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Web-based investigation of statin side-effects

Submission date 01/04/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 12/05/2016	**Overall study status** Completed	
Last Edited 11/06/2026	**Condition category** Circulatory System	

Plain English summary of protocol

Current plain English summary as of 11/10/2017:
Background and study aims
Statins reduce the risk of heart attacks and strokes, however many patients stop taking statins because they get aches and pains in their muscles. The link between taking statins and aches and pains is not fully understood. Aches and pains are really common among people who don't take statins, and this means when someone taking a statin develops pain, it is really difficult to know whether the pain is caused by their statin. This means it is very difficult for patients and doctors to know whether to stop the statin or to continue. This is an important decision, because by not taking a statin, a patient's risk of a heart attack or stroke goes up by about one third. This study aims to determine whether statins cause muscle pain, thus allowing patients to make well-informed decisions whether to stop them or not.

Who can participate?
Patients who have recently stopped or wish to stop taking statins due to unwanted muscle symptoms.

What does the study involve?
Everyone taking part will have agreed to do so voluntarily, knowing the study involves:
-Most people will need a single routine clinical blood test, to confirm if it is safe for the patient to re-start or continue taking statins.
-One main visit to your GP Practice. The Research Nurse will explain everything about the study, including what to do if you have queries. You can ask any questions that you may have.
-If you decide to go ahead, you will have your weight, height and blood pressure recorded and sign a consent form.
-Patients will be given the opportunity to provide a research blood sample for an genetic analysis as part of a larger collaborative effort investigating genetic associations with statins effects. This is entirely optional. Specific results from this blood test will not be given to clinicians or to patients.
-Taking atorvastatin or placebo (dummy treatment) daily for 1 year in 2-months sequences, switching between them in a random order. Neither you, nor your doctor, will know which you are taking in each 2-month period, except in an emergency.
-The study treatment is delivered though the post.
-Completing 7 short questionnaires on your muscle symptoms every 2 months. Patients will be reminded to submit symptom information prior to each data collection period.

-There are a four ways you can choose to complete the questionnaires: 1) via the internet, 2) verbally over the phone, 3) using a mobile phone app or 4) using a conventional paper form.
-Following the 12-months treatment, there will be one phone call or face-to-face appointment with your GP or Research Nurse to discuss your individual results.
-Your results will be based on the information you provided in your questionnaires.
-You can discuss the results with your GP and make a decision about whether you want to continue taking a statin or not.
-Three months after you stopped the study treatment, the study team will contact you to ask if you continued taking statins or not.

What are the possible benefits and risks of participating?
Benefits - This study will allow you and your GP to find out if any muscle symptoms you experience happen more when you are taking statins. This may help you to decide with your GP whether to take statins to reduce your risk of cardiovascular disease after the end of the study.
Risks - The study team do not know if statins cause milder muscle symptoms such as pain, which is why we are doing the study. Statins sometimes cause a very rare but serious muscle problem, but in less than 2 in 10,000 people.

Where is the study run from?
The Clinical Trials Unit at the London School of Hygiene and Tropical Medicine (UK)

When is the study starting and how long is it expected to run for?
April 2016 to October 2019

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
1. Professor Liam Smeeth (scientific)
2. Dr Kieran Brack (public)
statinwise@lshtm.ac.uk

Previous plain English summary:
Background and study aims
Cholesterol is essential for the body to work well, but too much ‘bad cholesterol’ (called low-density lipoprotein or LDL) is unhealthy. High levels of ‘bad cholesterol’ in the blood can lead to fatty deposits building up in our arteries. This can increase the risk of developing cardiovascular disease, which includes conditions such as coronary heart disease (leading to angina and heart attack) and stroke. Statins are drugs that are used to reduce the amount of ‘bad cholesterol’ the body makes while increasing levels of "good" cholesterol (high-density lipoprotein, or HDL). Statins are the most commonly prescribed treatment in the UK. Recently, the number of people eligible to receive statins increased by over 2 million due to updated National Institute for Health and Care Excellence recommendations. Statins are known to cause rare but serious side effects such as rhabdomyolysis (breakdown of muscle tissue) but many patients stop taking statins due to less severe symptoms, such as muscle pain or fatigue. Trials have not found any differences between those taking statins and those taking placebo in terms of these less severe muscle symptoms, but some have questioned whether the information collected was adequate. Given that it is known that statins can reduce heart attacks and strokes, it would be helpful to know how frequently the symptoms experienced during statin use are related to the statin and how frequently related to other causes. This will help inform patients’ and doctors’ treatment choices. This study is looking at side effects of atorvastatin compared to a matching placebo (dummy pill).

