
research study.**



Did you know that there is both **good** and **bad** cholesterol? And the more good cholesterol you have, the better it is for you?



Cholesterol, heart attacks and strokes

If you have had a heart attack or stroke, you will know about cholesterol and the need to keep its level low. It can be a struggle, but a good diet, plenty of exercise and statins can help.

But did you know that there is a good type of cholesterol? And the more good cholesterol you have, the better – because it may help to prevent further heart attacks and strokes.

REVEAL: what is the purpose?

REVEAL is a study to see if boosting levels of good cholesterol and further lowering levels of bad cholesterol can save more lives. REVEAL is doing this by testing a treatment called anacetrapib which raises levels of good cholesterol and lowers levels of bad cholesterol in your blood.



Why me?

Your hospital records suggest you may be suitable. We have also written to your GP to tell them that some of their patients are being asked to take part. If you agree to participate your GP will be informed about your participation.

You may have received a similar invitation to this a few years ago about a study called HPS2-THRIVE. This is a new study with a different drug.

You can take part whether or not you are already taking a statin to reduce your bad cholesterol. This is because this study is not looking at statins. Statins have been tried and tested successfully in similar studies over many years – to provide the evidence that they are safe and help protect people from heart attacks and strokes.

Who is running and who is funding the study?

REVEAL is being led by medical scientists at the University of Oxford who carried out the important Heart Protection Study (HPS). This study showed conclusively how effective statins were at saving lives and resulted in changes to medical practice around the world. Treatment for the study is provided free by Merck Sharp & Dohme Corp., which also contributes to the cost of running of the study, by a grant to the University of Oxford.



Do I need to take part?

You do not have to take part in this study. It is entirely your decision. But if you did help, many millions of people from around the world might benefit from this research in years to come.

Travel expenses

Reimbursement of reasonable expenses for travelling to your REVEAL appointment can be provided. Make sure you ask at the clinic.

What happens to me if I take part?

Your continued good health is the prime concern of the trained medical staff involved with the REVEAL study. They will monitor your health at regular intervals throughout the study. Your participation in this study will not affect any decisions about other medical treatment you might need or be receiving from your own doctors.

A new cholesterol tablet

The new tablets being tested in REVEAL contain a treatment called anacetrapib. It is known that anacetrapib increases levels of good cholesterol in the blood and also reduces levels of bad cholesterol. If anacetrapib is taken along with a statin, the bad cholesterol level is reduced even further than if you just take the statin alone. Doctors hope that this will reduce the number of heart attacks and strokes, but they do not know this for certain.

Lowering bad cholesterol

Everyone taking part in REVEAL will be given a statin to reduce their bad cholesterol. You will be asked to take a statin called atorvastatin. This may mean that you have to change from your current treatment. However, all statins work in very much the same way, and this should not cause you any problems.

'It is known that anacetrapib increases levels of good cholesterol and reduces levels of bad cholesterol.'



REVEAL researchers ask all participants to use the same statin so that the 'background' treatment to reduce bad cholesterol in all participants is the same. This helps the research scientists to know if any results they get from the trial of the new treatment being studied are 'real'.

The amount of atorvastatin you receive in the REVEAL study will aim to get your cholesterol to the current recommended target (below about 4.0 mmol/l).

Atorvastatin will be provided free to you by the study team. Even if you decide eventually not to carry on with the new study tablets, you can still continue with atorvastatin from the study.

Atorvastatin has been shown in large studies to be safe. It is an effective treatment for lowering levels of bad cholesterol and has been shown to help protect against heart attacks and strokes.

Getting started

At your first visit to the REVEAL clinic a trained researcher (usually a nurse) will ask you about your medical history. The researcher will take your blood pressure and a sample of blood and will test your cholesterol level while you are in the clinic. They will explain the study to you and you will be given plenty of opportunity to ask questions. If you are interested you will be asked to sign a form agreeing to take part and we will write and inform your GP.

You will then be provided with a supply of atorvastatin and asked to take one tablet daily, to control your bad cholesterol. You will also receive a supply of the new study treatment being tested and will be asked to take one of these tablets daily also. The tablets are to be taken with food.

Over the course of the next few weeks you will have the chance to try out the study tablets. This will allow you and the REVEAL doctors and nurses to be sure the tablets agree with you, and to find out if your bad cholesterol is under control.

'People already taking statins can take part in this study.'



After two months

After about 8 weeks of trying the study tablets you will be asked to attend another appointment to see if you would like to continue with the study. Your blood pressure will be rechecked and another blood sample will be taken to test your cholesterol again while you are in the clinic. You will also be measured and weighed at this visit.

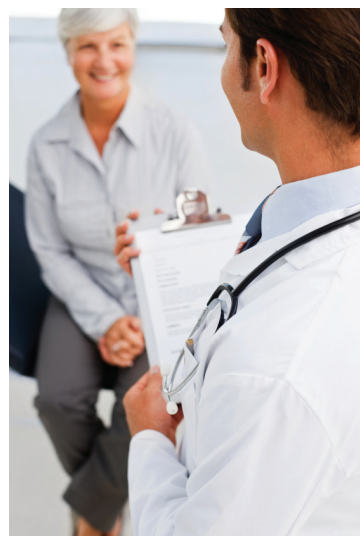
If you have had no problems with the study treatments during the first two months and are happy to continue, you will be asked to commit to the study for at least 4-5 years. However, this would usually involve attending appointments only every 6 months.

Ongoing study treatments

Everyone joining the long-term part of the study will continue to receive atorvastatin treatment (one tablet daily) for the duration of the study.

Everyone joining will also continue to receive the new treatment being tested. As the study scientists do not know if this new treatment will reduce heart attacks and strokes (this study should answer the question), only half the participants will receive study tablets containing anacetrapib. The other half will be given a dummy drug, called a "placebo".

Whether or not you receive anacetrapib is decided randomly. This means that you have as much chance of receiving it, as you do of receiving the placebo (like the toss of a coin). You will not know which treatment you receive, nor will your GP or the REVEAL staff. However, this information would be made available to your doctor if this was medically necessary.



Blood and urine samples

If you agree to continue into the main part of the study you will be asked to provide a urine sample which will be sent, along with your blood sample, to the central laboratory in Oxford.

We will use these samples to measure certain things (such as cholesterol levels) which we know affect the risk of circulatory problems. This allows us to see whether the effects of the treatments being used in the study vary between different types of people taking part.

We will also ask you if you are happy for these blood and urine samples to be stored long-term to help investigate the causes of heart disease, strokes and other circulatory diseases. However, you will still be able to continue in the REVEAL study even if you would prefer not to give permission for this long-term storage.



Stored samples and future research studies

REVEAL is aiming to discover whether anacetrapib protects against heart disease and strokes in people with circulatory problems. However, there are likely to be many causes of these conditions. Some causes, such as high LDL (bad) cholesterol, are already known and doctors are able to treat this problem with drugs. We suspect, however, that other factors also play a part in circulatory problems, but there is limited understanding of these processes. In particular, we have limited knowledge about the influence of genes on risk of heart disease, strokes or diabetes. If we have your permission to preserve your blood and urine samples in a very cold freezer, then future advances in medical knowledge might eventually enable us to answer some of these questions by defrosting and analysing such samples.

How much blood would be taken?

We only need about 4 teaspoons of blood for the immediate measurements and for the long-term storage. Numbered samples (without your name on) would be stored indefinitely at a secure location in the University of Oxford.

STUDY TIMETABLE

First Appointment

When you provisionally agree to take part and stop any statin you may be taking and start atorvastatin from the study.



Early phase: About 8 - 12 weeks

During this period you can try out the study tablets. We will check that your cholesterol is well controlled with atorvastatin.



Second Appointment

If you are happy with the study tablets and your cholesterol is well controlled, you decide whether or not to continue into the long-term part of the study.

All participants continue with the study atorvastatin.



Main study: 4 - 5 years

Participants are selected randomly (by chance) to receive either real anacetrapib or the dummy ("placebo") version. Doctors do not know which one is best.



Half of all participants receive anacetrapib.



Half of all participants receive a dummy tablet.



Follow-up Appointments

Regular check-ups are done whilst taking study tablets to monitor blood tests and find out about general health. First visit after 2 months, then 4 months later, and then an appointment every 6 months.



Study finishes

Results are announced.

Participants stop study tablets and clinic visits but, where possible, stay in contact with study scientists via postal or telephone questionnaires.



'It is important people stay in the study for as long as possible'.

Follow-up appointments

If you decide to continue with the long-term part of the study, your next appointment will be in another 2 months and then 4 months later. After that you will be seen every 6 months for about 4-5 years in total. You will be provided with more study treatment every 6 months. With regular check ups from the REVEAL specialist nursing team, you can be assured of the best possible follow-up care and attention. If any problems emerge for you while you are on the study, your GP will be informed.



At each follow-up appointment your blood pressure will be checked and a sample of blood will be taken to test the safety of the study tablets. You will not need to fast before your study clinic appointments. Sometimes the blood samples will be sent to the laboratory in Oxford for extra tests and, if you agree, for long-term storage. We will ask about any medical problems you may have had since your last visit and will check that you are still happy to take the study tablets.

'You will get regular check-ups from the specialist study team'...

We hope you will be able to continue taking the study tablets for the full course of the study. But, if you do choose to stop the study tablets, 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.

After the end of the study, when everyone stops the tablets and the study results are announced, we may still like to stay in touch, probably with a simple questionnaire or phone call once or twice a year. This way we can learn a lot more about the possible longer-term health effects of this new treatment.

What will I have to do?

For REVEAL to produce the best results, it is important that people stay in the study for as long as possible. We will ask you to commit to the study for at least 4-5 years. You will need to attend the REVEAL clinic three times in the first 6 months and then once every 6 months. Extra appointments can also be arranged if you are ever worried about the study tablets. However, you can withdraw from the study at any time.

You will be asked to take a statin called atorvastatin and either a new treatment to raise your good cholesterol, or a dummy treatment called a placebo. Scientists do not know which treatment is best.



You will also be asked to provide blood and urine samples and to allow these to be stored for future tests, including genetic analysis if you agree. You will be asked about your health and your blood pressure will be measured at every visit. At some visits extra measurements will be taken, including your height, weight, size of your waist and neck, and, at the end of the study, some questions about your memory.

What is the treatment being tested?

A new treatment called anacetrapib is being tested. It is known to lower bad cholesterol and to raise good cholesterol, but it is not known if it actually helps to prevent heart attacks and strokes. About 30,000 people in the UK, USA, Canada, Scandinavia, Italy, Germany and China will take part in REVEAL.

What are the benefits of taking part in this study?

You may be helping yourself, but you will most certainly 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. We hope that being in the study may help you by reducing the risk of having a heart attack or stroke. If successful, results from this study will help to prevent many thousands of heart attacks, strokes and bypass procedures around the world.



'Safety will be closely monitored by the REVEAL study scientists at Oxford University'.

Are there any risks?

Most treatments have side effects which some people may experience and others do not. If you do experience any side effects while on the REVEAL study they will be noted, so that scientists can learn from you. You can withdraw from the study if you wish.

◆ **Atorvastatin** is generally very well tolerated, tested in many thousands of patients and used by millions of people worldwide. A rare side effect is muscle pain and weakness.



◆ **Anacetrapib**, an unlicensed drug, is being tested in this study. Two similar drugs have been tried out in large studies. One drug is being tested in a study of 15,000 patients and is still going on. A study with the other drug was stopped because more people receiving the new rather than the dummy drug developed heart problems or died, possibly because that drug caused blood pressure to go up. Anacetrapib has been used in about 2000 people so far, 500 of whom have taken it for 18 months. It has

not shown any of the side effects of the drug that caused problems: in particular it does not appear to cause blood pressure to go up.

