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Heart Protection Study long-term follow-up of participants with electronic health records

Submission date 03/01/2023	**Recruitment status** Recruiting	[ ] Prospectively registered [X] Protocol
Registration date 07/03/2023	**Overall study status** Ongoing	[ ] Statistical analysis plan [ ] Results
Last Edited 17/01/2025	**Condition category** Other	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims

The Heart Protection Study (HPS) (https://doi.org/10.1186/ISRCTN48489393) was a large randomised controlled trial. Between 1994 and 1997, 20,536 individuals in the UK at increased risk of coronary heart disease were randomised to 40 mg simvastatin daily versus matching placebo, and to antioxidant vitamin supplementation with vitamins E, C and beta-carotene versus placebo. Participants took trial medications for an average of 5 years (scheduled treatment period), and the main trial closed in 2001. The aim of this study was to investigate the overall effects on survival by preventing heart attacks, strokes and other major vascular events. The main results of HPS (published in 2002) clearly showed that allocation to cholesterol-lowering therapy with simvastatin was associated with a reduction in the risk of heart attacks and stroke, and a reduction in all-cause mortality, chiefly driven by a very significant reduction in vascular deaths. These results changed clinical practice worldwide, and statins are now prescribed widely to many millions of patients. Following this, annual questionnaires were mailed to surviving participants between 2002 and 2007. This follow-up was supplemented with cause-specific mortality data provided by the Office for National Statistics (ONS) and incident cancers via national cancer registries. Additionally, and with the necessary approvals, Hospital Episodes Statistics (HES) data were provided by the NHS Information Centre (now called NHS England), giving details on non-fatal events occurring in the study population.

HPS found that:
1. Reduction in LDL-cholesterol with simvastatin 40 mg daily reduced the risk of death by 13% (due to a reduction in death from vascular causes by 18% with no adverse effect on non-vascular causes) and of major vascular events (MVEs i.e. heart attacks, strokes or coronary or non-coronary revascularisation) by about one quarter in a wide range of different types of patient (including women, people with diabetes, and the elderly) among whom there was previous uncertainty about the benefits of cholesterol-lowering
2. Supplementation with antioxidant vitamins is safe but does not reduce the risk of major vascular events
3. Cholesterol-lowering with simvastatin 40 mg daily was well tolerated, with no difference in the reports of muscle pain between those on statin versus placebo and a small excess of myopathy (muscle symptoms with raised blood creatine kinase) of about 1 per 10,000 per year.
4. Cholesterol-lowering with simvastatin 40 mg is cost-effective in a variety of settings

5. The effect of cholesterol-lowering for 5 years with simvastatin 40 mg has no adverse effects over 11 years on cancer or other causes of mortality.

These findings, which are based on large numbers of deaths and non-fatal cancers, provide considerable reassurance that lowering total cholesterol concentrations by more than 1 mmol/L for an average of 5 years does not produce adverse effects on non-vascular mortality or cancer incidence. Moreover, among the many different types of high-risk individuals studied, simvastatin 40 mg daily consistently produced substantial reductions in vascular (and, hence, all-cause) mortality, as well as in the rates of non-fatal heart attacks, strokes and revascularisation procedures.

Participants were recruited into the main trial using informed patient consent as a legal basis to process data. However, the researchers now have section 251 support (from the Confidentiality Advisory Group (Ref: 20/CAG/0113)) in place to carry out long-term research on this cohort. The researchers have approval from the South Central – Oxford B Research Ethics Service (Ref: 19/SC /0262) to follow up the cohort, with continued data linkage to allow for future analyses. The purpose of this HPS long-term follow-up study is to determine factors that contribute to the health of trial participants in the longer term.

Who can participate?
The cohort is the original HPS participants recruited in UK hospitals between 1994 and 1997. No further participants will be added to this trial.

What does the study involve?
This is a long-term follow-up study. That means that we will be using data previously collected from participants during the main trial, and also collecting data about them from electronic health records (e.g. from NHS England, and equivalent bodies in Scotland and Wales). Participants will not be contacted directly.

What are the possible benefits and risks of participating?
No interventions are taking place for this long-term follow-up study so there are no direct benefits or risks to participants.