Who can participate?
Patients who have recently stopped or wish to stop taking statins due to unwanted muscle symptoms.

What does the study involve?
Each participant is initially randomly allocated to either the atorvastatin group or placebo group. They are all recruited into in the study for one year, split into six two-month treatment periods. Each patient is sent their treatment though the post and asked to take it every day for the duration of the study. For the first six months, they receive one treatment. For the second, they receive the other. So, for example, the participants initially in the atorvastatin group will receive the placebo for the second half of the study. This allows them to act as their own control, so at the end of the study, they are able to compare their own level of symptoms between the statin and placebo treatment periods and use this information to help decide the best treatment options. This is called an 'N-of'1' study. Two months is enough for short-term side effects to emerge, and the study's one year duration is brief enough to minimise any adverse impact on cardiovascular outcomes from under-treatment. There is no break between the two treatments (i.e.wash-out period) but symptoms are measured at the end of each treatment period to ensure that they reflect the current treatment. At the end of each two-month period, patients are asked to submit symptom information using a specially-designed mobile app; outcomes are self-reported side effects. If patients are unable to use the mobile app, data can be submitted directly online by the patient or answers to the questions obtained by a researcher through a telephone call. Patients are free to choose a suitable method of follow-up. Patients are reminded to submit symptom information prior to each data collection period. This will be done by email, text, and phone calls. At the end of the trial, patients are shown summaries of their individual results, to help them to decide whether to continue taking statins. Symptom reports are collected 3 months later to assess whether this information impacts subsequent treatment choices and symptom severity.The results are combined from each individual to assess how frequently statins are causing side effects in people who perceive themselves to be intolerant. As part of the study, patients are asked to provide a blood sample for an optional genetic analysis as part of a larger collaborative effort investigating genetic associations with statins effects. Specific results will not be fed back to clinicians or to patients.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
The Keats Group Practice, London (UK)

When is the study starting and how long is it expected to run for?
April 2016 to April 2019

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
1. Professor Liam Smeeth (scientific)
2. Dr Kieran Brack (public)
statinwise@lshtm.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Liam Smeeth

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London School of Hygiene and Tropical Medicine
Dept of Non Communicable Diseases
London
United Kingdom
WC1E 7HT

Type(s)
Public

Contact name
Dr Kieran Brack

Contact details
Clinical Trials Unit
Faculty of Epidemiology & Public Health
London School of Hygiene & Tropical Medicine
Keppel Street
London
United Kingdom
WC1E 7HT
+44 207 958 8195
statinwise@lshtm.ac.uk

Additional identifiers

ClinicalTrials.gov (NCT)
NCT02781064

Clinical Trials Information System (CTIS)
2016-000141-31

Study information

Scientific Title
A series of randomised controlled N-of 1 trials in patients who have discontinued or are considering discontinuing statin use due to muscle-related symptoms to assess if atorvastatin treatment causes more muscle symptoms than placebo.

Acronym
StatinWISE

Study objectives

Statins are the most commonly prescribed treatment in the UK. Recently updated NICE guidelines have lowered the threshold for statin use to include all patients with a 10% or greater 10-year risk of cardiovascular disease. Previous randomised trials have established the prevalence of serious adverse effects of statins such as rhabdomyolysis, however, many patients discontinue statins due to less severe symptoms, such as muscle pain or fatigue. Randomised trials have shown no differences between those taking statin and placebo in terms of the prevalence of these side effects (approximately 9%), but currently there is no pathway of care for clinicians to empirically and objectively evaluate whether symptoms reported by a statin-user are caused by the statin itself or the so-called 'nocebo' effect (symptoms reflecting patient expectation of side effects). Given the effectiveness of statins in preventing cardiovascular disease, accurate data on the cause of symptoms experienced during statin use are needed to reliably inform patient and clinician about continuation of use. The proposed StatinWISE trial will provide definitive answers to this important uncertainty about statin therapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. MRHA Approval, 30/08/2016, ref: Reference – 17072/0009/001-0001
2. South Central – Hampshire A REC Approval ,14/07/2016, ref: Reference – IRA project ID 197990

Primary study design
Interventional

Study design
A series of randomised, double-blinded N of 1 trials.

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Cardiovascular disease

Interventions
Current interventions as of 11/10/2017:
Statinwise is a randomised, double blind, placebo controlled N-of-1 trial taking place in a primary care setting. The aim is to quantify the occurrence of self-reported muscle symptoms whilst taking daily atorvastatin and placebo. 200 patients are recruited.