At this stage, scientists cannot rule out the possibility of there being side effects (such as, diarrhoea or muscle pains), or effects on blood tests. In the largest study of anacetrapib, no adverse effects on liver or other blood tests were seen. However, in a small study among 80 Japanese patients, 2 had persistent increases in liver blood tests. It has been suggested that a death and a serious allergic reaction might have been related to anacetrapib (although this is not proven) and, overall, no serious medical problems (including deaths) have been seen more frequently with anacetrapib.

Throughout the study you would be carefully monitored by the study team for possible side effects. At every visit, the study staff would discuss any new information about the drug with you.

There is nothing to suggest that stopping the tablets will cause you harm. If you do experience side effects, you may choose,

or be advised by your doctor, to stop the tablets provided by the study but you can usually continue to take your statins.

If you do experience unexpected symptoms after joining the study you can contact your REVEAL nurse, or a study doctor on

Freefone 0800 585323.

Will my taking part be kept confidential?

Yes, absolutely. Information about you is entered onto a computer and stored securely. The University of Oxford is a world-leader in developing systems to ensure that information is stored safely for studies such as REVEAL.

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

The coordinating centre will ask for information from your doctors and from NHS and other central registries about any serious illnesses that you have. All information received is used in confidence only for medical research purposes and for routine regulatory and audit purposes. Nurse monitoring staff from the coordinating centre in Oxford may occasionally ask your permission to be present during your clinic visit to ensure procedures are being properly followed.

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. The information used for scientific analysis will not include any details that identify you.

Any information from stored samples, including details of your genes, will not be provided to you, your doctors, or anybody else. In particular, having these samples stored and subsequently tested would not affect your ability to obtain insurance.

What will happen at the end of the study?

The results will be published widely 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 anacetrapib in addition to a statin. No individual participant



will be identified in any report or publication. We will endeavour to inform participants and their GPs of the results, and any ensuing publicity.



How is this study organised?

Scientists and doctors consider the questions being asked by REVEAL to be important because they could improve treatment for people who have had, or may be at high risk of, a heart attack or stroke. REVEAL is built on the success of the Heart Protection Study which showed how useful statins are in saving lives.

Scientists at the University of Oxford, who are carrying out the project, have had to get permission from ethics committees to do so (Oxfordshire Research Ethics Committee B have approved the study in the UK, reference 10/H0605/83). 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 independent, honest and professional manner.

An independent committee also watches over the study and keeps an eye on results. This committee could stop the study early if important new evidence emerged that had an impact on the need for the study to continue.

REVEAL has been designed and is coordinated by Oxford University's Clinical Trial Service Unit (CTSU), one of the world's leading centres for this type of work. The study is led by Dr Martin Landray and Dr Louise Bowman at CTSU and involves many heart doctors and nurses around the UK and other parts of the world.

Independent studies such as REVEAL are costly to run. Treatment for the study is provided free by Merck Sharp & Dohme Corp., which also contributes to the cost of running of the study, by a grant to the University of Oxford. Merck Sharp & Dohme Corp. also provided some of the funding for the Heart Protection Study which provided clear evidence of the benefit of statin treatment to reduce heart attacks and strokes.

However, REVEAL is conducted independently of Merck Sharp & Dohme Corp. and the study information will be collected, analysed and published independently of the source of funding.



What if there is a problem?

You retain all the usual rights of an NHS patient.

The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor.

In the unlikely event of your being harmed by taking part, insurance cover is provided by Merck Sharp & Dohme Corp. Any compensation would be paid in accordance with the guidelines of the Association of British Pharmaceutical Industry (ABPI). Any payment would be without legal commitment.

If you have a concern about any aspect of the study you can speak with the researchers. They can be contacted on 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. Details can be obtained 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.

More information is available from the REVEAL research team, by calling the telephone number above, or from the REVEAL web site: www.revealtrial.org