Where is the study run from?
University of Oxford and is managed by researchers at at Oxford Population Health, Nuffield Department of Population Health (UK)

When is the study starting and how long is it expected to run for?
The extended follow-up approvals were granted in April 2017. The HPS long-term study will collect data from the start of the original trial in 1994 until at least 2035. Analyses are planned to be run at approximately 5-yearly intervals based on ongoing linkage to NHS records.

Who is funding the study?
University of Oxford (UK)
Health Data Research UK (HDRUK)

Who is the main contact?
Dr Richard Bulbulia (Investigator), hps@ndph.ox.ac.uk (UK)

Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
262231

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
HPS/P/2/0894, IRAS 262231

Study information

Scientific Title
MRC BHF Heart Protection Study long-term follow-up

Acronym
HPS

Study objectives
To determine the factors that contribute to the health of UK participants of the original Heart Protection Study (HPS) (ISRCTN48489393) over many years, using electronic health records.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/04/2017, South Central - Oxford B Research Ethics Committee (Whitefriars, Level 3, Block B, Lewin's Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8052; oxfordb.rec@hra.nhs.uk), current ref: 19/SC/0262, previous ref: C02.261

Study design
Randomized Controlled Trial with extended post-trial observation via electronic health records

Primary study design
Observational

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Cardiovascular disease, dementia, cancer

Interventions
Record-level electronic health data will be requested from NHS England and equivalent registries in Scotland & Wales. These records will be used to follow up the original HPS cohort for an extended period after the end of the original trial in 2007. No direct intervention will take place, and participants will not be contacted directly.
[During the scheduled treatment period, which ended in October 2001, the drug allocation was to active versus placebo simvastatin and anti-oxidant vitamin supplementation.]

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)

Simvastatin, anti-oxidant vitamin supplementation (vitamins E, C, and beta-carotene)

Primary outcome(s)
Risk ratios for the first occurrence post-randomisation of each outcome of interest (dementia, stroke, all major cardiovascular disorders, other vascular disease complications, myopathies, heart failure, renal impairment, other health and care outcomes and death) between both allocated treatment groups measured using appropriate analysis methods. This will be based on at least 25 years of follow-up from trial initiation with further analyses planned at approximately 5 yearly intervals based on ongoing linkage to NHS records

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
31/12/2035

Eligibility

Key inclusion criteria
Participants are all part of the original HPS cohort (randomised between 1994 and 1997). They were between 40 and 80 years old when invited to participate. Eligibility criteria were broad and included:
1. Patients at high risk of CHD (e.g., because of a history of vascular disease or diabetes)
2. Without clear indication for or contra-indication to statin
3. Male and female adults
4. Non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L (135 mg/dL)
For inclusion into the legacy cohort, participants had to be residents of the UK.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
40 years

Upper age limit
80 years

Sex
All

Key exclusion criteria
1. The patient's doctor considered statin therapy to be clearly indicated or contra-indicated
2. A past history of: stroke, myocardial infarction or angina hospitalisation within the previous six months

3. Chronic liver disease or evidence of abnormal liver function
4. Severe renal disease or evidence of substantially impaired renal function
5. Inflammatory muscle disease or evidence of muscle problems
6. Concurrent treatment with cyclosporin, fibrates or high-dose niacin
7. Child-bearing potential
8. Severe heart failure
9. Life-threatening conditions other than vascular disease or diabetes (including any cancer except non-melanoma skin cancer)
10. Any other condition that might limit long-term compliance

Date of first enrolment
15/06/2022

Date of final enrolment
31/12/2035

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Nuffield Department of Population Health
University of Oxford
Old Road Campus
Roosevelt Drive
Oxford
United Kingdom
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
University/education

Funder Name
University of Oxford

Alternative Name(s)
University in Oxford, Oxford University, , Universitas Oxoniensis

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Funder Name
Health Data Research UK

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available later. Procedures for accessing the data for this study are available at: https://www.ndph.ox.ac.uk/data-access

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Other files	LTFU Information for HPS participants – this is a participant facing document (not a PIS) developed on request by CAG. version 2.1	07/06/2021	06/03/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version HPS/P/2/0894/ADD100821	10/08/2021	06/03/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes