ISRCTN14416153 https://doi.org/10.1186/ISRCTN14416153

Long-term follow-up of participants in the electronic health records from the SEARCH Study

Submission date
16/08/2022

Recruitment status
Recruiting

Registration date
25/08/2022

Overall study status
Ongoing

Last Edited
30/01/2026

Condition category
Other

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The SEARCH study (https://doi.org/10.1186/ISRCTN74348595) was a randomised, multi-centre, factorial trial of LDL (low-density lipoprotein) cholesterol lowering, comparing higher versus standard dose simvastatin (a drug used to lower cholesterol for people diagnosed with high blood cholesterol), and homocysteine (an amino acid) lowering comparing folic acid and vitamin B12 supplementation versus placebo in 12,064 patients with an average age of 64 and with a history of heart attacks (myocardial infarction (MI)). It was run in 88 UK clinical centres for ten years. Participants in SEARCH were recruited to the trial between September 1998 and October 2001, with all final follow-up assessments completed by June 2008. Results were presented at the American Heart Association meeting in 2008 and published in the Lancet & JAMA in 2010.

SEARCH found that:
1. The allocation of simvastatin 80 mg daily versus 20 mg daily reduced LDL-cholesterol by 0.35 mmol/L and reduced major vascular events (i.e. heart attacks, strokes or coronary or non-coronary revascularisation) by 6% (95% CI 12% to +1%). This reduction was in line with expectations and contributed to the Cholesterol Trialists' Collaboration (CTT) meta-analysis that showed that more intensive LDL-cholesterol lowering produces additional benefits.
2. Supplementation with folic acid plus vitamin B12 significantly reduced homocysteine levels and is safe, but did not reduce the risk of major vascular events or cancer
3. Simvastatin 80 mg daily was associated with an increased risk of myopathy (muscle symptoms with raised blood creatine kinase) with 53 versus 2 cases respectively among those allocated 80 mg versus 20 mg simvastatin daily

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: 19/CAG/0167)) in place to carry out long-term research on this cohort. The data controller has approval from the West of Scotland Research Ethics Service (Ref: 19/WS /0115) to follow up on the cohort, with continued data linkage to allow for future analyses.

The purpose of this SEARCH 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 SEARCH participants recruited in UK hospitals between 1998 and 2001. 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 risks or benefits to participants.

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

When is the study starting and how long is it expected to run for?
July 2019 to December 2035

Who is funding the study?
University of Oxford (UK)

Who is the main contact?
Professor Richard Bulbulia (Chief Investigator), search@ndph.ox.ac.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)
266042

Protocol serial number
IRAS 266042, PID14408-SP001-AC001

Study information

Scientific Title
SEARCH trial legacy study: Long-term follow-up of participants using electronic health records

Study objectives
To determine the factors that contribute to the health of UK participants of the original SEARCH trial (ISRCTN74348595) over many years, using electronic health records

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/08/2019, West of Scotland REC 3 (Research Ethics, Clinical Research & Development, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, United Kingdom; +44 (0) 141 314 0211; WoSERC3@ggc.scot.nhs.uk), ref: 19/WS/0115

Study design

Extended follow-up study

Primary study design
Observational

Study type(s)
Other, Treatment

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 on the original SEARCH cohort for an extended period after the end of the main trial in 2008. No direct intervention will take place, and participants will not be contacted directly.

Intervention Type
Other

Primary outcome(s)
The first planned analyses will be based on at least 15 years' follow-up from trial initiation with further analyses planned at approximately 5 yearly intervals based on ongoing linkage to NHS records. Appropriate analysis methods will be used to compare the risk ratios for 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.

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

Completion date
31/12/2035

Eligibility

Key inclusion criteria
Participants were part of the original SEARCH cohort (randomised between 1998 and 2001). They were between 18 and 75 years old when invited to participate. Participants had to fulfil all of the following criteria:
1. History of prior myocardial infarction
2. Current use of a statin or clear indication for statin therapy
3. No clear indication for folic acid
4. No clear contraindications to the study treatments
5. No other medical problem

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
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Participants who have opted out of having their data provided by NHS England
2. Participants who have read the privacy notice and have decided that they do not want their data used in this study

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
Oxford Population Health
University of Oxford
Richard Doll Building
Old Road Campus
Oxford
England
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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, uniofoxford

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Procedures for accessing the data for this study are available at https://www.ndph.ox.ac.uk/data-access

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 1	15/05/2019	17/08/2022	No	No
Protocol file	version 2.0	13/11/2025	30/01/2026	No	No

Study website	11/11/2025	11/11/2025	No	Yes