The trial treatment consists of once daily oral administration of Atorvastatin (20mg, capsule form) or a matching placebo (Microcrystalline Cellulose). The treatment phase of the trial will be one year in duration. Atorvastatin or placebo are provided in two-month treatment packs. A blinded placebo, identical in size, colour, smell and packaging to the active statin, has been chosen to prevent knowledge of treatment from affecting symptom scores.

Patients receive their allocated trial medication through the post. There should be no break between treatment periods. However, if for any reason there is a break; patients can restart taking the trial medication as soon as possible. Patients are asked to take the treatment at a time of day convenient to them. Capsules should be swallowed whole. Patients are given written instructions on how to take the study medication in English or Welsh.

At the start of each treatment period, patients are asked to inform the trial team about the first date of study medication. A Freephone telephone number and a pre-paid postage reply slip is available for the patient to use, whichever is easier to ensure data collection occur on the correct days. At the end of each treatment period patients are asked to report their pain scores using questionnaires. There are a four ways to choose to complete these: 1) via the internet, 2) verbally over the phone, 3) using a mobile phone app or 4) using a conventional paper form.

During the last week of the last treatment period, the Research Nurse contacts patients to thank them for their participation and to inform them that this is the last treatment period. Patients will informed that they receive their individual results at the beginning of month 14. The Research Nurse and patient should arrange a telephone or face-to-face appointment to discuss the individual results during month 14. The Research Nurse also informs patients that if they want to continue taking statin without a break, to arrange a separate clinical appointment with their GP prior to the end of the treatment period.

At month 15, trial staff contact the patient to document their decision to continue statin use and whether their results helped them reach this decision. This will be the last data collection point of the trial for each patient.

Throughout the trial, continued patient care will be at the discretion of their GP. In primary care, the patient will be recorded as having an ongoing statin prescription.
1. Where treatment with an interacting drug is needed that will be for less than one-month duration, the patient will be asked to stop the trial treatment for that period.
2. Where treatment with an interacting drug is needed for longer than one month, the patient will be asked to withdraw from study treatment completely.

Previous interventions:
Statinwise is a randomised, double blind, placebo controlled N-of-1 trial taking place in a primary care setting, to quantify the occurrence of self-reported muscle symptoms whilst taking daily atorvastatin. A total of 200 patients who fulfil the eligibility criteria will be recruited. The trial treatment consists of once daily oral administration of Atorvastatin (20mg) capsules, which will be compared with matching placebo (Microcrystalline Cellulose). The treatment phase of the trial will be one year in duration for each patient. A blinded placebo, identical in size, colour, smell and packaging to the active statin, has been chosen to prevent knowledge of treatment from affecting symptom scores.

Patients will receive their allocated trial medications through the post and they will be asked to take the study medication daily through the six two-month treatment periods. Ideally there should be no break between treatment periods. However, if for any reason there is a break; patients can simply restart taking the trial medication as soon as possible.

Patients will be asked to take one capsule orally once daily at a time of day convenient to them. Capsules should be swallowed whole. Patients will be given written instructions on how to take the study medication. At the start of each two month treatment period, patients will be asked to inform the trial team about their first date of study medication use using the trial's mobile application (app), email, text message, Freephone telephone service or a pre-paid postage reply slip, whichever is easier to ensure data collection occur on the correct days. A Freephone telephone number will be provided for patients to call if they have any questions. Adherence to the study medication will be collected on the same days as other data as part of the outcome data collection.

During the last week of treatment period, the Research Nurse will contact patients to thank them for their participation so far, inform them that this is the last treatment period, and that they, together with their GP, will receive their individual results at the beginning of month 14. The Research Nurse and patient will arrange a telephone or face to face appointment to discuss the individual results during month 14. The Research Nurse will also inform patients that if they want to continue taking statin without a break, to arrange a separate clinical appointment with their GP prior to the end of the treatment period.

At month 15, trial staff will email/telephone the patient to document their decision on future statin use and whether their results helped reach this decision. This will be the last data collection point of the trial.

Throughout the trial, continued patient care will be at the discretion of their GP. In primary care, the patient will be recorded as having an ongoing statin prescription.
1. Where treatment with an interacting drug is needed that will be for less than one-month duration, the patient will be asked to stop the trial treatment for that period.
2. Where treatment with an interacting drug is needed for longer than one month, the patient will be asked to withdraw from study treatment completely.

This will be the last data collection point for the study.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Atorvastatin

Primary outcome(s)
Muscle symptoms (pain, weakness, tenderness, stiffness or cramp) reported every 7-week during treatment, measured using the Visual Analogue Score (VAS) score

Key secondary outcome(s)
Relationship between individual trial result and patient decision whether to continue statins long term at month 15, measured by checking if a statin prescription was issued by the General Practitioner.

