Patient information leaflet

A study of low dose theophylline in Chronic Obstructive Pulmonary Disease (COPD)

Theophylline With Inhaled CorticoSteroids (TWICS) study.

We would like to invite you to take part in a research study into COPD treatment. COPD is the term now used instead of chronic bronchitis and emphysema. In this study we are trying to find out if flare-ups of COPD can be prevented by low doses of the established COPD drug theophylline. We believe that you might be eligible to take part in this study because you may have had 2 or more flare-ups of your COPD in the last year. Before you decide whether you would like to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. If you are interested in taking part you can make contact with us (our contact details are at the end of this leaflet).

Thank you for reading this.
What is the purpose of the study?
COPD is a common lung condition and one of the features of COPD is that it can suddenly get worse. These ‘flare ups’ are known as exacerbations and are usually treated with antibiotics and steroids. Often exacerbations result in people being admitted to hospital.

One of the aims of our research into COPD is to prevent exacerbations occurring. Our study is trying to find out if low doses of the established COPD drug theophylline reduces the number of COPD exacerbations. Theophylline has been used at ‘high dose’ for about 70 years, but it has fallen out of favour because of new inhalers containing steroids. Recent laboratory work has shown that low doses of theophylline make inhaled steroids work better in COPD. In our study, we want to show that low-dose theophylline used alongside inhaled steroids works in people with COPD. Theophylline will not reduce how well your existing medication works.

Why have I been chosen?
We are approaching you because we understand that you have COPD. We are approaching people with COPD who attend certain General Practices, or who have been admitted to hospital with COPD, or who attend chest clinics, or who have been cared for in the community or have attended pulmonary rehabilitation classes.

We are aiming to recruit 1424 people with COPD who have had two or more exacerbations in the last year. In order to get 1424 people with COPD, the study is taking place in and around major cities in the UK.

Do I have to take part?
No. It is up to you to decide whether to take part. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or
a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
To find out if low dose theophylline reduces the number of exacerbations we are comparing the effects of low dose theophylline against the effects of a placebo ‘dummy treatment’, which looks like the genuine medicine but contains no active ingredient.

To try to make sure the low dose theophylline and placebo groups are the same to start with, each person is put into a group selected by chance (randomly by a computer). Half of the 1424 people will take low dose theophylline and half will take the placebo for a year (as well as your usual medicines). To make sure that the true effects of ‘low dose theophylline are being studied neither you nor your doctor will know which treatment group you are in (although, if your doctor needs to find out he/she can do so).

If you are interested in taking part we will make plans to see you in a local study centre at a time convenient to you.

At the first visit, we will ask you:
• To sign a consent form saying that you are willing to take part in the study.
• To fill in a short questionnaire to find out how COPD is affecting your life.
• To let us know what medicines and inhalers you are taking.
• To let us measure your height and weight.
• To do some blowing tests (spirometry) to measure your lung function.

We will ask you to take one study tablet once a day or one study tablet twice a day for a year depending on your weight and whether you currently smoke. There is a 50:50 chance
that you will be taking low dose theophylline or placebo ‘dummy treatment.’

At this visit, we will provide you with a months supply of study tablets. After about two weeks, we will telephone you to see how you are getting on. We will then arrange a further supply of study tablets to be delivered to your house by courier. We will telephone you again to make sure you received the further supply of tablets.

*We will ask you to continue taking all of your normal medicines and tablets* and if you do have a flare up/exacerbation of your COPD needing treatment that you make a note of the dates and treatment. You will be able to write these details down on the tablet box.

After 6 months of treatment we will invite you to come along to the local study centre at a time convenient to you and ask you to:

- Let us know how you are getting on with the tablets.
- Let us know if you have had any flare ups of your COPD.
- To fill in a short questionnaire to find out how COPD is affecting your life.
- To let us know what medicines and inhalers you are taking.
- To let us measure your weight.
- To do some blowing tests (spirometry) to measure your lung function.

A further supply of study tablets will be delivered to your house by courier approximately two weeks later. We will telephone you to make sure you received the further supply of tablets.

After 12 months of treatment we will invite you to come along again to the local study centre at a time convenient to you and ask you to:

- Let us know how you are getting on with the tablets.
• Let us know if you have had any flare ups of your COPD.
• To fill in a short questionnaire to find out how COPD is affecting your life.
• To let us know what medicines and inhalers you are taking.
• To do some blowing tests to see how well your lungs are working.

If you are not able to come along to the local study centre after 6 or 12 months of treatment, we may be able to arrange a home visit for you, or telephone you to collect your information, or send you a questionnaire to fill in at home.

**Expenses and payments**

You can receive travel expenses to attend your local study centre. Please ask your research nurse for information about how to claim travel expenses.

**What will I have to do?**

We ask that you:

• Take the study tablet once or twice a day as directed, for a year,
• That you attend three study visits (first visit, at 6 months, at 12 months).
• That you make a record of any flare ups of your COPD whilst on the study tablets.
• That you carry a card explaining you are in the study.

Otherwise you should continue on your normal medicines and inhalers and carry on as normal. If you need to go to your GP for treatment you should go, any flare ups/exacerbations of your COPD can be treated as they normally would.

**What is the drug that is being tested?**

The drug being tested is low dose theophylline (Uniphyllin MR) 200mg one tablet once a day or twice a day depending on your weight and whether you smoke. Theophylline has been
used at a higher dose to treat COPD and asthma for about 70 years.

In order to prevent exacerbations of COPD the laboratory studies show that theophylline must be at low dose levels in the blood. Doctors have known for many years that a number of drugs increase the level of theophylline in the blood above low dose levels and that these drugs should be avoided if a patient is taking theophylline.

We will let your GP know that you are in the study, which drugs to avoid and what to do if (s)he wants to put you on one of these drugs. The study card will also let doctors know where to find a list of these drugs. If your doctor wants to start you on one of these drugs then they will tell you to stop taking the study tablets whilst on these drugs.

For reference, the list of drugs to avoid is:

- **antibiotics**: aciclovir, clarithromicin, ciprofloxacin, erythromycin, fluconazole, ketoconazole, levofloxacin, norfloxacin;
- **heart drugs**: diltiazem, mexiletine, pentoxiphylline, verapamil;
- **neurological**: bupropion, disulfiram, fluvoxamine, lithium;
- **hormones**: medroxyprogesterone, oestrogens;
- **immunological drugs**: methotrexate, peginterferon alpha, tacrolimus;
- **others**: cimetidine, deferasirox, febuxostat, roflumilast, thiabendazole.

These drugs are not frequently used in patients with COPD. But if you have any questions about any of these drugs, please get in touch with us, or ask your GP.

If you stop smoking or lose or gain weight during the study, please tell us. Our contact details are at the end of this leaflet.
What are the side effects of any treatment received when taking part?

It has long been known that some people can develop side effects when taking high dose theophylline and this is one of the reasons why high dose theophylline is rarely used nowadays.

By using low dose theophylline at levels well below high dose we anticipate that very few people will have any side effects, (less than 1 person in 20). If side effects do develop then they should stop when the study tablets are stopped. The possible side effects include nausea, vomiting, diarrhoea, headache, anxiety and a fast heart rate. If you decide to participate in our study, we will give you another information leaflet with your medicine that will tell you more about the study tablets, how to take them, and the possible side effects. Please read all the information contained in this leaflet.

If you feel unwell at any point, please seek medical help as you would do usually. If you are concerned that you may have developed side effects, you should contact your local study centre or your GP and they will provide help and advice.

What are the possible benefits of taking part?

We cannot promise the study will help you but we expect the information we get from this study will help improve the treatment of people with COPD, reduce the need for antibiotics and steroids and reduce hospital admissions for COPD. The lung function measurements we make during the study will be useful to your GP.

We hope to show that low dose theophylline reduces the number of exacerbations in people with COPD.

What happens when the research study stops?

When you have attended for the 12 month follow-up, we will not give you any more study tablets. Stopping the tablets is
safe. If, at the end of the study, you feel that the study tablets have improved your COPD we can let your GP know and (s)he will be able to prescribe low dose theophylline. You would need to discuss this with your GP though.

