Study of the **E**ffectiveness of **A**dditional

SEARCH

Reductions in **C**holesterol and **H**omocysteine

Invitation to join a large medical research project

SEARCH/PIL/1/399

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You are being invited to join a nationwide study of long-term treatment to prevent further heart attacks and the need for heart surgery. Big differences are not likely, so the study is designed to look for small — but worthwhile — differences (and to look for any serious side-effects of long-term treatment). In order not to overlook such effects, more than 10,000 men and women in Britain who — like you — have had a heart attack are being invited to participate.

This invitation is made with the agreement of your own doctors. You are, of course, free to choose not to join the study (or, if you do decide to take part, to withdraw from the study treatment at any time) without affecting the medical care you can expect from your own doctors. If, after reading this leaflet, you have any questions, then please discuss them either with the study clinic staff or with your own doctor.

Cholesterol and heart disease

Heart attacks ("coronaries") are the leading cause of death in Britain. One of the main things that makes a heart attack more likely is having too much cholesterol (a fatty substance) in the blood. Some cholesterol in the bloodstream is necessary for normal body processes, but too much of it can narrow the vessels supplying blood to the heart and so increase the chances of having a heart attack. Blood cholesterol levels may be too high in most British men and women.

Cholesterol levels in the blood can be reduced by reducing the amount of animal fat in the diet, and you will have been given information about how to do this (for example, by eating less butter, cheese and fatty meat). In addition, blood cholesterol levels can be further reduced by special cholesterol-lowering drugs, such as the "statins" (trade names: Lescol, Lipitor, Lipobay, Lipostat, Zocor).

Millions of people worldwide are taking these drugs, and they have been widely studied — particularly in patients who have already had heart attacks. Lowering cholesterol has been shown clearly to reduce the chances of having another heart attack or of needing heart surgery, and it seems that bigger cholesterol reductions may produce bigger benefits. But, more intensive lowering of cholesterol might have some unsuspected adverse effects that counterbalance any further reduction in heart attacks.

The purpose of this study, "SEARCH", is to find out whether lowering cholesterol to a greater extent with a higher dose of the statin called simvastatin (trade name: Zocor), rather than with a standard dose, produces worthwhile benefits.

Vitamins and heart disease

Although your level of cholesterol affects your chances of having a heart attack, other factors (particularly cigarette smoking and high blood pressure) also play a part. There have been suggestions that certain vitamins — such as folic acid and vitamin B_{12} — can help protect against heart attacks, but this is unproven.

Moreover, taking regular supplements of these vitamins may have little or no beneficial effect among people living in a country, such as Britain, where most may get adequate amounts in their diet. It is also possible that long-term use of these vitamins could, on balance, be slightly harmful, but this too is unproven.

It is not yet known whether these vitamins are of any importance in reducing the chances of having a heart attack. SEARCH will also help to answer this question.

What taking part in SEARCH involves

SEARCH will involve many thousands of men and women from around Britain. Like you, they are being invited to take part because they have had a heart attack and statin cholesterol-lowering treatment is considered to be necessary. Everyone taking part will have agreed to do so voluntarily, knowing that it may involve them in taking study treatment for 4-5 years.

If you do choose to participate in the study, you will first be given a box of conveniently packaged study treatments, and asked to take one 20 mg simvastatin tablet and one vitamin-supplement tablet every evening for the next 2 months. After completing these first 2 months, you will be seen again in the clinic, and can decide whether or not you would be willing to take study treatment long-term. If you decide to continue, you would then be given further supplies of the study treatment, and asked to take 3 tablets every evening for the next 4-5 years.

For the cholesterol-lowering part of the study, you would be taking one small tan tablet (containing either a standard 20 mg dose of simvastatin, or a similar-looking inactive substance called a "placebo") and one pink capsule-shaped tablet (containing either a larger 80 mg dose of simvastatin, or a matching placebo). Only one of these two tablets will really contain simvastatin — that is, by taking both tablets each day you would receive either 20 mg or 80 mg simvastatin.

In addition, for the vitamin-supplement part of the study, you would be taking one white tablet (containing either 2 mg folic acid plus 1 mg vitamin B_{12}, or a matching placebo). All of your other medical care would be left unchanged, except that you would be asked to stop any other statin tablets prescribed by your own doctor. You would also be asked to avoid taking non-study folic acid supplements (but would be free to take other vitamin supplements).

The type of study treatment being taken — whether standard-dose or larger-dose simvastatin, and whether active or placebo vitamin-supplement — would not generally be known by you, or by the research clinic nurse, or by your doctor. This information will be known only by the staff at the central administration, but it would be made available to your own doctor if this was ever medically necessary. This design ensures that reliable information will be obtained about the effects of these potentially important treatments.

Follow-up in study clinics

Following the initial 2-month treatment period, you would be seen in the study clinics after 2, 4, 8 and 12 months in the first year, and then every 6 months for about 4 more years. In general, these visits to the study clinic should involve very little waiting and take no more than about 15-20 minutes.

Side-effects with standard doses of simvastatin are extremely uncommon, and usually are not serious and disappear on stopping treatment. Experience with higher doses is more limited, so you would be monitored carefully by the clinic nurses throughout the study. In a small proportion of patients taking simvastatin or other statins, changes in blood measurements related to the liver (which have only very rarely been associated with any liver problems) or muscles (which are occasionally associated with muscle pain or weakness) have been observed.

Such problems may be more common, particularly with higher doses of statins, in patients who are also taking certain other cholesterol-lowering drugs (that is, "fibrates" or high-dose niacin), cyclosporin, an antidepressant called Dutonin, certain "azole" antifungal drugs and the "macrolide" antibiotics clarithromycin and erythromycin. Consequently, patients who have serious liver or muscle disease, or who are taking these other drugs, should not enter the study — and nor should women who are likely to become pregnant.

As a safety check in the study, a small blood sample would be collected each time we saw you so that liver and muscle measurements could be made (but cholesterol would not be re-measured routinely). Some blood samples will also be stored for future analyses. The doses of folic acid and vitamin B_{12} being used in this study are somewhat higher than are commonly taken. Such doses are not known to cause any particular problems (except that they may interfere with the drug methotrexate), but again we shall monitor their effects carefully.

If, after joining the study, you do develop some unexpected symptoms — in particular, soreness or weakness of your muscles which is not the result of exercise or some other activity — you should contact one of the staff in the study clinic, or in the coordinating centre on the 24-hour Freefone service: 0800-585323. (N.B. If you are taking an oral anticoagulant, like warfarin, then the dose will need to be checked by your doctor when the study tablets are started, and when they are stopped for more than a few days.)

Long-term commitment

Participation in this study does require a commitment to take the study treatment for 4–5 years, with regular visits to the clinic. **If you do not think that you would be willing or able to do this then it would be better not to join in the first place**. (Unfortunately, we are not able to reimburse travel expenses routinely.)

If you do decide to take part, you would, of course, be free to withdraw from the study treatment at any time without necessarily giving any reason (and without adversely affecting the medical care you can expect from your own doctors). In particular, you will be encouraged to withdraw after the first 2 months if you have any second thoughts or problems with study treatment or clinic attendance.

If you do stop during the first 2 months then no further enquiries will be made of you. But, if you decide to continue, then we would like to see you regularly for the next 4-5 years to check on your health — even if you stop taking the study treatment during this period. **Throughout the study, your own doctors would remain fully responsible for all your other medical care, as usual**.

The important details of your progress would be sent to the study coordinating centre in Oxford. The coordinating centre would seek information from participating patients' own doctors and from central registries about any serious illnesses (such as heart attacks, strokes, cancers, etc) that occur. All such information would be used, **in confidence**, only for medical research purposes and for routine regulatory and audit purposes.

N.B. SEARCH involves the collaboration of several dozen British hospitals, and is organised centrally by the British Heart Foundation supported Clinical Trial Service Unit at the University of Oxford. The study is funded by the manufacturers of simvastatin (Merck Sharp & Dohme), but it is conducted independently of the pharmaceutical company.

If you have any questions about the study then please feel free to ask the clinic staff

Thank you for your help