Completion date
30/09/2019

Eligibility

Key inclusion criteria
1. Adults (aged 16 years and over)
2. Prescribed statin treatment in the last 3 years
3. Stopped OR considering stopping statin treatment due to muscle symptoms
4. Provided fully informed consent

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 Years

Upper age limit
120 Years

Sex
All

Total final enrolment
200

Key exclusion criteria
1. Any previously documented serum alanine aminotransferase (ALT) levels at or above three times the upper limit of normal
2. Have persistent, generalised, unexplained muscle pain (whether associated or not with statin use) and have creatinine kinase (CK) levels greater than 5 times the upper limit of normal
3. Should not be using atorvastatin 20mg daily in the opinion of the general practitioner

Date of first enrolment
01/12/2016

Date of final enrolment
04/06/2018

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
Albion Street Practice
87 Albion Street
Rotherhithe
London
England
SE16 7JX

Study participating centre
Bay Medical
Heysham Primary Care Centre
Middleton Way
Heysham NO COUNTRY SPECIFIED, assuming England
England
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Study participating centre
Bentley Surgery
128 High Street
Bentley
Doncaster
England
DN5 0AT

Study participating centre
Brigstock & South Norwood Partnership
141 Brigstock Road
Thornton Heath
Surrey
England
CR7 7JN

Study participating centre
Bromley Common Practice
Crown Medical Centre
3 Mackintosh Street
Bromley
England
BR2 9GT

Study participating centre
Brownlow Health
70 Pembroke Place
Liverpool
England
L69 3GF

Study participating centre
Clarence Medical Centre
West Kinmel Street
Wales
Rhyl
Wales
LL18 1DA

Study participating centre
Cleverleys Group Practice
Kelso Avenue, Lancashire
Thornton-Cleveleys
England
FY5 3LF

Study participating centre
Conisbrough Group Practice
Stone Castle Centre
Doncaster
Conisbrough
England
DN12 3JW

Study participating centre
Creffield Medical Centre
15 Cavalry Road
Colchester
England
CO2 7GH

Study participating centre
Everglades Medical Practice
Grahame Park Health Centre
The Concourse
London
England
NW9 5XT

Study participating centre

The Exchange Surgery
2-8 Gracefields Gardens
London
England
SW16 2ST

Study participating centre
Falkland Surgery
Falkland Way
Bradwell
Great Yarmouth
England
NR31 8RW

Study participating centre
Freshney (Littlefields) Green Primary Care Centre
Sorrel Road
Grimsby
England
DN34 4GB

Study participating centre
Great Sutton Medical Centre
Old Chester Road
Ellesmere Port
Chester
England
CH66 3SP

Study participating centre
Hampstead Group Practice
75 Fleet Road
London
England
NW3 2QU

Study participating centre
Hope Family Medical Centre
Hope Health Centre
Hawarden Road
Hope

Nr Wrexham
Wales
LL12 9NP

Study participating centre
Hornsey Rise Health Centre
Hornsey Rise Health Centre, Hornsey Rise
London
England
N19 3YU

Study participating centre
Hoveton and Wroxham Medical Centre
Stalham Road
Norfolk
Hoveton
England
NR12 8DU

Study participating centre
Hurley Clinic
Kennington Lane
Lambeth
London
England
SE11 4HJ

Study participating centre
Jorvik Gillygate Practice
Woolpack Surgery
Stonebow
York
England
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Study participating centre
Keats Medical Practice
Keats Medical Practice, 1b Downshire Hill
London
England
NW3 1LR

Study participating centre
Kings Road Surgery, Mumbles
2-6 Kings Road, Mumbles
Swansea
Wales
SA3 4AJ

Study participating centre
Long Stratton Medical Partnership
Swan Lane, Tharston, Norfolk
Norwich
England
NR15 2UY

Study participating centre
Mathukia's Surgery
281 Ilford Lane, Essex
Ilford
England
IG1 2SF

Study participating centre
Mattishall & Lenwade Surgeries
15 Dereham Road, Mattishall, Norfolk
Dereham
England
NR20 4QA

Study participating centre
Mayfield Surgery
246 Roehampton Lane
London
England
SW15 4AA

Study participating centre
Mitcham Family Practice
55 Mortimer Road

Surrey
Mitcham
England
CR4 3HS

Study participating centre
North House Surgery
28 North Street
Ripon
England
HG4 1HL

Study participating centre
Oak Lodge Medical Centre
234 Burnt Oak Lane
Edgware
London
England
HA8 0AP