**Involvement of the General Practitioner (GP)**

We will ask your permission to let your GP know that you are taking part in the study. We will also ask your permission to send your GP copies of the lung function readings we take during the study. At the end of the study, again with your permission we will ask your GP if we can look at your GP records to count up the number of times you have visited your GP and the number of exacerbations you have had whilst on the year of study treatment.

**What if relevant new information becomes available?**

Sometimes we get new information about the study treatment. If this happens, your local study team will tell you and discuss with you whether you should continue in the study. If you decide not to carry on, arrangements will be made for your usual care to continue. This may be with your GP, or may be with the chest clinic at the hospital. If you decide to continue in the study you may be asked to sign an updated consent form.

**What will happen if I don’t want to carry on with the study?**

You are still free to withdraw at any time and without giving a reason and this will not affect the standard of care you receive. You can stop the study treatment but keep in contact with us to let us know your progress. Information collected may still be used.

**What if there is a problem?**

If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek compensation through the research sponsors of the study - the University of Aberdeen and NHS Grampian.
Contact details for both research sponsors are available through the research team.

As a patient of the NHS if you are harmed due to someone’s negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

If you have a concern about any aspect of this study you should ask to speak to the study doctors who will answer your questions (contact details are at the end of this information leaflet). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints mechanisms (or Private Institution). Contact details can be obtained from your local hospital. In addition to this, you may contact the chairman of the TWICS Trial Steering Committee (who is independent from the study) through the TWICS study office.

**Will my taking part in the study be kept confidential?**
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. All information which is collected about you during the research will be kept strictly confidential and will be held securely in accordance with the Data Protection Act. Only certain members of the research team will have access to your information.

We will ask you to give us the name and address of someone that you know who we can contact if we cannot get in touch with you. This might be a family member, friend or neighbour. Again, with your permission, we will tell this person that you are taking part in the study.
With your permission we will need to pass on your name and address to the company who will package the study tablets for you and the courier company who will deliver the study tablets to your home. These details will be kept strictly confidential, and be used only to send you the tablets.

The statistical analysis of the study is being conducted at the University of Aberdeen, and to maintain confidentiality, the statistical team will only analyse completely anonymous data. (Anonymous data does not include names or addresses, and it is not possible to identify individual participants from anonymous data). Any reports or publications arising from the study will contain totally anonymous data so that you cannot be recognised from it.

Other researchers may wish to access anonymous data from this study in the future. If this is the case, the Chief Investigator will ensure that the other researchers comply with legal, data protection and ethical guidelines.

If you join the study, the data collected for the study, together with any relevant medical records, may be looked at by authorised persons from the University of Aberdeen, the Research and Development Department of your local NHS Organisation and the Regulatory Authorities to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant.

**What will happen to the results of the research study?**
The results of the study will be published in scientific journals and presented at scientific meetings. In addition with the help of the British Lung Foundation and Chest Heart Stroke Scotland we will pass on the results to other people with chest disease. We will also send you a summary of the findings.
Who is organising and funding the research?
This study is being organised by the University of Aberdeen and chest doctors in Aberdeen, Birmingham, Glasgow, Hull, Liverpool, Newcastle, and Norwich. The research is being funded by the National Institute for Health Research, Health Technology Assessment programme: NIHR-HTA.

The study is being co-ordinated by the Centre for Healthcare Randomised Trials (CHaRT), a registered clinical trials unit at the University of Aberdeen.

Who has reviewed the study?
The study has been reviewed by an NHS Research Ethics Committee, which has responsibility for scrutinising proposals for medical research on humans. In this case, the reviewing committee was Scotland A Research Ethics Committee, who have raised no objections to the study.

In addition, the study has also been reviewed and approved by the Medicines and Healthcare Products Regulatory Agency. The Research and Development Department of your local hospital and/or local primary care organisation has also reviewed and approved the study.

Contact for further information
If you have any questions or would like more information, please contact us. Our contact details are on the back of this leaflet.

If you are interested in taking part in this research please let us know. You can telephone us, email us, or use the reply slip and freepost envelope. Our contact details are on the back of this leaflet.
Thank you for taking the time to read this information leaflet. We hope that you have found it useful in deciding whether or not to take part in the TWICS study.