Study participating centre
Oak Tree Surgery
Whitethorn Drive, Brackla, Bridgend
NO COUNTRY SPECIFIED, assuming England
England
CF 31 2PQ

Study participating centre
Open Door Surgery
47 Boundaries Road
Balham
London
England
SW12 8EU

Study participating centre
Parliament Hill Medical Centre
113-117 Highgate Road
London
England
NW5 1TR

Study participating centre
Paxton Green Group Practice
1 Alleyn Park
London
England
SE21 8AU

Study participating centre
Pendle View Medical Centre
47 Arthur Street, Brierfield
Nelson
England
BB9 5RZ

Study participating centre
Queen Square Medical Practice
2 Queen Square
Lancaster
England
LA1 1RP

Study participating centre
Regent House Surgery
21 Regent Road
Chorley
England
PR7 2DH

Study participating centre
Riverside Medical Practice
Hobart House, Vauxhall
London
England
SW8 2JB

Study participating centre
Rosedale Surgery
Ashburnham Way, Carlton Colville

Lowestoft
England
NR33 8LG

Study participating centre
School Lane Surgery
School Lane
Thetford
England
IP24 2AG

Study participating centre
Scott Practice
Greenfield Lane, Balby
Doncaster
England
DN4 0TG

Study participating centre
Snaith & Rawcliffe Medical Group The Marshes Surgery
But Lane Snaith
Goole
England
DN14 9DY

Study participating centre
Station House Surgery
Station Rd
Kendal
England
LA9 6SA

Study participating centre
Strawberry Place Surgery
5 Strawberry Place, Morriston
Swansea
Wales
SA6 7AQ

Study participating centre
Streatham Common Practice
St Andrews Church Room, Guildersfield Road
London
England
SW16 5LS

Study participating centre
Tottenham Health Centre
759 High Road, Tottenham
London
England
N17 8AH

Study participating centre
Vanbrugh Group Practice
Greenwich Square Health Centre, 2nd Floor, 12 Lombarde Square
London
England
SE10 9GB

Study participating centre
Village Practice Thornton
Thornton Medical Centre, Church Road
Thornton-Cleveleys
England
FY5 2TZ

Study participating centre
Watling Medical Centre
108 Watling Avenue, Burnt Oak
Edgware
England
HA8 0NR

Study participating centre
West Hampstead Medical Centre
9 Solent Road
London
England
NW6 1TP

Study participating centre
Windermere & Bowness Surgery
Goodly Dale
Windermere
England
LA23 2EG

Study participating centre
Woodlands Practice
11 Red Hill
Chislehurst
England
BR7 6DB

Study participating centre
William Harvey Heart Centre
Barts and The London School of Medicine & Dentistry
William Harvey Heart Centre
Charterhouse Square
London
England
EC1M 6BQ

Study participating centre
Wallington Family Practice
Jubilee Health Centre
Shotfield
Wallington
England
SM6 0HY

Study participating centre
Vale of Neath
102 High Street, Glynneath
Neath
Wales
SA11 5AL

Study participating centre
Honor Oak Group Practice
20 Turnham Road
London
England
SE4 2LA

Study participating centre
Bicester Health Centre
The Health Centre, Coker Close
Bicester
England
OX26 6AT

Study participating centre
Beechtree Surgery
68 Doncaster Road
Selby
England
YO8 9AJ

Sponsor information

Organisation
London School of Hygiene and Tropical Medicine

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
For participant level data, please see the study website (http://statinwise.lshtm.ac.uk/live/)

Previous publication and dissemination plan:
The trial protocol and results will be published in peer-reviewed journals. All publications will follow the CONSORT statement.21 Links to the publication will be provided in all applicable trial registers. Dissemination of results to patients will take place via the media, trial website and relevant patient organisations. Collaborating investigators will play a vital role in disseminating the results to colleagues and patients.

The success of the trial depends entirely upon the collaboration of nurses and doctors in the participating practices and those who hold key responsibility for the trial. Hence, credit for the study will be assigned to the key collaborator(s) from a participating site as it is crucial that those taking credit for the work have actually carried it out. The results of the trial will be reported first to trial collaborators.

IPD sharing statement:
For participant level data, please see the study website (http://statinwise.lshtm.ac.uk/live/)

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	24/02/2021	25/02/2021	Yes	No
Results article	results	01/03/2021	15/03/2021	Yes	No
Results article		05/11/2019	14/06/2023	Yes	No
Protocol article	protocol	01/12/2017		Yes	No
Protocol (other)			11/06/2026	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes