



Statin treatment and muscle symptoms: a series of randomised, placebo controlled N-of-1 trials

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10 placebo controlled N-of-1 trials
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Abstract

Objective: The extent to which statins cause symptomatic muscle adverse effects remains uncertain. This trial aimed to establish the effect of statins on muscle symptoms among people who experienced muscle symptoms whilst taking statins.

Design: 200 double-blinded N-of-1 trials.

Setting: Primary care across 50 sites in the UK.

Participants: 200 participants who recently discontinued statins or were considering discontinuing statins due to muscle symptoms were recruited between December 2016 and April 2018.

Interventions: Participants were randomised to a sequence of six double-blinded treatment periods (each two months) of atorvastatin 20mg daily or matching placebo.

Main outcome measure: At the end of each period, participants rated their muscle symptoms on a visual analogue scale (0-10). The primary analysis aggregated data from participants' symptom scores, comparing statin versus placebo periods.

Results: 151 participants provided symptoms scores during at least one period each of statin and placebo and were included in the primary analysis. Overall there was no difference in muscle symptom scores between statin and placebo periods (mean difference statin minus placebo -0.11 (95% CI -0.36, 0.14; P=0.40)). Eighteen participants (9%) withdrew during a statin

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3 period and 13 (7%) during a placebo period due to intolerable muscle symptoms. There were
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6 13 serious adverse events, none considered attributable to the study medication, including 2
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8 fatal events (1 during statin treatment and 1 after end of treatment) and 11 nonfatal events (5
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10 during statin treatment and 6 during placebo).
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14 **Conclusions:** Among participants who previously reported severe muscle symptoms while
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16 taking statins, there was no overall effect of statins on muscle symptoms compared to placebo.
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18 The slight difference in withdrawals due to muscle symptoms suggests that statins may
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20 contribute to symptoms in a small number of patients. N-of-1 trials can assess drug effects at
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22 the group level and guide individual therapy.
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27 **Trial registration:** The trial was registered on ISRCTN registry (ISRCTN30952488), the European
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29 Union Drug Regulating Authorities Clinical Trials Database (EUDRACT 2016-000141-31) and on
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31 Clinicaltrials.gov (NCT02781064).
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Introduction

Statins reduce cardiovascular disease events in primary and secondary prevention, among men and women, and across all age groups.^{1,2} Systematic reviews and meta-analyses of randomised trials have demonstrated the safety of statins.³ Although severe adverse effects are rare, statins increase the risk of myopathy (absolute excess risk around 1 case per 10,000 people treated per year), which can progress to severe rhabdomyolysis (around 0.2 case per 10,000 people treated per year).³ However, uncertainty persists about less severe muscle symptoms. Many people believe that statins commonly cause muscle pain⁴⁻⁶ and this belief has been reinforced by results from unblinded observational studies^{6,7} and media reports.⁸⁻¹⁰ This has led to patients commonly discontinuing treatment,^{6,11} exposing them to increased cardiovascular disease risk.¹²

For a patient in routine clinical care, it is not easy for the clinician or patient to determine reliably whether muscle symptoms are caused by statins.¹³⁻¹⁵ One way to tackle this uncertainty is to conduct blinded N-of-1 trials in individual patients with symptoms during statin use. N-of-1 trials are a randomised trial in individual patients,¹⁶ that can provide information to help determine the best course of action in an individual. When a number of N-of-1 individuals are combined in analysis, the result can also be used to assess the overall effect of a treatment. The current report describes the results of StatinWISE (Statin Web-based Investigation of Side Effects), a series of N-of-1 trials comparing periods of statin and placebo treatment in people who had previously reported muscle symptoms while taking statins, which

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3 aimed to establish (i) the effect of statins on all muscle symptoms, and (ii) the effect of statins
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5 on muscle symptoms that are perceived to be statin related.
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9 **Methods**

10 11 12 13 **Trial design**

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17 StatinWISE was a series of randomised, double-blind, placebo-controlled, N-of-1 trials. The
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19 overall duration of the trial was one year for each participant and comprised six two-month
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21 treatment periods (three of placebo, three of active treatment) in a randomly allocated order.
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25 The trial received a favourable opinion from South Central - Hampshire A Research Ethics
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27 Committee. The approved protocol is available online here:

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30 <https://statinwise.lshtm.ac.uk/live/gp/>.
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33 **Patient and public involvement**

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37 A StatinWISE patient involvement group was involved in trial design, specifically the packing
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39 and distribution of the drug, design of data collection tools and the content and wording of
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41 patient documents. The group was involved in trial conduct through membership in the Trial
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43 Steering Committee and provided substantial input into the individual participants' results
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45 feedback document. Patient representatives provided active input into the interpretation and
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47 presentation of the results.
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Participants

Participants were recruited from General Practices in England and Wales and were either considering discontinuation of their statin, or had stopped taking a statin in the last three years, due to muscle symptoms.

We excluded participants with previously elevated serum alanine aminotransferase levels (≥ 3 times the upper limit of normal), with persistent, generalised, unexplained muscle pain (whether associated or not with statin use) and creatine kinase levels ≥ 5 times the upper limit of normal, any contraindications to atorvastatin 20mg, or who the general practitioner deemed unsuitable to participate in the trial.

StatinWISE was given a favourable opinion by the South-Central Hampshire A Research Ethics Committee (16/SC/0324), approval by the Health Research Authority and regulatory approval (17072/0009/001-0001) by the Medicines and Healthcare products Regulatory Authority.

Sample size

We planned to recruit 200 participants to provide approximately 90% power to detect a treatment effect of at least one full unit on the visual analogue scale, assuming a Type I error of 5% and allowing for loss to follow-up of 40% of participants, thus able to include 120 in the analysis (further details in supplementary appendix).

Randomisation and masking

Randomisation codes were generated and held securely by an Information Technology team and Sponsor representative at the London School of Hygiene & Tropical Medicine Clinical Trials Unit who were independent of the StatinWISE trial management team. The codes were made available to a Good Manufacturing Practice certified clinical trial supply company (Sharp Clinical Services (UK) Ltd) for the treatment packs to be manufactured in accordance with the randomisation list.

Participants were allocated with equal probability to one of eight possible sequences (Appendix Figure 1), which ensured that (i) all participants received one period of statin and one period of placebo in their first two treatment periods (in random order) and (ii) no one would be allocated to three sequential periods of the same treatment. Randomisation codes were generated and held securely and confidentially by an Information Technology team and Sponsor representative at the London School of Hygiene & Tropical Medicine Clinical Trials Unit (CTU) who were independent of both the StatinWISE trial management team and GP surgery staff thus ensuring allocation concealment. A physical copy of the randomisation codes was stored in a sealed and signed envelope in the locked office of the CTU director. The codes were made available to a Good Manufacturing Practice certified clinical trial supply company (Sharp Clinical Services (UK) Ltd, Marketing Authorisation Number 10284) for the treatment packs to be manufactured in accordance with the randomisation list.

Placebo was manufactured and packaged to match the atorvastatin by Sharp Clinical Services (UK) Ltd.

Interventions

Daily atorvastatin (20mg) was compared with matching placebo over six two-month treatment periods.

Outcomes

The primary outcome was self-reported muscle symptoms, defined as pain, weakness, tenderness, stiffness or cramp of any intensity. The primary outcome was measured each day using a validated visual analogue scale (0-10)¹⁷ for the last seven days of each treatment period.

We aimed to collect symptoms using a web-based database or mobile app, but our patient representatives recommended that participants should also be permitted to submit their scores over the phone or by paper questionnaire. Participants reporting by phone were asked to score their symptoms on an analogue severity scale, and thus did not use a visual analogue scale. Measuring symptoms only during the last week of each two-month treatment period was designed to avoid any carry-over effect.

Secondary outcomes were collected on the last day of each two-month treatment period via questionnaire. These included: binary measures for experience of muscle symptoms and attribution of symptoms to the study medication, site of muscle symptoms, visual analogue scale scores (0-10) for the effect of their muscle symptoms on general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life, and any other symptoms that the participant attributed to the study medication. Adherence to study medication was self-reported and verified by a drug accountability count of returned treatment

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3 packs. Three months after the end of the final treatment period we determined whether the
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5 participant had, or intended to, re-initiate statin treatment, and asked participants whether
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7 they had found their own trial result helpful in making the decision about future statin use.
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10 11 Statistical methods

12 13 14 15 **Individual N-of-1 trials**

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18 At the end of each N-of-1 trial, participants received numerical and graphical summaries of
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20 their individual data, in relation to their statin and placebo periods (Supplementary material)
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22 and were invited to discuss these with their GP who also received a copy. The N-of-1 trial
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24 methodology allows for the use of the personalised results document. Participants were then
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26 asked if this was helpful and whether they would re-start a statin.
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30 31 32 **Combined analysis of N-of-1 trials**

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35 To estimate the overall effect of the trial treatment on muscle symptom scores, data from each
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37 N-of-1 trial were aggregated. The primary analysis included all participants who entered data
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39 on muscle symptoms at least once during a treatment period with statin and at least once
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41 during a treatment period with placebo. The primary analysis was a linear mixed model for
42
43 visual analogue scale muscle symptom scores with random effects for participant and
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45 treatment. The analysis accounted for correlation between the seven daily measurements by
46
47 modelling the residual errors using a first-order auto-regressive error structure within each
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49 treatment period, and non-normality of the symptom scores by using robust standard errors.
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3 For the primary outcome, 95% confidence intervals are presented with a two-sided p-value, and
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5 99% confidence intervals for secondary outcomes.
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9 Period effects were explored in sensitivity analyses. To assess differences between data
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11 collection methods, the primary analysis was repeated additionally adjusting for the data
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13 collection method and allowing both the treatment effect and the residual variance to vary by
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15 the data collection method.
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18 19 20 **Secondary analyses** 21

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23 The single binary measure of whether the participant reported having or not having muscle
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25 symptoms during that treatment period was analysed using a logistic mixed model with random
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27 participant and treatment effects. This binary measure was then combined with the follow-up
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29 question about attribution, to obtain a single binary measure of whether the participant
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31 reported having muscle symptoms that could not be attributed to another cause. This was
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33 analysed using a similar logistic mixed model.
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39 Secondary outcomes relating to the impact of the statin on other aspects of life were analysed
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41 in a similar manner to the primary outcome, omitting the auto-regressive correlation structure.
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45 Graphical and descriptive summaries were used to explore how withdrawals and adherence
46
47 related to the statin and placebo periods.
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51 A data monitoring committee oversaw the study. The trial was registered on ISRCTN registry
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53 (ISRCTN30952488), the European Union Drug Regulating Authorities Clinical Trials Database
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55 (EUDRACT 2016-000141-31) and on Clinicaltrials.gov (NCT02781064).
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Results

Recruitment and participant flow

Two hundred participants were recruited between 20th December 2016 and 5th April 2018, and the last participant follow-up was on 5th July 2019.

Baseline characteristics

Median age was 69.5 (inter-quartile range 63-76) years, and 115 (58%) were male; 140 (70%) had a history of cardiovascular disease. Mean total cholesterol was 5.4mmol/L (standard deviation 1.4) (Table 1).

Numbers analysed

Of the 200 participants recruited, 151 (76%) provided one or more visual analogue scale measurements in both a statin period and a placebo period and were included in the primary analysis (Figure 1). Eighty-six (43%) participants did not complete the whole trial (2 died, 4 lost to follow-up, 80 withdrawals).

The 151 participants included in the primary analysis contributed 2,638 measurements during 392 statin periods and 2,576 symptom score measurements during 383 placebo periods. The mean number of scores per participant was 34.5 (range 8-42). In period 1, 164 (82%) participants provided at least one daily report of muscle symptoms, dropping to 75% in period 2 (n=149) and 58% (n=115) in period 6. Most (91%) participants provided outcome data online or by paper (Appendix Table 1).

Primary outcome

There were no differences in mean muscle symptom scores between statin and placebo periods (mean difference statin minus placebo -0.11 (95% CI -0.36, 0.14); P=0.40). The mean muscle symptom score was numerically lower during statin treatment periods (mean 1.68, standard deviation 2.57) compared with placebo (mean 1.85, standard deviation 2.74).

The effect of statins on the primary outcome was not modified by the method of data collection (Appendix table 2).

Secondary outcomes

Among the 152 participants that contributed at least one secondary outcome measurement in a statin period and one in a placebo period (one additional participant provided secondary outcome data than primary outcome data), there was no evidence of an effect of statins on muscle symptoms overall (OR 1.11 (99% CI 0.62, 1.99), or when restricting to muscle symptoms that could not be attributed to another cause (OR 1.22 (99% CI 0.77, 1.94)) (Table 2). Of the other secondary outcomes (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life), there were no differences in symptom scores between statin and placebo periods (Table 2).

Withdrawals

Reasons for withdrawal are shown in Appendix table 3. Of the 80 withdrawals, 34 (43%) occurred during a statin period, 39 (49%) during a placebo period, and 7 (9%) after randomisation but prior to any study medication being taken. While overall withdrawals were

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3 not related to statin or placebo periods, withdrawal due to intolerable symptoms was
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5 numerically more common during statin periods (18/200 (9%)) compared to during placebo
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7 periods (13/200 (7%)).
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10 11 **Adherence**

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15 Participant reported adherence was confirmed through verification of the number of pills
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17 remaining in returned medication packs. Adherence to the study medication was high, with at
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19 least 80% of participants reporting taking their study medication “every day” or “most days”
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21 during each period, among participants who had not yet withdrawn (Appendix Table 4 and
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23 Appendix Figure 2).
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26 27 28 **Participant decisions about ongoing statin use**

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31 Of the 114 participants who completed six treatment periods, 113 (57% of randomised
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33 participants) received their results during an end of trial discussion. One participant did not
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35 attend. Of these 113 participants, 99 (88%) said that the trial had been helpful, and 74 (66%)
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37 said that they had already or intended to resume statins. Of the 113 participants, 17 (15%) had
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39 a mean muscle symptom score at least 1 unit higher during statin compared to placebo periods
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41 and had been informed statins may be contributing to their muscle symptoms. Among these 17
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43 patients, 9 (53%) said they planned to re-start statin therapy. Among the remaining 96
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45 participants who had been informed that statins were unlikely to be contributing to their
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47 muscle symptoms, 65 (68%) said they planned to re-start statin therapy.
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Adverse events

During the trials there were 13 serious adverse events; none were considered attributable to the study medication. There were 2 fatal events (1 during statin treatment and 1 after end of treatment) and 11 nonfatal events (5 during statin treatment and 6 during placebo).

Discussion

Summary of results

This series of N-of-1 trials recruited participants who were either considering discontinuation of their statin, or had stopped taking a statin, due to muscle symptoms. We showed that overall there were no differences in the frequency or severity of muscle symptoms between statin and control periods. Additionally, there were no differences between statin and control periods in terms of the impact of muscle symptoms on aspects of daily life (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life). Missing outcome data for treatment periods were equally distributed between statin and placebo periods, so it is unlikely that muscle symptoms contributed to missed outcome data collection. Of those completing the trial, most (88%) said that their N-of-1 trial had been helpful, with nearly two thirds reporting that they intended to resume statins.

Withdrawal due to intolerable symptoms was slightly more common during statin periods and it is likely that some participants did experience statin related muscle symptoms. However, overall among this highly selected population of participants, who at trial entry had identified themselves as experiencing symptoms on statins that were severe enough to discontinue,

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3 withdrawal due to intolerable symptoms was uncommon and the excess comparing statins and
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5 placebo was only 2%.
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8 **Comparison with other literature** 9

10 This is the first large series of N-of-1 trials to investigate the effect of statins on muscle
11 symptoms. Our findings support the limited evidence from one previous small N-of-1 trial and
12 large systematic reviews and meta-analyses of randomised trials that have not established a
13 clear effect of statins on muscle symptoms in the absence of myopathy.^{2,3,18,19} An ongoing
14 meta-analysis²⁰ is investigating adverse event data from blinded, randomised trials of statins.
15 While our trial cannot exclude the possibility of adverse effects in some patients, it clearly
16 indicates that most patients taking statins do not experience symptoms causally related to their
17 statin, and highlights the importance of blinding when assessing adverse effects.
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20 Observational studies have reported muscle adverse effects,²¹ and experience of muscle
21 symptoms during statin use in clinical practice causes patients to discontinue.⁶ Various
22 explanations have been offered for this: first, the nocebo effect, in which expectations of
23 adverse effects may lead patients to attribute muscle symptoms occurring during statin use to
24 the statins themselves.²² Second, muscle aches and pains are common among the age group
25 taking statins, and so will occur co-incidentally with statin use, causing patients and clinicians to
26 erroneously attribute pain to statins.²³ Lack of randomisation and blinding in observational
27 studies mean that for a subjective symptom such as muscle pain, an association with statin
28 exposure may not be causal. The large proportion of our participants who intended to resume
29 statin use after their trial, is in line with observational data showing that, among those willing,
30 statin re-challenge can be tolerated by most patients.^{24,25}
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Strengths

We collected data on muscle symptoms in the setting of a double-blind series of trials, with randomised order of statin and placebo treatments to minimise bias and confounding.

Within-subject designs tend to have greater statistical power and this was increased by repeated measurements in each treatment period, allowing us to investigate differences between statin and placebo with more precision. The design also permitted us to feed back to individual participants information about whether their muscle symptoms occurred more frequently during statins or placebo periods and allowed them to decide for themselves whether to continue statin treatment.

In delivering this series of trials, we allowed participants to demonstrate whether their symptoms were likely to be caused by statins or not. The N-of-1 trial could be adopted by clinicians who are looking to establish the best course of treatment for patients who present with statin associated muscle symptoms.

Limitations

Of the 200 randomised participants, 86 did not complete the whole trial, of whom 49 did not provide sufficient data to contribute to the primary analysis. Adherence was similar between statin and placebo periods, and the trial was adequately powered to account for this level of attrition. Among participants withdrawing because of muscle symptoms, creatine kinase was not measured so we do not know what proportion of participants had biochemical evidence of muscle effects. For simplicity and pragmatism, the trial assessed the effect of statins on muscle symptoms using only atorvastatin 20mg so we are unable to extrapolate our results to other statins or higher doses. Though we intended to collect outcomes using web-based

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3 methodology, over half of participants preferred to report their symptoms on paper or by
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6 phone.

8 **Interpretation**

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10 The overall analysis of our series of N-of-1 trials found that among a group of participants
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12 selected on the basis of having experienced severe muscle symptoms during previous statin
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14 treatment, there was no overall effect of statins on muscle symptoms. Slightly more people
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16 withdrew due to muscle symptoms during statin treatment periods compared to placebo,
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18 suggesting that statins may have contributed to muscle symptoms in a small number of
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20 patients. Statin therapy for those at high risk has potential health benefits that are foregone by
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22 those discontinuing therapy. The availability of 'N-of-1 trial' packs in clinical care would enable
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24 patients and clinician to replicate this study at an individual level. Our results suggest that most
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26 patients would resume therapy following such a trial.
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16 LS.
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19 EW designed the study, analysed the results and reviewed the manuscript.
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25 DB designed and managed the study and reviewed the manuscript.
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28 AP managed the study, and reviewed the manuscript.
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31 AT coordinated data collection and reviewed the manuscript.
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36 reviewed the manuscript.
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56 JA designed the study and reviewed the manuscript.
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59 JW was PI at the top recruiting site and reviewed the manuscript.
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3 PM was lead research nurse at the top recruiting site and reviewed the manuscript.
4

5 JS was lead research nurse at top recruiting network of sites and reviewed the manuscript
6
7

8 LB was research co-ordinator at the first site to recruit and reviewed the manuscript.
9

10 the study
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12 MM provided oversight of the whole study and reviewed the manuscript.
13
14

15 MH contributed to study design and conduct as a patient representative and reviewed the
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18 manuscript.
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20 LS designed and led the study and wrote the first draft of the manuscript with EH.
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 - 49 • Caite Guest
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- 56 • Daniel Tacagni (PI)
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Watling Medical Centre

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Data Sharing Statement:

Deidentified, patient-level trial data will be shared along with the protocol, statistical analysis plan and analytic code using the LSHTM Data Compass Repository [link to be confirmed]. Data will be available from the time of publication with no set end date.

Transparency Statement:

The corresponding author, Liam Smeeth, affirms that the manuscript is an honest, accurate, and transparent account of the study being report; that no important aspects of the study have

1
2
3 been omitted; and that any discrepancies from the study as originally planned and registered
4
5 have been explained.
6
7

8 **Role of the funding source**

9
10
11
12 The funder of the study had no role in study design, data collection, data analysis, data
13
14 interpretation, or writing of the report. The corresponding author had full access to all the data
15
16 in the study and had final responsibility for the decision to submit for publication.
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20

21 **Declaration of interests**

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23
24
25 All authors have completed the ICMJE uniform disclosure form at
26
27 www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the
28
29 submitted work; no financial relationships with any organisations that might have an interest in
30
31 the submitted work in the previous three years; no other relationships or activities that could
32
33 appear to have influenced the submitted work.
34
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37

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39
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54 of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT.
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Confidential: For Review Only

References

1. Cholesterol Treatment Trialists Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet (London, England)* 2015; **385**(9976): 1397-405.
2. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet (London, England)* 2019; **393**(10170): 407-15.
3. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet (London, England)* 2016.
4. Abramson JD, Rosenberg HG, Jewell N, Wright JM. Should people at low risk of cardiovascular disease take a statin? *BMJ (Clinical research ed)* 2013; **347**: f6123.
5. Malhotra A. Saturated fat is not the major issue. *BMJ (Clinical research ed)* 2013; **347**: f6340.
6. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. *Annals of internal medicine* 2013; **158**(7): 526-34.
7. Garavalia L, Garavalia B, Spertus JA, Decker C. Exploring patients' reasons for discontinuance of heart medications. *The Journal of cardiovascular nursing* 2009; **24**(5): 371-9.
8. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *European heart journal* 2016; **37**(11): 908-16.
9. Schaffer AL, Buckley NA, Dobbins TA, Banks E, Pearson SA. The crux of the matter: Did the ABC's Catalyst program change statin use in Australia? *The Medical journal of Australia* 2015; **202**(11): 591-5.
10. Matthews A, Herrett E, Gasparrini A, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. *BMJ (Clinical research ed)* 2016; **353**: i3283.
11. Vinogradova Y, Coupland C, Brindle P, Hippisley-Cox J. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. *BMJ (Clinical research ed)* 2016; **353**: i3305.
12. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *British journal of clinical pharmacology* 2014; **78**(4): 684-98.
13. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *European heart journal* 2015; **36**(17): 1012-22.
14. American College of Cardiology. Statin Intolerance Tool. 2019. <http://tools.acc.org/StatinIntolerance/#/> (accessed 10 October 2019).
15. Laufs U, Filipiak KJ, Gouni-Berthold I, Catapano AL. Practical aspects in the management of statin-associated muscle symptoms (SAMS). *Atherosclerosis Supplements* 2017; **26**: 45-55.
16. Guyatt G, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. Determining optimal therapy--randomized trials in individual patients. *The New England journal of medicine* 1986; **314**(14): 889-92.
17. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. *Psychological medicine* 1988; **18**(4): 1007-19.
18. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; **114**(25): 2788-97.
19. Joy TR, Monjed A, Zou GY, Hegele RA, McDonald CG, Mahon JL. N-of-1 (single-patient) trials for statin-related myalgia. *Annals of internal medicine* 2014; **160**(5): 301-10.
20. Cholesterol Treatment Trialists Collaboration. Protocol for analyses of adverse event data from randomized controlled trials of statin therapy. *American heart journal* 2016; **176**: 63-9.

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- 2
- 3
- 4 21. Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D, Ebrahim S. Unintended effects of
- 5 statins from observational studies in the general population: systematic review and meta-analysis. *BMC*
- 6 *medicine* 2014; **12**: 51.
- 7 22. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo
- 8 phenomenon. *Jama* 2002; **287**(5): 622-7.
- 9 23. Gupta A, Thompson D, Whitehouse A, et al. Adverse events associated with unblinded, but not
- 10 with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm
- 11 (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind
- 12 extension phase. *Lancet (London, England)* 2017.
- 13 24. Zhang H, Plutzky J, Shubina M, Turchin A. Continued Statin Prescriptions After Adverse Reactions
- 14 and Patient Outcomes: A Cohort Study. *Annals of internal medicine* 2017; **167**(4): 221-7.
- 15 25. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance:
- 16 the Cleveland Clinic experience. *American heart journal* 2013; **166**(3): 597-603.
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Tables

Table 1. Baseline characteristics

Characteristic	Frequency	%
Randomised		
	Total	200
		100
Age (years)		
	Mean (SD)	69.1 (9.5)
Age category		
	35-49	7
	50-64	49
	65-79	115
	>=80	29
		14.5
Sex		
	Female	85
		42.5
	Male	115
		57.5
Ethnicity		
	Asian	11
		5.5
	Black	8
		4
	Other	2
		1
	White	179
		89.5
Smoking status		
	Current smoker	14
		7
	Ex-smoker	105
		52.5
	Non-smoker	81
		40.5
Diabetes		
	No	167
		83.5
	Yes	33
		16.5
CVD history		
	No	60
		30
	Yes	140
		70
Cholesterol (mmol/L) ^a		
	Median (25 th to 75 th percentile)	5.3 (4.4, 6.2)
Q risk, for participants with no history of CVD		
	Median (25 th to 75 th percentile)	18.3 (9.6, 28.8)

^a 1 value missing

SD: standard deviation

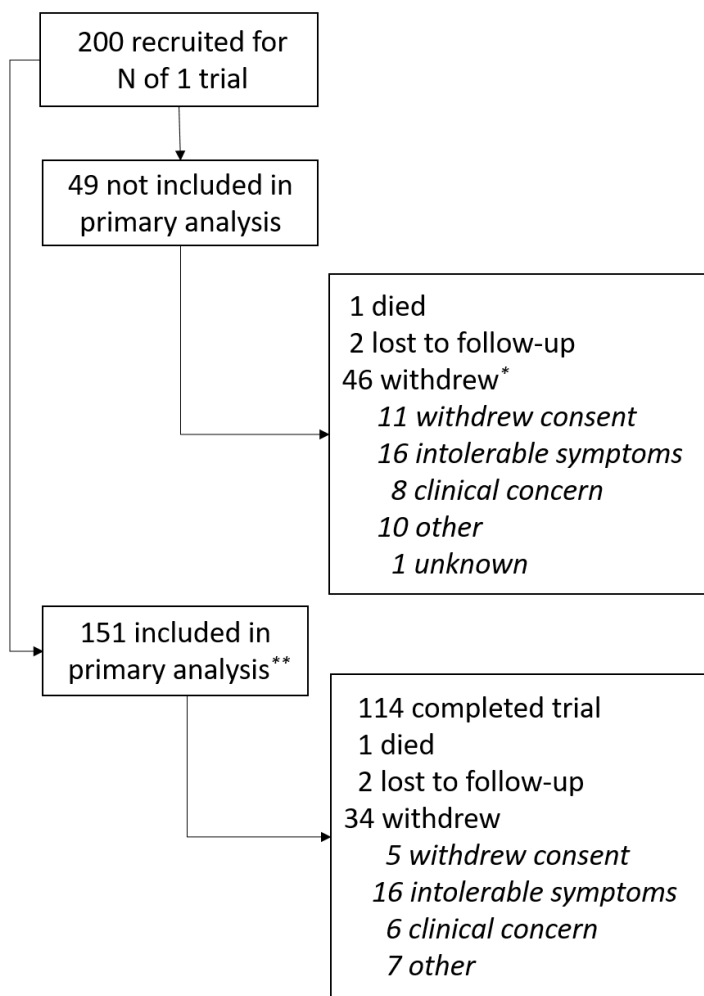
Table 2. Estimated effects for secondary outcomes comparing statin periods to placebo (from participant questionnaire)

	Participants analysed ^a	Odds ratio (99% CI)
Muscle symptoms	152	1.11 (0.62, 1.99)
Muscle symptoms, not attributed to other causes	152	1.22 (0.77, 1.94)
	Participants analysed ^a	Mean difference, cm (99% CI)
General activity	152	0.09 (-0.25, 0.42)
Mood	152	0.26 (-0.04, 0.56)
Walking ability	152	0.11 (-0.22, 0.43)
Normal work	152	0.15 (-0.17, 0.46)
Relations with other people	152	0.15 (-0.09, 0.39)
Sleep	152	-0.02 (-0.32, 0.29)
Enjoyment of life	152	0.13 (-0.22, 0.48)

^a The number of participants contributing to each analysis; each analysis includes all participants with at least one measurement for that outcome in a placebo period, and at least one measurement in a statin period.

CI: confidence interval

Figures



*7 of whom never received any treatment
 (1 withdrew consent, 1 intolerable symptoms, 1 clinical concern, 4 other)
 ** 152 included in the secondary analysis (1 completed the patient questionnaire in two periods but the primary outcome in only one)

Figure 1. Recruitment and participant flow

View Only

Information for Summary Box

What is already known on this topic

- Statins effectively reduce cardiovascular disease (CVD)
- The link between statins and severe muscle disorders is well characterised but uncertainty persists about less severe muscle symptoms
- There have been no large sets of N-of-1 trials exploring the effect of statins on muscle symptoms

What this study adds

- This is the first large series of double-blind N-of-1 trials to examine the effects of statins on muscle symptoms
- Our study found no overall difference in the frequency or severity of muscle symptoms between statin and placebo treatment periods

Supplementary material

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Supplementary Information

Sample size calculation

The power calculations are based on being able to detect a 1cm difference in the VAS pain score. This was chosen to represent the smallest VAS change in pain which patients would perceive as being beneficial, and might therefore change a patient's decision regarding subsequent statin use. Two studies have concluded that the smallest change in VAS pain score corresponding to "a little more" or "a little less" pain was 1.3cm, with a lower limit of the confidence interval at 1cm.[1,2] A 1.3cm minimum change value was used to power a pilot series of N-of-1 trials for statin adverse effects,[3] and our study is therefore powered for a 1cm change as a conservative estimate of the smallest beneficial change.

Using simulation, we estimated that a sample size of 64 participants provides approximately 90% power to detect a treatment effect of at least 1cm, assuming a Type I error of 5%. Allowing for loss to follow-up of 40% of participants through the trial inflates the required sample size to 107 participants.

Period effects (changes in underlying VAS pain score due to factors other than randomised treatment, e.g. seasonal, activity-related, etc.), variability in individual statin effects across participants, and imperfect adherence to the assigned treatment were investigated by further detailed simulations. VAS pain scores are not normally distributed, since they are bounded (0-10cm) and can display large fluctuations in response. Therefore, further power calculations were performed drawing the outcome from a Beta distribution, and from a distribution with normal variance components on a logit scale, to assess the robustness of the sample size estimates to the distribution chosen. These factors all have the effect of decreasing power, thus increasing the sample size required. An approximate 80% increase in the sample size required in the absence of these effects provided approximately 90% or more power across a plausible range of these potential effects, thus we determined that a final sample size of 200 was required.

Supplementary Tables

Appendix Table 1. Data collection method chosen

All	
Randomised	
	Total 200 (100)
Collection method	
Mobile app	2 (1.0)
Online	88 (44.0)
Paper	93 (46.5)
Phone	17 (8.5)

Appendix Table 2. Estimated treatment effect from a linear mixed model allowing the statin effect to vary by data collection method chosen

	Estimated mean difference	95% CI	p-value*
Statin effect among people reporting outcomes online	0.008	(-0.358, 0.373)	0.968
Difference in statin effects for people reporting using the following methods:			0.594
App	-0.065	(-0.704, 0.574)	
Paper	-0.159	(-0.676, 0.358)	
Phone	-0.681	(-1.680, 0.318)	
Collection method			
Online	Reference		
App	0.563	(-0.223, 1.349)	0.161
Paper	0.604	(-0.081, 1.289)	0.084
Phone	1.949	(0.352, 3.545)	0.017
Constant	1.441	(1.053, 1.829)	<0.001

* p-value for interaction: joint test for three interaction parameters (i.e. testing the null hypothesis that statin effect does not vary by data collection method).

Appendix Table 3. Further details of withdrawals by treatment being taken

	All withdrawn participants N=80		During a placebo Period N = 39		During a statin Period N = 34		Neither N= 7	
	N	% ^a	N	% ^a	N	% ^a	N	% ^a
Data from trial withdrawal form								
Withdrawal of consent	16	8	8	4	7	3.5	1	.5
Intolerable muscle symptoms	32	16	13	6.5	18	9	1	.5
Clinical concern	14	7	9	4.5	4	2	1	.5
Other	17	8.5	8	4	5	2.5	4	2
Unknown	1	0.5	1	0.5	0	0	0	0
Blinded further details derived from free text and comments								
No reason given	9	4.5	5	2.5	3	1.5	1	.5
Not medication related	21	10.5	8	4	9	4.5	4	2
Intolerable muscle symptoms	32	16	13	6.5	18	9	1	.5
Muscle side-effect	2	1	2	1	0	0	0	0
Non-muscle side effect	12	6	8	4	4	2	0	0
Switch to statin for clinical reasons	4	2	3	1.5	0	0	1	.5

^a of 200 participants randomised to a sequence of treatments

Appendix Table 4. Self-reported adherence to study medication by period

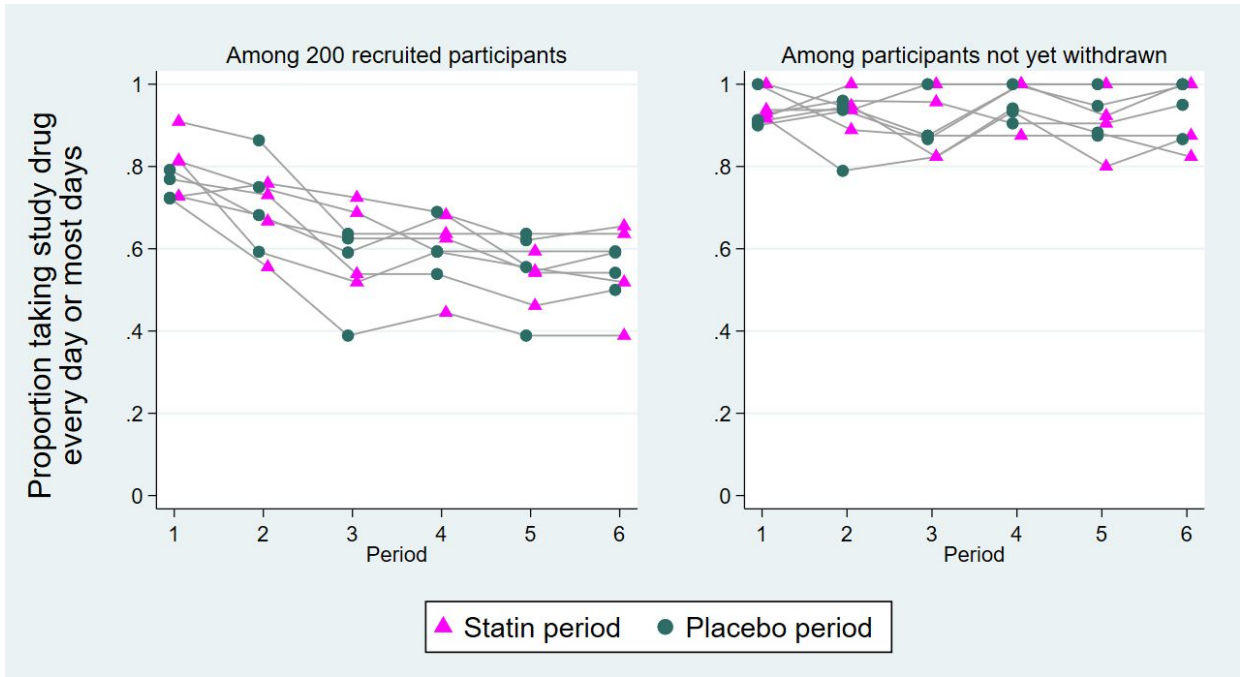
	Period	All	Sequence 1 PSPSPS	Sequence 2 PSPSSP	Sequence 3 PSSPPS	Sequence 4 PSSPSP	Sequence 5 SPPSPS	Sequence 6 SPPSSP	Sequence 7 SPSPPS	Sequence 8 SPSPSP
Total		200 (100)	18 (100)	24 (100)	29 (100)	26 (100)	22 (100)	22 (100)	27 (100)	32 (100)
Reported^a taking study drug every day or most days, n (%)	1	157 (78.5)	13 (72.2)	19 (79.2)	21 (72.4)	20 (76.9)	20 (90.9)	16 (72.7)	22 (81.5)	26 (81.3)
	2	141 (70.5)	10 (55.6)	16 (66.7)	22 (75.9)	19 (73.1)	19 (86.4)	15 (68.2)	16 (59.3)	24 (75)
	3	120 (60)	7 (38.9)	15 (62.5)	21 (72.4)	14 (53.8)	14 (63.6)	13 (59.1)	14 (51.9)	22 (68.8)
	4	121 (60.5)	8 (44.4)	15 (62.5)	20 (69)	14 (53.8)	14 (63.6)	15 (68.2)	16 (59.3)	19 (59.4)
	5	110 (55)	7 (38.9)	13 (54.2)	18 (62.1)	12 (46.2)	14 (63.6)	12 (54.5)	15 (55.6)	19 (59.4)
	6	112 (56)	7 (38.9)	13 (54.2)	19 (65.5)	13 (50)	14 (63.6)	13 (59.1)	14 (51.9)	19 (59.4)
Reported^b taking study drug 5+ days in last week of period, n (%)	1	152 (76)	13 (72.2)	18 (75)	21 (72.4)	20 (76.9)	19 (86.4)	14 (63.6)	21 (77.8)	26 (81.3)
	2	137 (68.5)	11 (61.1)	16 (66.7)	21 (72.4)	19 (73.1)	16 (72.7)	15 (68.2)	17 (63)	22 (68.8)
	3	117 (58.5)	7 (38.9)	15 (62.5)	19 (65.5)	14 (53.8)	14 (63.6)	11 (50)	15 (55.6)	22 (68.8)
	4	115 (57.5)	8 (44.4)	14 (58.3)	19 (65.5)	13 (50)	13 (59.1)	14 (63.6)	14 (51.9)	20 (62.5)
	5	107 (53.5)	7 (38.9)	13 (54.2)	16 (55.2)	13 (50)	12 (54.5)	13 (59.1)	14 (51.9)	19 (59.4)
	6	109 (54.5)	7 (38.9)	13 (54.2)	18 (62.1)	12 (46.2)	14 (63.6)	13 (59.1)	13 (48.1)	19 (59.4)
Median (25th - 75th percentile) number days reported^b taking study drug in last week	1	7 (5,7)	7 (0,7)	7 (3.5,7)	7 (2,7)	7 (5,7)	7 (6,7)	6.5 (0,7)	7 (5,7)	7 (6.5,7)
	2	7 (0,7)	6.5 (0,7)	7 (0,7)	7 (4,7)	7 (0,7)	7 (4,7)	7 (0,7)	7 (0,7)	7 (1,7)
	3	7 (0,7)	0 (0,7)	7 (0,7)	7 (0,7)	6.5 (0,7)	7 (0,7)	4.5 (0,7)	5 (0,7)	7 (0,7)
	4	6.5 (0,7)	0 (0,7)	7 (0,7)	7 (0,7)	5 (0,7)	6 (0,7)	7 (0,7)	5 (0,7)	7 (0,7)
	5	6 (0,7)	0 (0,7)	6 (0,7)	7 (0,7)	2.5 (0,7)	7 (0,7)	7 (0,7)	5 (0,7)	6.5 (0,7)
	6	6 (0,7)	0 (0,7)	6 (0,7)	7 (0,7)	1 (0,7)	7 (0,7)	7 (0,7)	3 (0,7)	6.5 (0,7)

^a in participant questionnaire (once per period); ^b in daily reports in last week of period.

Supplementary Figures

Allocated sequence over the six periods	Frequency (n=200)	%
PSPSPS	18	9.0
PSPSSP	24	12.0
PSSPPS	29	14.5
PSSPSP	26	13.0
SPPSPS	22	11.0
SPPSSP	22	11.0
SPSPPS	27	13.5
SPSPSP	32	16.0

Appendix Figure 1. Treatment sequences in StatinWISE (S=statin, P=placebo)



Appendix Figure 2 Adherence to study medication by period and sequence, for all recruited participants (left) and those who had not yet withdrawn (right)

CONSORT extension for N-of-1 trials

CENT 2015 checklist[†]; CONSORT 2010 checklist items with modifications or additions for individual or series of N-of-1 trials; empty items in the CENT 2015 column indicate no modification from the CONSORT 2010 item

*It is strongly recommended that this checklist be read in conjunction with the CENT 2015 Explanation and Elaboration²⁴ for important clarification on the items. The copyright for CENT (including checklist) is held by the CENT Group and is distributed under a Creative Commons Attribution (CC-BY 4.0) license.

†Caution should be taken when reporting potentially identifying information pertaining to CENT items 4a, 4b, 14a, and 15.

Section/ Topic	CONSORT 2010		Page number	CENT 2015		Page number
	No	Item		No	Item	
Title and abstract						
	1a	Identification as a randomised trial in the title	1	1a	Identify as an “N-of-1 trial” in the title <i>For series:</i> Identify as “a series of N-of-1 trials” in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3	1b	<i>For specific guidance, see CENT guidance for abstracts (table 2)</i>	2-3
Introduction						
Background and objectives	2a	Scientific background and explanation of rationale	4	2a.1		
	2b	Specific objectives or hypotheses	4	2a.2	Rationale for using N-of-1 approach	4
				2b		
Methods						
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5	3a	Describe trial design, planned number of periods, and duration of each period (including run-in and wash out, if applicable) <i>In addition for series:</i> Whether and how the design was individualized to each participant, and explain the series design	5
	3b	Important changes to methods after trial start (such as eligibility criteria), with reasons	n/a	3b		
Participant(s)	4a	Eligibility criteria for participants	6	4a†	Diagnosis or disorder, diagnostic criteria, comorbid conditions, and concurrent therapies. <i>For series:</i> Same as CONSORT item 4a	6
	4b	Settings and locations where the data were collected	6	4b†		
				4c	Whether the trial(s) represents a research study and if so, whether institutional ethics approval was obtained	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8	5	The interventions for each period with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8	6a.1		
				6a.2	Description and measurement properties (validity and reliability) of outcome assessment tools	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a	6b		
Sample size	7a	How sample size was determined	6	7a		

1		7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a	7b		
2	Randomisation:						
3	Sequence generation	8a	Method used to generate the random allocation sequence	7	8a	Whether the order of treatment periods was randomised, with rationale, and method used to generate allocation sequence	7
4		8b	Type of randomisation; details of any restriction (such as blocking and block size)	7	8b	When applicable, type of randomisation; details of any restrictions (such as pairs, blocking)	7
5					8c	Full, intended sequence of periods	Appendix fig 1
6							
7							
8	Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7	9		
9							
10	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7	10		
11	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7	11a		
12		11b	If relevant, description of the similarity of interventions	7	11b		
13	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-10	12a	Methods used to summarize data and compare interventions for primary and secondary outcomes	9-10
14		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a	12b	For series: If done, methods of quantitative synthesis of individual trial data, including subgroup analyses, adjusted analyses, and how heterogeneity between participants was assessed, (for specific guidance on reporting syntheses of multiple trials, please consult the PRISMA Statement)	9
15					12c	Statistical methods used to account for carryover effect, period effects, and intra-subject correlation	9-10
16	Results						
17	Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11	13a.1	Number and sequence of periods completed, and any changes from original plan with reasons	11
18					13a.2	For series: The number of participants who were enrolled, assigned to interventions, and analysed for the primary outcome	11
19		13b	For each group, losses and exclusions after randomisation, together with reasons	11 and Figure 1	13c	For series: losses or exclusions of participants after treatment assignment, with reasons, and period in which this occurred, if applicable	11 and Figure 1
20	Recruitment	14a	Dates defining the periods of recruitment and follow-up	11	14a†		
21		14b	Why the trial ended or was stopped	n/a	14b	Whether any periods were stopped early and/or whether trial was stopped early, with reason(s).	n/a

1	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1, page 33	15†			
2	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11	16	For each intervention, number of periods analysed.	11	
3						<i>In addition for series:</i> if quantitative synthesis was performed, number of trials for which data were synthesized		
4	Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12 and table 2	17a.1	For each primary and secondary outcome, results for each period; an accompanying figure displaying the trial data is recommended.	-	
5						17a.2	For each primary and secondary outcome, the estimated effect size and its precision (such as 95% confidence interval)	12 and Table 2
6						<i>In addition for series:</i> if quantitative synthesis was performed, group estimates of effect and precision for each primary and secondary outcome		
7	Ancillary analyses	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a	17b			
8						18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12-13
9	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14	19	<i>In addition for series:</i> If done, results of subgroup or sensitivity analyses		
10						19	All harms or unintended effects for each intervention. (<i>for specific guidance see CONSORT for harms</i>)	14
11	Discussion							
12	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16	20			
13	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-17	21			
14	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-17	22			
15	Other information							
16	Registration	23	Registration number and name of trial registry	10	23			
17	Protocol	24	Where the full trial protocol can be accessed, if available	5	24			
18	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	29	25			

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6 **References**

7 [1] Todd, K.H. and J.P. Funk, The minimum clinically important difference in physician-assigned visual analog pain scores. Acad Emerg
8 Med, 1996. 3(2): p. 142-6.

9 [2] Gallagher, E.J., M. Liebman, and P.E. Bijur, Prospective validation of clinically important changes in pain severity measured on a visual
10 analog scale. Ann Emerg Med, 2001. 38(6): p. 633-8.

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12 [3] Joy, T.R., et al., N-of-1 (single-patient) trials for statin-related myalgia. Ann Intern Med, 2014. 160(5): p. 301-10.
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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

CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: ISRCTN30952488

VERSION NUMBER	DATE	REASON FOR CHANGE
1.0	25 May 2016	First version
2.0	08 August 2016	Substation Amendment 1: addition of exclusion criterion and changes to Adverse Event reporting
2.1	28 October 2016	Non-substantial Amendment 1: Correction of typographical errors
3.0	27 June 2017	Substantial Amendment 3. i) modifying recruitment pathway description ii) modifying Appendix 6 (PIS) and Appendix 7 (ICF) iii) including Appendix 6a (PIS, optional genetic study), Appendix 7a (ICF, optional genetic study) and Appendix 9 (patient recruitment pathway) iv) general editing of document
3.1	03 November 2017	Substantial Amendment 5. i) recruitment period extended ii) general editing of document



SUMMARY

FULL TITLE OF STUDY	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		
SHORT TITLE	STATIN: WEB-BASED INVESTIGATION OF SIDE EFFECTS		
TRIAL ACRONYM	STATINWISE		
PROTOCOL /ISRCTN NUMBER	ISRCTN30952488		
EUDRACT NUMBER	2016-000141-31	CLINICAL TRIALS.GOV	NCT02781064
<p>BACKGROUND: 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.</p>			
<p>AIM: To determine whether statins cause muscle symptoms.</p>			
<p>PRIMARY OUTCOME: Patient reported muscle symptoms (pain, weakness, tenderness, stiffness or cramp).</p> <p>SECONDARY OUTCOME: Relationship between individual trial result and patient decision whether to continue statins long term.</p>			
<p>TRIAL DESIGN: A series of randomised, double-blinded N-of-1 trials.</p>			
<p>DIAGNOSIS AND INCLUSION/EXCLUSION CRITERIA:</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Adults (aged 16 and over) • Prescribed statin treatment in the last 3 years • Stopped OR considering stopping statin treatment due to muscle symptoms • Provided fully informed consent. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Any previously documented serum alanine aminotransferase (ALT) levels at or above three times the upper limit of normal; 			

- 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
- Any contraindications listed in the Summary of Product Characteristics for Atorvastatin 20 mg (Appendix 8)
- Should not be using atorvastatin 20mg daily in the opinion of the general practitioner.

TEST PRODUCT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION: Once daily oral atorvastatin 20mg or placebo for 12 months.

SETTING: This trial is coordinated from the Clinical Trials Unit at London School of Hygiene & Tropical Medicine and conducted in patients registered in General Practice in England and Wales.

DURATION OF TREATMENT AND PARTICIPATION: Eligible patients should be randomised as soon as possible after the screening. Treatment period is for 12 months with a final follow-up within 3 months of the end of treatment period.

CRITERIA FOR EVALUATION: Patients who enter data on muscle symptoms at least once during a treatment period with the IMP and at least once during a treatment period with placebo.

CLINICAL PHASE	4
PLANNED TRIAL START	01/09/2016
PLANNED DATE OF LAST PATIENT ENROLMENT	31/07/2018
PLANNED DATE OF LAST PATIENT FINAL FOLLOW-UP	31/10/2019



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1. INTRODUCTION



Statins reduce cardiovascular disease (CVD) risk¹ and are recommended as part of the treatment strategy for primary and secondary prevention of CVD in the NHS.² Although statins are the most commonly prescribed treatment in the UK,³ there is still uncertainty about adverse effects.^{4,5}

Severe statin adverse effects are extremely rare (rhabdomyolysis 0.1 and myopathy 0.5 per 1000 people over 5 years).⁶ However, there has been widespread reporting of other less well-defined statin-related symptoms in the media, notably muscle pain and weakness. These reports have largely been prompted by data from non-randomised, non-blinded observational studies,^{7,8} but have not been confirmed in blinded randomised controlled trials (RCTs).⁹ A major limitation of observational studies is lack of blinding: patients taking a medication expect to experience adverse effects¹⁰ and therefore reporting of symptoms may be higher than in a comparable statin-free population. This phenomenon, the “nocebo” effect, can lead to bias in unblinded studies.

In RCTs expectations of adverse effects can lead to inflated reporting in both active and placebo groups. In the Odyssey ALTERNATIVE trial, statin ‘intolerant’ patients initially underwent a double-blind four week phase where they received placebo. Interestingly, during this time, 7% dropped out due to myalgia. In the main phase of this three armed trial (alirocumab vs ezetimibe vs atorvastatin), rates of adverse events were the same across all groups at roughly 80%, but dropped to 55% among alicumab when unblinded.¹¹ Therefore in some trials of statins, expectation of adverse effects among both placebo and active treatment arms may have diluted any true effect of statins on muscle symptoms. A systematic review of randomised trials of statins found that the prevalence of myalgia varied from 0% to 30%, but was not different in the active and placebo arms.⁹

There have also been two other important criticisms of the existing RCT evidence. First, not all trials have collected data on subjective symptoms and recording may be inconsistent due to the definitions used. Studies have shown that adverse events are rarely fully presented in journal publications.¹² Second, while there have been trials among specific vulnerable patient groups,¹³⁻¹⁵ there is a perception that trial participants do not reflect populations taking statins in routine care.

We are working closely with the Cholesterol Treatment Trialists’ Collaboration performing a meta-analysis of statin adverse events reported in RCTs of statins, which will determine using individual participant data whether there is an excess of adverse events among those allocated statin compared with placebo, and whether to date there has been any bias in the reporting of adverse events in statin trials. However, for the reasons outlined above, re-analysis of the existing evidence may not alleviate individual patient concerns.

Despite evidence-based recommendations about the risks and benefits of statin use, many patients believe their symptoms are due to statins, leading to discontinuation, and are therefore potentially missing out needlessly on an effective drug intervention. General Practitioners (GPs) are faced with the challenge of decision making when patients present with symptoms during statin use as there

1
2 is currently no diagnostic tool allowing clinicians to empirically evaluate whether symptoms
3 reported by an individual statin user are caused by the statin itself or by the 'nocebo' effect.
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5
6 N-of-1 trials offer the opportunity for individual patients to discover whether the symptoms that
7 they are experiencing are attributable to statins. Each patient acts as their own control, and
8 therefore their optimal treatment can be established.^{16, 17} Importantly, N-of-1 trials offer individual
9 patients the opportunity to observe their own response to active and placebo treatments. We
10 anticipate that this knowledge will be an important determinant of subsequent statin use and
11 therefore we will follow patients for three months after their blinded treatment period has ended.
12 At the end of these three months we will be able to ascertain as to whether they are using statins.
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17 The proposed trial will address some of the criticisms of previous evidence. The trial will be blinded
18 and placebo-controlled to minimise bias and the sequence of statin and placebo treatments will be
19 randomised to avoid confounding. Additionally, the within-patient comparisons of symptoms
20 experienced while on placebo and statins will allow us to determine, definitively: (i) whether
21 individual patient symptoms are caused by statins and (ii) the extent to which symptoms attributed
22 to statins appear to be causally related.
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2. Trial design

2.1 OVERVIEW

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.

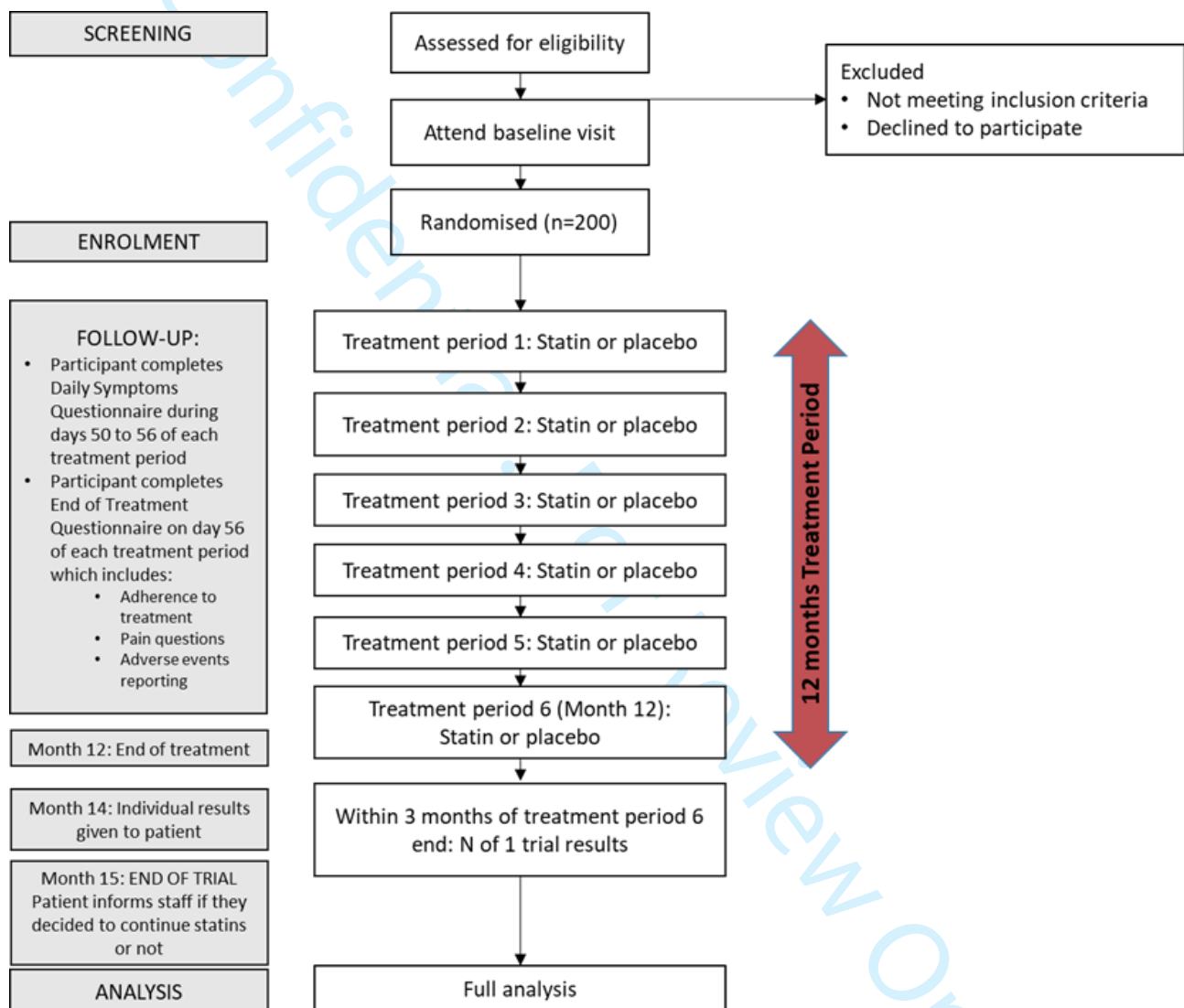


Figure 1: Trial overview

2.2 OPTIONAL GENETIC STUDY

A genetic component to statin myopathy (pain accompanied by rises in CK or ALT) has been suggested (the *SLCO1B1* variant).¹⁸ However, it is not clear whether this variant will be found among the patients included in our study (who have experienced muscle symptoms while on statins but no substantial rises in CK or ALT). Therefore, as part of the trial, we will ask patients 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.

Where patients have consented for the genetic blood test, one nine millilitres blood sample will be obtained in an EDTA Vacutainer tube, labelled with the genetic study ID number, patient's gender, and the date and time of sample collection. It will then be sent to the genetics laboratory at the University of Liverpool via first class post in pre-paid Royal Mail Safeboxes (each containing a maximum of four tubes) as soon as possible after collection. No patient identifiable data will be included or separately provided to the University of Liverpool.

2.3 NUMBER OF PARTICIPANTS NEEDED

A feasibility study in the Clinical Practice Research Datalink has indicated that on average 35 patients per practice per year will be eligible to take part in the trial. We anticipate an average uptake of 15% among primary care patients invited to participate in our trial. Therefore, we estimate that we will need to invite approximately 1300 patients from over 50 general practices to the trial to achieve our recruitment target of 200.

Power calculations: Our power calculation was performed via simulation.¹⁹ An initial sample size, n , was chosen. The treatment allocation sequence for each of the n patients was drawn by randomly allocating the participant to either statin or placebo separately for periods 1, 3, and 5, thereby determining the order of the 6 treatment periods. For each participant, a random effect was drawn from a normal distribution, with zero mean and variance equal to 30^2 . Residual errors (6 for each participant; one for each period) were drawn from a normal distribution with zero mean and variance equal to 25^2 . Then a VAS pain score was simulated for each participant in each period, adding a treatment effect of 10 to each statin period, incorporating the patient random effect and the participant's residual error for that period. This simulated dataset was analysed using the primary analysis model (as if this were the real data) and the two-sided p-value for the treatment effect was stored. After repeating this process a large number of times (e.g. 500), the statistical power was estimated by the proportion of simulated datasets in which the P-value was less than 0.05. If the power was less than 90%, the sample size was increased and the power re-estimated. The rationale for the parameters chosen within this model is detailed below.

Minimum clinically significant difference in VAS pain score (10 mm): This value was chosen to represent the smallest VAS change in pain which patients would perceive as being beneficial, and might therefore change the patient's decision regarding subsequent statin use. Two studies conducted within an Accident and Emergency setting²⁰⁻²³ both concluded that the smallest change in VAS pain score corresponding to "a little more" or "a little less" pain was 13mm, with confidence intervals (95% CI: 10 to 17mm) and (95% CI: 10 to 16mm). We took the lower limit of the confidence interval to represent the smallest change likely to be perceived as being beneficial.

Within and between-participant variability in VAS pain score: (30^2 and 35^2 , respectively). These values were obtained by fitting a mixed model to the data from a pilot series of N-of-1 trials for statin adverse effects²⁴ (data obtained by approximation from figures presented therein). These

1
2 variance components can be poorly estimated, thus we took values from the higher end of the
3 confidence intervals, giving conservative estimates of these components.
4

5 6 **2.4 SAMPLE SIZE** 7

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9 A sample size of 64 participants provides approximately 90% power to detect a treatment effect of
10 at least 10mm, assuming a Type I error of 5%. Allowing for loss to follow-up of 40% of participants
11 through the trial inflates the required sample size to 107 participants.
12

13
14 Period effects (changes in underlying VAS pain score due to factors other than randomised
15 treatment, e.g. seasonal, activity-related, etc.), variability in individual statin effects across patients,
16 and imperfect adherence to the assigned treatment were investigated by further detailed
17 simulations. VAS pain scores are not normally distributed, since they are bounded (0-100mm) and
18 can display large fluctuations in response. Therefore, further power calculations were performed
19 drawing the outcome from a Beta distribution, and from a distribution with normal variance
20 components on a logit scale, to assess the robustness of the sample size estimates to the distribution
21 chosen. These factors all have the effect of decreasing power, thus increasing the sample size
22 required. An approximate 80% increase in the sample size required in the absence of these effects
23 provided approximately 90% or more power across a plausible range of these potential effects, thus
24 we determined that a final sample size of 200 was required.
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31 **Multiple testing:** Rather than making formal adjustments for multiple testing, we follow an
32 approach advocated by Pocock²⁵ of clearly specifying our primary analysis (which provides a single
33 test for treatment effect), while explicitly presenting and interpreting all other tests as secondary
34 analyses.
35
36

37
38 **Power for individual N-of-1 trials:** In order to increase the statistical power for the analysis of
39 individual N-of-1 trials, we will ask participants to report symptoms daily in the last week of each
40 period, rather than once per period. Full adherence through the trial will provide between 55 and
41 70% power to detect effects of 10mm or greater for individual treatment comparisons.
42
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44

45
46 **Estimates of recruitment and retention rates:** We anticipate that some patients will not complete
47 data in each treatment period, and that some will not complete their 12-month follow-up. By
48 designing this study as a series of N-of-1 trials, which offer individual participant benefit in the form
49 of an individualised estimate of effect, we hope to minimise this type of dropout. However, we have
50 accounted for this in our sample size calculation by allowing for 40% loss to follow-up.
51
52
53

54 **2.5 SETTINGS** 55

56
57 Research sites will be recruited through the Clinical Research Network across England and Wales
58 and we will continue to add practices to ensure the sample size is achieved. Suitable collaborating
59 practices and investigators will be assessed on their ability to conduct a trial. In advance of the trial
60 starting at a practice, the Principal Investigator (PI) must agree to follow Good Clinical Practice

Guidelines and all relevant regulations. All relevant regulatory and ethics approvals must be in place prior to practices recruiting their first patient.

2.6 RECRUITMENT OF PARTICIPANTS

Participants will be recruited directly from GP Practices or by advertising to the public.

Participating practices will recruit eligible patients from two groups as follows:

1) Patients who are considering discontinuation of their statin due to muscle symptoms:

These patients will be invited to take part in the trial when they visit the GP to report muscle symptoms believed to be associated with statins and where the patient/GP is considering stopping statins because of the muscle symptoms. The GP or Research Nurse will approach the patient and give the patient information sheet (Appendix 6 and Appendix 6a). If interested, patients will be able to consent (Appendix 7 and Appendix 7a) and complete the screening visit with the GP or the Research Nurse during this appointment or it can be arranged for another suitable time.

2) Patients who have stopped taking a statin in the last 3 years due to muscle symptoms:

A search of the practice electronic records will be performed by the delegated site staff on a two-monthly basis for one year (or until recruitment targets are reached) to identify potentially eligible patients. All screened patients will be documented on a screening log. The list will be reviewed by the GP to confirm clinical eligibility before patients are invited to take part. A letter inviting them to attend a screening visit, accompanied with the patient information sheet (Appendix 6 and Appendix 6a) for the patient to consider, will be sent by the trial team from their GP practice. Contact details of the Research Nurse will be provided should the patient have any questions. A reply slip will be enclosed for the patient to complete if they wish to attend the screening visit, which will be returned to the Clinical Trials Unit (CTU), during which the trial will be explained, and they will have the opportunity to ask questions. Patients will be sent a letter of invitation to consider participation up to a maximum of three times.

3) Patients who contact the CTU from advertising:

Patients who contact the CTU in response to advertising material will be sent a letter to request their GP details on a reply slip. Following receipt of these documents the CTU will contact their GP with their consent. The GP will be asked to confirm that the patient is potentially suitable for the trial and to provide brief clinical information to allow eligibility to be assessed. This information will then be provided to the research site responsible for recruiting the patient.

Once informed consent has been obtained, eligibility, demographic and medical history data (Appendix 1) will be collected directly onto an online trial database.

2.7 ELIGIBILITY

Inclusion criteria:

- Adults (aged 16 and over)
- Registered in a participating GP practice

- Previously prescribed statin treatment in the last 3 years
- Stopped OR is considering stopping statin treatment due to muscle symptoms
- Provided fully informed consent.

Exclusion criteria:

- Any previously documented serum alanine aminotransferase (ALT) levels at or above three times the upper limit of normal
- 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
- Any contraindications listed in the Summary of Product Characteristics for Atorvastatin 20 mg (Appendix 8)
- Should not participate in the trial in the opinion of the general practitioner.

2.8 RANDOMISATION

Patients eligible for inclusion will be randomised by the Research Nurse/GP practice trial team using the online London School of Hygiene & Tropical Medicine (LSHTM) CTU randomisation system to a sequence of blinded placebo and atorvastatin treatment periods. There are six paired (statin-placebo or placebo-statin) treatment periods each of two months' duration. In practice, this means that each individual is randomised (with equal probability) to one of the following eight sequences (with P=placebo, S=statin):

	Treatment Period					
	1	2	3	4	5	6
Sequence 1	S	P	S	P	S	P
Sequence 2	S	P	S	P	P	S
Sequence 3	S	P	P	S	S	P
Sequence 4	S	P	P	S	P	S
Sequence 5	P	S	S	P	S	P
Sequence 6	P	S	S	P	P	S
Sequence 7	P	S	P	S	S	P
Sequence 8	P	S	P	S	P	S

Randomisation codes will be generated and secured by the Information Technology team at LSHTM CTU, who has procedures to ensure the trial team remains blinded. The codes will be made available to a Good Manufacturing Practice (GMP) certified clinical trial supply company explicitly for the treatment packs to be created in accordance with the randomisation list.

2.9 TREATMENT

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.

Two months' supply of allocated treatment will be posted to the patient every 2 months. Treatment should start within 4 weeks of randomisation. Patients who have not started by the 3rd week post randomisation will be contacted by the CTU. Such patients will therefore have a longer study period.

2.9.1 DOSE SELECTION

Atorvastatin is recommended by the current NICE guidelines for lipid modification;² 20mg is the recommended dose for primary prevention of cardiovascular disease. Atorvastatin is also recommended by NICE for secondary prevention² and for patients with a high risk of adverse events (our patient population), a dose lower than 80mg is recommended. The most commonly used dose is 20mg. A visually matched placebo has been chosen as an appropriate comparator for two reasons. Firstly, patient expectation of symptoms while on statins is likely to affect their experience of symptoms. A placebo control should minimise bias arising from knowledge of allocation. Secondly, withholding statin treatment from patients during placebo treatment periods is justified because the trial will recruit patients who have recently stopped using statins (and therefore are not currently receiving any benefit from statins) and those who wish to discontinue. If patients in the trial tolerate the active treatment periods with few symptoms, then this trial is likely to increase their usage of statins in the long term.

2.9.2 DRUG MANUFACTURE, BLINDING AND SUPPLY OF TRIAL MEDICATION

The active trial drug atorvastatin (as atorvastatin calcium trihydrate) will be purchased on the open market. Atorvastatin is manufactured by Sharp Clinical Services (UK) Ltd under Marketing Authorisation Number 10284. The Marketing Authorisation guarantees that the product has been manufactured and released in accordance with the United Kingdom's Good Manufacturing Regulations.

Placebo will be manufactured specially to match the atorvastatin by a GMP certified manufacturer. Capsules and packaging will be identical in appearance for both active treatment and placebo. DBcaps[®] capsules which has a unique locking mechanism to help with assuring the integrity of the blind will be used for over encapsulation of both active and placebo treatments. Additionally, patients will be asked to swallow the capsule whole without chewing or breaking it. The blinding process and first stage Qualified Person (QP) release will be done by the designated clinical trial supply company. The blinding process will involve encapsulating the active tablet, complete removal

1
2 of the original manufacturer's label and replacement with the clinical trial label bearing the
3 randomisation number which will be used as the pack identification. Other pack label text will be
4 identical for both atorvastatin and placebo treatments and will be in compliance with requirements
5 for investigational medicinal products.
6
7

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9 The designated clinical trial supply company will also be responsible for maintaining the Product
10 Specification File (PSF) until final database lock and unblinding of the trial data. The CTU will be
11 responsible for assuring all relevant approvals are available and that the patient is eligible for the
12 trial before release of the trial medication to a patient. A separate Manual of Operating Procedures
13 (MOP) will detail the drug accountability system. The MOP will also detail labelling of the trial
14 treatment and other processes for assuring adherence to Good Manufacturing Practice.
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18 19 **2.9.3 ADMINISTRATION OF TRIAL MEDICATION**

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21 Patients will receive their allocated trial medications through the post and they will be asked to take
22 the study medication daily through the six two-month treatment periods. Ideally there should be
23 no break between treatment periods. However, if for any reason there is a break, patients can
24 simply restart taking the trial medication as soon as possible.
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28 Patients will be asked to take one capsule orally once daily at a time of day convenient to them.
29 Capsules should be swallowed whole. Patients will be given written instructions on how to take the
30 study medication. At the start of each two-month treatment period, patients will be asked to
31 inform the trial team about their first date of study medication use using the trial's mobile
32 application (app), email, text message, Freephone telephone service or a pre-paid postage reply slip
33 - whichever is easier to ensure data collection occurs on the correct days. A Freephone telephone
34 number will be provided for patients to call if they have any questions. Adherence to the study
35 medication will be collected on the same days as other data as part of the outcome data collection.
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41 **2.10 DATA COLLECTION**

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44 This trial will be coordinated from the CTU at LSHTM and conducted at GP practices in England and
45 Wales.
46
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48 Baseline data will be collected and will be entered online to the trial database provided by the
49 LSHTM CTU. Follow up data will be collected directly from each patient at the end of each two-
50 month period.
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54 Patients will be allowed to choose the method of data collection most suitable for them from the
55 following:

- 56 1. Bespoke mobile app which will require patients to use their own smartphone.
- 57 2. Online database using a computer, phone or tablet.
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3. Paper forms which they will receive by post at the same time with their trial treatment and which they can complete themselves or they can request a trial team member to contact them by phone to help with completing the forms.
 4. Trial staff will telephone the patient on each data collection day and complete the questionnaire based on the patient answers.

For patients with a smartphone who choose to submit outcome data using the trial's bespoke mobile app, the GP, PI or Research Nurse will help the patient to install and set-up the app for use. The GP, PI or Research Nurse will also give a demonstration to ensure the patient understands how to use it. Each GP, PI or Research Nurse will have access to the internet so that the patient can download the app without using their own mobile network (ensuring that download of the app is free of charge to the patient).

The GP or Research Nurse will also show the patient how to complete the symptoms data for the Baseline form (Appendix 2) using their preferred method. Any questions can be addressed at this stage. Once baseline procedures have been completed and the patient confirmed as being eligible and consented, the patient can then be randomised.

A screening log will be used to record all patients who were identified as potentially eligible using the research site database, including those who were ineligible and those who declined participation. The Screening Log will remain at the relevant research site and only anonymised information regarding number of screened patients and number and reasons for screen failure will be shared with the CTU.

Only data outlined on the baseline, follow up, end of trial and adverse events data forms will be collected as part of the trial database.

2.10.1 BASELINE AND RANDOMISATION DATA

Baseline data will be collected by the PI, GP or Research Nurse performing the assessment at the Screening Visit (Appendix 2). Baseline data will be collected via a bespoke online trial database, to which each PI, GP and Research Nurse will have a unique log-in ID and password. Eligible patients will then be randomised and data about the randomisation (date, time and randomisation number) is generated.

2.10.2 TREATMENT PHASE FOLLOW UP DATA

In the seventh week of each treatment period, patients will receive reminders (format agreed at baseline) to alert them that follow-up data collection is approaching. During the 8th week of each treatment period, the Patient Questionnaire and VAS Pain Scale forms (Appendices 4 and 5) will be completed by the patient. Patients can choose to receive daily reminders on each day their data is due to be collected. Non-responders will automatically receive a reminder after 24 hours of due date by the trial team.

2.10.3 END OF TRIAL DATA

During the seventh week of treatment period 6, the GP, PI or 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, the PI and Research Nurse, 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 a 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 contact 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.

- 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.
- Where treatment with an interacting drug is needed for longer than one month, the patient will be asked to withdraw from study treatment completely.

When the patient is randomised, a temporary Read code indicating StatinWISE participation will be recorded in their primary care record, the code will be removed at the end of the trial.

Patients will also be given an alert card that identifies them as a StatinWISE patient. Patients will be asked to present this card to anyone providing medical care outside of their usual general practice. This card will have a link to the trial website and a trial contact number.

2.10.4 PATIENTS REPORTING INTOLERABLE SYMPTOMS

The GP will remain as the first point of contact for patients during the trial for their care. Intolerable muscle symptoms should be reported to the GP who will provide clinical care as directed by the appropriate NICE guidelines. Where a patient reports intolerable symptoms, Figure 2 shows the decision making pathway for the GP and the patient.

For patients who experienced intolerable muscle symptoms, and who do not want to be withdrawn early from the trial, the GP will be asked to confirm that the patient still meets the trial eligibility criteria. Patients who continue to meet the eligibility criteria can be offered the following options by the GP, depending on their clinical judgement:

- continue with their current treatment
- reduce the frequency of tablet use to every other day rather than daily
- stop for that treatment period and resume at the start of the next period

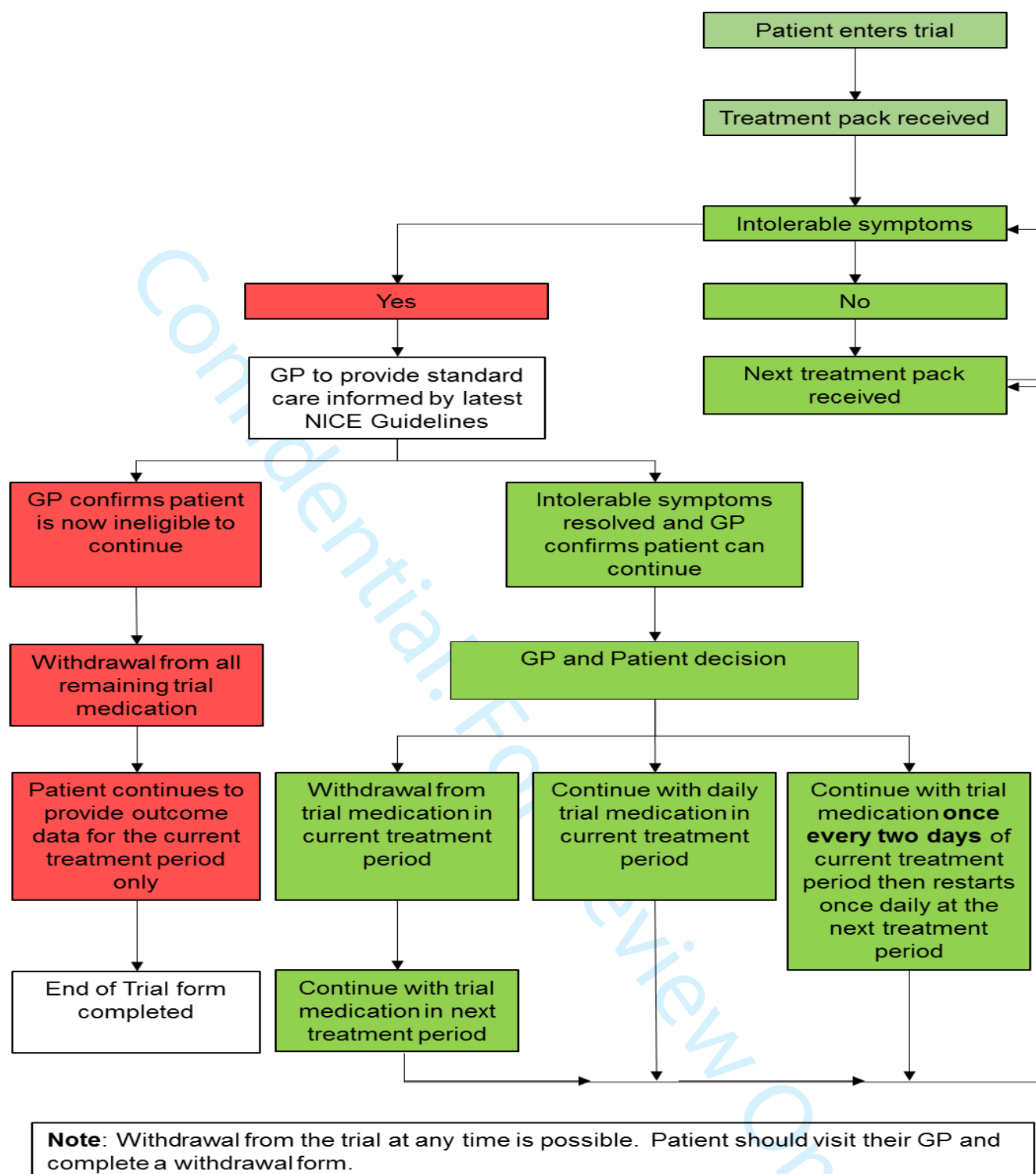


Figure 2: Intolerable symptoms pathway

Patients who withdraw from treatment temporarily or permanently will be asked to inform the study team and report symptoms at the time of stopping, and continue to submit outcome data for their current treatment period.

2.10.5 EARLY WITHDRAWAL OF PATIENTS FROM THE TRIAL

A patient is free to change their minds about participation at any time. We would advise that the patient see their GP to discuss future routine care. A GP can withdraw a patient at any time if clinical

concerns arise or if the patient presents with any reason to stop atorvastatin as described in the Summary of Product Characteristics for Atorvastatin 20 mg (Appendix 8). In each case, an end of trial form (Appendix 3) should be completed.

2.11 ADVERSE EVENTS

Reporting of Adverse Events for this trial: Atorvastatin is not a new drug and has a well-documented safety profile. Furthermore, this trial is being conducted in a population in which statin use is clinically indicated. It is anticipated that patients in this trial are at higher risk of cardiovascular diseases because of underlying clinical conditions requiring statin use. Additionally, as participation is for 15 months it is likely that they will have common medical problems (e.g. colds, coughs, fevers etc). On the basis that patients: (1) would have had prior exposure the trial treatment, (2) the trial treatment is clinically indicated for their medical condition, and (3) the known safety profile of the trial treatment, we will limit adverse events to be reported to those events that fulfill the Serious Adverse Event (SAE) criteria as described below.

Patient Self-report: In the two-monthly questionnaire, patients will be asked to self-report any event which resulted in unplanned hospital admissions. Where a patient indicates that there was an unplanned admission, the PI/GP/Research Nurse will be asked to submit a brief report to the CTU.

General Practitioner report: Participating research sites will report any event to the CTU that fulfill the Serious Adverse Event (SAE) criteria as described below within 24 hours of becoming aware of the event. To minimize the risk of unreported events, at two-monthly intervals, the Research Nurse/GP will conduct a search of their database for any StatinWISE patients who have been recorded as having died.

Definitions:

Adverse Event (AE): Any untoward medical occurrence not listed in the Investigational Medicinal Product Dossier (IMPD) and /or Summary of Product Characteristics (SmPC) affecting a trial participant during the course of a clinical trial.

Serious Adverse Event (SAE): A serious adverse event (experience) is an adverse event (as defined above) which at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation; or
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Adverse Reaction (AR): An AE when there is at least a possibility that it is causally linked to a trial drug or intervention.

1
2 **Serious Adverse Reaction (SAR):** SAE that is thought to be causally linked to a trial drug or
3 intervention.

4 **Suspected Unexpected Serious Adverse Reaction (SUSAR):** An *unexpected* occurrence of a SAR that
5 is inconsistent with the list of expected events in the Summary of Product Characteristics for
6 atorvastatin 20 mg dated 02/09/2015 (Appendix 8); there need only be an index of suspicion that
7 the event is a previously unreported reaction to a trial drug or a previously reported but exaggerated
8 or unexpectedly frequent adverse drug reaction.
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13 All SAEs assigned by the PI or delegate as both suspected to be related to IMP-treatment and
14 unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines
15 and Healthcare Products Regulatory Agency (MHRA). The Sponsor (or delegate) will inform the
16 MHRA, and the ethics committee of UK-relevant SUSARs within the required expedited reporting
17 timescales (no later than 7 days after the Sponsor was first made aware for fatal/life threatening
18 reactions; no later than 15 days for other reactions).
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23 As this is a blinded trial, all SUSARs must be reported to the Sponsor (or delegate) assuming the
24 active compound is involved. All expedited reports submitted to the regulatory authorities will be
25 unblinded.
26
27
28

29 **2.12 UNBLINDING**

30 In general, there should be no need to unblind the allocated treatment during the treatment phase.
31 If some contraindication to statins develops after randomisation, the trial treatment can be stopped
32 and all usual standard care given. Unblinding should be done only in those rare cases where the
33 clinician believes that clinical management depends importantly upon knowledge of whether the
34 patient is receiving statin or placebo. In those few cases when urgent unblinding is considered
35 necessary, a 24-hour telephone service will be provided by the CTU and details provided in the
36 Investigator's Study File and the Patient Alert Card. The caller will be told whether the patient is
37 receiving statin or placebo. An unblinding report form will be completed by the person requesting
38 the unblinding. Participation will not restart once unblinding has occurred.
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44 In this trial, it is important that the CTU is contacted for unblinding as any request is likely to
45 originate from emergency departments or hospital clinics needing to know the treatment allocation
46 urgently. As most GPs and research surgery staff do not provide a 24-hour cover, for patient safety
47 reasons, the CTU will provide a 24 hour on-call unblinding service.
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51 **2.13 OUTCOME MEASURES**

52 **Primary outcome:** The primary outcome is self-reported 'muscle symptoms', defined as pain,
53 weakness, tenderness, stiffness or cramp to the body of any intensity, recorded where the
54 participant believes they are associated with the study medication; these are the symptoms most
55 commonly reported by patients and are often the reasons for discontinuation. The primary outcome
56 will be assessed by the mean difference in VAS scores (range 0 to 100) between treatment periods
57 with the trial treatment and treatment periods with placebo, estimated via a linear mixed model.
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2 **Secondary outcomes:** Secondary outcomes relating to participant belief about the cause of their
3 muscle symptoms, the site of muscle symptoms, how the muscle symptoms affected the participant
4 and information about any other symptoms will be collected on the last day of each two-month
5 treatment period, using a questionnaire (Appendix 5). The other secondary outcomes are adherence
6 to medication, the participant's decision about statin treatment following the trial, and whether
7 they found their own trial result helpful.
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9

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11 Specifically, secondary outcomes will be:
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- 13 1. The proportion of patients with muscle symptoms during each two-month period who report
14 that they believe their symptoms were caused by the study medication, comparing periods
15 of IMP treatment with placebo.
16
- 17 2. Site of muscle symptoms (single or multiple; head and neck/upper limbs/lower limbs/trunk).
18
- 19 3. Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to
20 100) for the following, comparing periods of IMP treatment with placebo:
21
 - 22 a. General activity
 - 23 b. Mood
 - 24 c. Walking ability
 - 25 d. Normal work (includes both work outside the home and housework)
 - 26 e. Relations with other people
 - 27 f. Sleep
 - 28 g. Enjoyment of life
- 29 4. Other symptoms that the patient believes can be attributed to the study medication
30 (grouped: musculoskeletal; gastrointestinal; respiratory; neurological; psychological; other).
31
- 32 5. Adherence to study medication as assessed by: (a) self-report and (b) counting pills
33 remaining in returned packages, and the relationship between adherence and muscle
34 symptoms.
35
- 36 6. Participant decision regarding future statin use and the relationship to their primary
37 outcome.
38
- 39 7. Whether patients found their own trial result helpful in making the decision about future
40 statin use.
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45 2.14 MONITORING

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48 GCP section 5.18.3 states in regard to monitoring, *"The determination of the extent and nature of*
49 *monitoring should be based on considerations such as the objective, purpose, design, complexity,*
50 *blinding, size and endpoints of the trial. In general, there is a need for on-site monitoring, before,*
51 *during, and after the trial; however, in exceptional circumstances the sponsor may determine that*
52 *central monitoring in conjunction with procedures such as investigators training and meetings, and*
53 *extensive written guidance can assure appropriate conduct of the trial in accordance with GCP.*
54 *Statistically controlled sampling may be an acceptable method for selecting the data to be verified."*
55
56
57

58
59 StatinWISE is a pragmatic, randomised placebo controlled trial. The intervention (atorvastatin) has
60 marketing authorisation in the United Kingdom and has been in clinical use for decades. The trial
will collect data on SAEs which may be associated with this product and other clinical conditions

1
2 which will be common in this population. These events will be reviewed routinely by the trial
3 Medical Advisor and will be reported routinely to the Trial Steering Committee. The trial involves
4 getting consent, giving the trial drug in the usual way and collecting information regarding muscle
5 symptoms directly from the patients. There are no extra tests or procedures unless patients agree
6 to take part in the genetic study, for which 9 ml of blood is required. Apart from the trial drug, any
7 other medication will be issued as per usual practice under the care of the GP. For these reasons,
8 we believe that the risk of harm or injury (whether physical, psychological, social or economic) to
9 trial patients is low. We will use central monitoring along with investigators' training and meetings,
10 and extensive written guidance to make sure the trial is carried out properly. Statistically controlled
11 sampling will be used to select data to be verified at research sites. We plan to carry out on-site
12 monitoring where central statistical monitoring show abnormality. Consent forms will be monitored
13 centrally at the CTU.
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20 Investigators/practices are required to provide direct access to source data/documents for trial-
21 related monitoring, audits, ethics committee review and regulatory inspection. Source data will be
22 low as the majority of patients will enter data using the mobile application method directly. All trial-
23 related and source documents must be kept for five years after the end of the trial.
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27 **2.15 AUDITS AND INSPECTIONS**

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30 The trial may be subject to audit by the London School of Hygiene & Tropical Medicine under their
31 remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence
32 to GCP.
33
34
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36 **2.16 END OF TRIAL FOR PARTICIPANTS**

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39 The follow-up period ends 15 months after the first treatment day with a final contact with the PI,
40 GP or Research Nurse as described above. This will be considered as the end of trial for patients.
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43

44 **2.17 ANALYSIS**

45 **Individual N-of-1 trials:** The purpose of these analyses is to inform the individual patient of the
46 effect of the IMP on their VAS muscle symptom score. The analysis and presentation of individual
47 level results will be developed in collaboration with the Patient and Public Involvement (PPI) group.
48 We will examine a range of graphical summaries and statistical analyses in order to identify the most
49 informative presentation of individual results. As a result of this process, at the end of each
50 individual trial the participant will be shown numerical and graphical summaries of their individual
51 data, in relation to their IMP and placebo periods.
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56 **Combined analysis of N-of-1 trials**

57 **Primary analysis:** To estimate the population average estimate of the trial treatment n VAS muscle
58 symptom score, data from each N-of-1 trial will be aggregated to form a powerful dataset. We will
59 adopt an intention-to-treat approach. Patients who enter data on muscle symptoms at least once
60

1
2 during a treatment period with the IMP and at least once during a treatment period with placebo
3 will be included in the primary analysis.
4
5

6 The primary analysis will be a linear mixed model for VAS muscle symptom score with random
7 effects for participant and treatment and fixed period effects. Residual errors will be modelled using
8 a first-order auto-regressive error structure within each treatment period to account for correlation
9 between the 7 daily measurements, with robust standard errors to account for non-normality of the
10 VAS scores. Although VAS muscle symptom scores are unlikely to be exactly normally distributed,
11 analysing such data using normal-based methods is likely to be a sufficiently robust approach.²⁶ All
12 tests will be two-sided. $p < 0.05$ will be considered statistically significant.
13
14
15
16

17 **Secondary analyses:** Secondary outcomes relating to the impact of the IMP on other aspects of life
18 will be analysed in a similar manner to the primary outcome, omitting the auto-regressive
19 correlation structure since these secondary outcomes are measured once per treatment period. We
20 will investigate whether the excess muscle symptoms, if any, experienced during treatment periods
21 with the IMP appears to be concentrated in multiple sites.
22
23
24
25

26 Descriptive statistics will be used to summarise the measures of adherence to randomised
27 treatment, and their relationship to the IMP and placebo periods. We will use the measures of
28 adherence to randomised treatment to perform an efficacy analysis based around an instrumental
29 variables approach.²⁷ Because these analyses require much stronger assumptions than the
30 intention-to-treat analysis above, the results of the efficacy analysis will be presented and
31 interpreted as a secondary analysis. The secondary outcomes include a single binary measure of
32 whether the participant reports having muscle symptoms during that treatment period or not. This
33 will be combined with the follow-up question pertaining to attribution, to obtain a single binary
34 measure of whether the participant reports having muscle symptoms that they attribute to the
35 study medication or not. These two binary outcome measures will be assessed using a logistic mixed
36 model with random participant and treatment effects and fixed period effects.
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43 We will relate the patients' decision regarding future statin use, and whether or not the participant
44 found their own result helpful in making their subsequent treatment decisions, to their individual
45 estimated effect of the IMP.
46
47

48 **Subgroup analyses:** There are no priori subgroup analyses planned. If an overall population-level
49 effect is detected, we may investigate whether the effect varies within subgroups defined by
50 measured baseline characteristics. These analyses will be regarded and interpreted as being
51 exploratory.
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3. Trial Organisation and Responsibilities



3.1 SPONSORSHIP AND TRIAL MANAGEMENT

The StatinWISE trial is sponsored by the LSHTM and its responsibilities coordinated by the CTU. The CTU may delegate responsibilities to third parties which will be outlined in relevant agreements. The responsibilities of the CTU will be overseen by the Trial Management Group (TMG).

3.2 INDEMNITY

LSHTM accepts responsibility attached to its sponsorship of the trial and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this trial. The indemnity is renewed on an annual basis and LSHTM assures that it will continue renewal of the indemnity for the duration of this trial.

3.3 PROTOCOL DEVELOPMENT

The Protocol Committee consists of the following investigators who will be responsible for the development of and agreeing to the final protocol. Subsequent changes to the final Protocol will require the agreement of the Trial Steering Committee (TSC).

NAME	AFFILIATION
Jane Armitage	University of Oxford, UK
Danielle Beaumont	LSHTM, London, UK
Elizabeth Crellin	LSHTM, London, UK
Ben Goldacre	LSHTM, London, UK
Emily Herrett	LSHTM, London, UK
Ian Roberts	LSHTM, London, UK
Haleema Shakur	LSHTM, London, UK
Liam Smeeth	LSHTM, London, UK (Chair)
Tjeerd van Staa	University of Manchester, UK
Elizabeth Williamson	LSHTM, London, UK
Nabila Youssouf	LSHTM, London, UK
Kieran Brack	LSHTM, London, UK

Lori Miller

LSHTM, London, UK

3.4 INDEPENDENT DATA MONITORING COMMITTEE (DMC)

MEMBERSHIP

NAME	AFFILIATION	EXPERTISE
Professor John Norrie	Chair of Medical Statistics and Trial Methodology. Director of Edinburgh Clinical Trials Unit (ECTU), University of Edinburgh	Chair – Senior Statistician & Trialist
Professor Nicholas L Mills	Chair of Cardiology and Consultant Cardiologist, BHF Senior Clinical Research Fellow	Clinical Expert
Dr Hannah Castro	Freelance	Medical Statistician

To provide protection for study participants, an independent DMC has been appointed for this trial to oversee the safety monitoring. The DMC will review on a regular basis accumulating data from the ongoing trial and advise the TSC regarding the continuing safety of current participants and those yet to be recruited, as well as reviewing the validity and scientific merit of the trial.

The DMC composition, name, title and address of the chairman and of each member, will be given in the DMC Charter which will be in line with that proposed by the DAMOCLES Study Group (DAMOCLES Study Group 2005). Membership includes expertise in the relevant field of study, statistics and research study design. An independent statistician will be appointed to provide the analysis service required by the DMC.

The DMC Charter includes, but is not limited to, defining:

- the schedule and format of the DMC meetings
- the format for presentation of data
- the method and timing of providing interim reports
- stopping rules

STANDARD OPERATING PROCEDURES

The DMC has the responsibility for deciding whether, while randomisation is in progress, the unblinded results (or the unblinded results for a particular subgroup), should be revealed to the TSC. The DMC Charter states that they will do this if, and only if, the following two conditions are satisfied: (1) the results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favorable for all, or for a particular category of participants in terms of the major outcome; and (2) the results, if revealed, would be expected to substantially change the prescribing patterns of clinicians who are already familiar with any other trial results that exist. Exact criteria for “proof beyond reasonable doubt” are not, and cannot be, specified by a purely mathematical stopping rule, but they are strongly influenced by such rules. The DMC Charter is in agreement with the Peto-Haybittle stopping rule whereby an interim analysis of a major endpoint would generally need to involve a difference between treatment and control of at least three

standard errors to justify premature disclosure (Haybittle 1971; Peto 1977). An interim subgroup analysis would, of course, have to be even more extreme to justify disclosure. This rule has the advantage that the exact number and timing of interim analyses need not be pre-specified. In summary, the stopping rules require extreme differences to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgment.

3.5 TRIAL STEERING COMMITTEE (TSC)

The composition of the TSC is provided in the table below:

NAME	AFFILIATION	EXPERTISE
Michael Moore	University of Southampton	Independent Chair Professor of Primary Healthcare Research and General Practitioner
Brian Mac Kenna	Chief Pharmaceutical Office Medical Directorate, NHS England	Independent member 2 Pharmacist
Irwin Nazareth	University College London and Keat's GP Practice, Hampstead	Independent member 3 Professor of Primary Care and General Practitioner
Maurice Hoffman	StatinWISE PPI Group	Independent member 4 Patient Representative
David Symes	StatinWISE PPI Group	Independent member 5 Patient Representative
Rebecca Harmston	StatinWISE PPI Group	Independent member 6 Patient Representative
Haleema Shakur	LSHTM	Trials Expert Senior Lecturer
Liam Smeeth	LSHTM	Chief Investigator Professor of Clinical Epidemiology and General Practitioner

The role of the TSC is to provide overall supervision of the trial. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consideration of new information. The TSC must be in agreement with the final protocol and, throughout the trial, will take responsibility for:

- ensuring relevant regulatory approvals are in place
- major decisions such as a need to change the protocol for any reason
- monitoring and supervising the progress of the trial
- reviewing relevant information from other sources
- informing and advising the TMG on all aspects of the trial

Face-to-face meetings or teleconferences will be held at regular intervals determined by need, but no less than once a year. A TSC Charter, which will detail how it will conduct its business, will be agreed at the first meeting.

3.6 PRINCIPAL INVESTIGATOR'S RESPONSIBILITIES

Coordination within each participating research site will be through a local PI whose responsibility will be detailed in an agreement in advance of starting the trial and will include:

- ensure all necessary regulatory approvals are in place prior to starting the trial
- delegate trial related responsibilities only to suitably trained and qualified personnel
- train relevant medical and nursing staff who see patients and ensure that they remain aware of the state of the current knowledge, the trial and its procedures (there are wall charts, pocket summaries and PowerPoint presentations to assist with this)
- agree to comply with the final trial Protocol and any relevant amendments
- ensure that all patients who meet the eligibility criteria are considered promptly for the trial
- ensure consent is obtained in line with local approved procedures
- ensure that the patient baseline data are completed and transmitted to the CTU in a timely manner
- ensure the Investigator's Study File is up-to-date and complete
- ensure all adverse events are reported promptly to the CTU
- ensure the trial is conducted in accordance with ICH GCP and fulfils all national and local regulatory requirements
- allow access to source data for monitoring, audit and inspection
- be responsible for archiving all original trial documents including data forms for five years after the end of the trial

3.7 TRIAL MANAGEMENT GROUP AND CLINICAL TRIALS UNIT RESPONSIBILITIES

The TMG will consist of the Protocol Committee members (Section 3.3) plus trial manager(s), data manager and other key trial staff as required.

The CTU will act on behalf of the Sponsor and will be responsible to the TMG to ensure that all of the Sponsor's responsibilities are carried out. The responsibilities include (but are not limited to):

- report to the TSC
- maintain the Trial Master File
- identify trial sites
- confirm all approvals are in place before release of the trial treatment and the start of the trial at a site
- provide training about the trial
- provide study materials
- data management centre
- Investigational Medicinal Product management
- 24-hour advice and unblinding service
- give collaborators and patients regular information about the progress of the study
- respond to any questions (e.g. from collaborators and patients) about the trial
- ensure data security and quality and observe data protection laws

- safety reporting
- ensure trial is conducted in accordance with the ICH GCP including trial monitoring
- statistical analysis
- publication of trial results

3.8 CONTACTING THE CTU IN AN EMERGENCY

For urgent enquiries, adverse event reporting and unblinding queries investigators and patients can contact the 24-hour telephone service provided by the CTU. This number is given in the Investigator's Study File and the Patient Alert Card.

3.9 PUBLICATION AND DISSEMINATION OF RESULTS

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 (statinwise.Lshtm.ac.uk) 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.

3.10 FINANCIAL SUPPORT

The StatinWISE trial is funded by the NIHR Health Technology Assessment programme. Funding for this trial covers trial materials, meetings and central organisational costs. The design and management of the study are entirely independent of the manufacturers of atorvastatin, which is not a new product.



4. ABBREVIATIONS USED

AE	Adverse Event
ALT	Alanine aminotransferase
AR	Adverse Reaction
CK	Creatinine Kinase
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trials Unit
CVD	Cardiovascular Disease
DMC	Data Monitoring Committee
GP	General Practitioner
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
LSHTM	London School of Hygiene & Tropical Medicine
mg	milligram
MOP	Manual of Operating Procedures
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PSF	Product Specification File
QP	Qualified Person
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale



5. REFERENCES

1. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; **376**(9753): 1670-81.
2. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 181. London, 2014.
3. Scholes S, Faulding S, Mindell J. Chapter 5: Use of Prescribed Medicines, Health Survey for England 2013. 2014.
4. Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *European journal of preventive cardiology* 2014; **21**(4): 464-74.
5. Maningat P, Breslow JL. Needed: pragmatic clinical trials for statin-intolerant patients. *The New England journal of medicine* 2011; **365**(24): 2250-1.
6. Armitage J. The safety of statins in clinical practice. *Lancet* 2007; **370**(9601): 1781-90.
7. Garavalia L, Garavalia B, Spertus JA, Decker C. Exploring patients' reasons for discontinuance of heart medications. *The Journal of cardiovascular nursing* 2009; **24**(5): 371-9.
8. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. *Annals of internal medicine* 2013; **158**(7): 526-34.
9. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; **114**(25): 2788-97.
10. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *Jama* 2002; **287**(5): 622-7.
11. Moriarty PM. ODYSSEY ALTERNATIVE demonstrates complexity of statin-intolerant patients. *AHA* 2014; 2014.
12. Wieseler B, Wolfram N, McGauran N, et al. Completeness of reporting of patient-relevant clinical trial outcomes: comparison of unpublished clinical study reports with publicly available data. *PLoS medicine* 2013; **10**(10): e1001526.
13. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *The New England journal of medicine* 2007; **357**(22): 2248-61.
14. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**(9326): 7-22.
15. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; **377**(9784): 2181-92.
16. Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. The n-of-1 randomized controlled trial: clinical usefulness. Our three-year experience. *Annals of internal medicine* 1990; **112**(4): 293-9.
17. Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? *Personalized medicine* 2011; **8**(2): 161-73.
18. Search Collaborative Group, Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy—a genomewide study. *The New England journal of medicine* 2008; **359**(8): 789-99.
19. Sakaeda T, Kadoyama K, Okuno Y. Statin-associated muscular and renal adverse events: data mining of the public version of the FDA adverse event reporting system. *PLoS One* 2011; **6**(12): e28124.
20. Todd KH, Funk JP. The minimum clinically important difference in physician-assigned visual analog pain scores. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 1996; **3**(2): 142-6.

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21. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Annals of emergency medicine* 2001; **38**(6): 633-8.
22. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *Journal of clinical lipidology* 2012; **6**(3): 208-15.
23. Keech A, Collins R, MacMahon S, et al. Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *European heart journal* 1994; **15**(2): 255-69.
24. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. *British journal of anaesthesia* 2008; **101**(1): 17-24.
25. Arnold BF, Hogan DR, Colford JM, Jr., Hubbard AE. Simulation methods to estimate design power: an overview for applied research. *BMC medical research methodology* 2011; **11**: 94.
26. Dexter F, Chestnut DH. Analysis of statistical tests to compare visual analog scale measurements among groups. *Anesthesiology*, 1995, 82:896-902
27. White IR, Kalaitzakib E, Thompson SG. Allowing for missing outcome data and incomplete uptake of randomised interventions, with application to an Internet-based alcohol trial. *Statistics in Medicine*, 2011, 30: 3192–3207



6. Appendices

Appendix 1: Trial assessment timelines

Appendix 2: Baseline data form

Appendix 3: End of Trial data form

Appendix 4: Patient questionnaire

Appendix 5: VAS Pain Scale data form

Appendix 6: Patient Information Sheet

Appendix 6a: Patient Information Sheet, Optional Genetic Study

Appendix 7: Informed Consent Form

Appendix 7a: Informed Consent Form, Optional Genetic Study

Appendix 8: Summary of Product Characteristics for Atorvastatin 20 mg tablets

Appendix 9: Recruiting pathway

StatinWise Trial Assessment timelines, Version 1.1, 27/06/2017

Appendix 1 StatinWISE Trial assessment timelines

	Database search	PIS posted to eligible patients	Baseline Visit	TP1 (month 1-2)	TP2 (month 3-4)	TP3 (month 5-6)	TP4 (month 7-8)	TP5 (month 9-10)	TP6 (month 11-12)	Follow-up Visit (F2F/Phone)	Secondary outcome data capture
SCREENING											
Trial team performs GP practice patients' list screening to identify potentially eligible patients	x										
GP reviews screening list and confirms patients are clinically eligible		x									
Trial team posts PIS with reply slip		x									
Patients contact trial team to arrange Baseline visit		x									
ENROLMENT											
Patients attend enrolment visit with Research Nurse and sign consent form			x								
Research Nurse completes the Baseline Form on electronic trial database. Baseline data will include: - Personal Details - Demographic data - Eligibility assessment - General medical history which may include blood test to measure total non-fasting cholesterol if none available in notes - Randomisation data			x								

	Database search	PIS posted to eligible patients	Baseline Visit	TP1 (month 1-2)	TP2 (month 3-4)	TP3 (month 5-6)	TP4 (month 7-8)	TP5 (month 9-10)	TP6 (month 11-12)	Follow-up Visit (F2F/Phone)	Secondary outcome data capture
ENROLMENT											
Patients are randomised and trained on data entry tool of their choice			x								
TREATMENT PERIOD											
IMP posted to patients' address				x	x	x	x	x	x		
Patients confirm receipt of IMP				x	x	x	x	x	x	x	
Patients take study medication orally once daily				x	x	x	x	x	x	x	
Reminder to submit outcome data				x	x	x	x	x	x	x	
Patients enter outcome data and report any adverse events				x	x	x	x	x	x	x	
Patients post unused IMP to Pharmacy				x	x	x	x	x	x	x	
IMP accountability by Pharmacy				x	x	x	x	x	x	x	
Trial newsletter sent to patients						x			x		x
FOLLOW-UP											
Individual results ready to disclose										x	
Appointment (face-to-face or telephone call) with Research Nurse to discuss individual results										x	
END OF TRIAL											
Research Nurse telephones patients to record outcome data											x

StatinWISE Baseline data form, Version 3.1, 28/10/2016

Appendix 2: StatinWISE Baseline data form

1. Patient Initials				2. Patient Screening ID				-				3. Site ID			
4. Visit date	dd/mm/yyyy			5. Gender											
6. Ethnicity	a. White: (i) British (ii) Irish (iii) Traveller (iv) Other b. Black: (i) African (ii) Caribbean (iii) Black British (iv) Other c. Asian: (i) Asian British (ii) Indian (iii) Pakistani (iv) Chinese (v) Other d. Mixed e. Other: (describe) _____										Circle main group and sub-group				
7. Age	<input type="text"/>	<input type="text"/>	Years												

Patient Personal Details: The following information is needed for trial management purposes (sending trial medication and reminders) only and will not be collected as part of the trial database.

A. Full name	First name		Last name		
B. Postal address	House number/Name				
	Street name				
	Town/City				
	Postcode				
C. Email (primary)			D. Email (secondary)		
E. Home Telephone			F. Mobile number		

ELIGIBILITY ASSESSMENT (Circling any RED box means patient is NOT eligible)	Eligibility Please circle	
8. Written informed consent obtained?	YES	NO*
9. Is the patient aged 16 and over?	YES	NO*
10. Patient has a clinical reason for treatment with atorvastatin 20mg daily?	YES	NO*
11. Used statin within the last 3 years?	YES	NO*
12. Is patient considering discontinuation of their statin due to muscle related adverse effects OR Has patient stopped taking a statin due to muscle related adverse effects?	YES	NO*
13. Can atorvastatin 20mg daily be started or continued in the GP's opinion?	YES	NO*
14. Has patient had previously documented ALT levels at or above three times the upper limit of normal (ULN)? Test date: dd/mm/yyyy Result: <input type="text"/> <input type="text"/> <input type="text"/> iU/L (must be within 3 months of visit)	YES*	NO
15. Does the patient 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? Test date: dd/mm/yyyy Result: <input type="text"/> <input type="text"/> <input type="text"/> U/L (must be within 3 months of visit)	YES*	NO

*if circled, patient is NOT eligible

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PATIENT GENERAL MEDICAL HISTORY																										
16. Symptoms experienced during statin use that the patient believed were caused by the statin:																										
(a) Muscle pain	YES/NO	(f) Sore throat YES/NO																								
(b) Joint pain	YES/NO	(g) Digestive problems YES/NO																								
(c) Muscle weakness	YES/NO	(h) Headache YES/NO																								
(d) Tiredness/fatigue	YES/NO	(i) Feeling sick YES/NO																								
(e) Nosebleeds	YES/NO																									
17. Does the patient think something other than statin may have caused their muscle pain? YES/NO																										
17(a) If YES to Question 17, please describe:																										
18. Does the patient have any history of cardiovascular disease? YES/NO																										
18a. If YES to Question 18, please indicate all that apply :																										
(a) Angina or diagnosed coronary heart disease	YES/NO	(c) Previous ischaemic stroke YES/NO																								
(b) Previous myocardial infarction	YES/NO	(d) Peripheral vascular disease YES/NO																								
(e) Other	YES/NO (If yes, describe) _____																									
19. Current use of high blood pressure medication? YES/NO																										
20. Blood pressure measurement (mmHg):																										
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a. Systolic			b. Diastolic																							
21. Diabetes? YES /NO		22. Smoking status: (a) non-smoker (b) ex-smoker (c) current smoker																								
23. Total cholesterol measurement [mmol/L] (within last 3 years):		24.																								
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If no reading, in line with NICE guidelines, organise non-fasting blood test for total cholesterol		b. Weight: <table border="1" style="display: inline-table;"><tr><td style="width: 25px;"> </td><td style="width: 25px;"> </td><td style="width: 25px;"> </td></tr></table> Kg																								
25. QRISK2 score:																										
26. Record all current medication:																										
Name of drug (generic)		Total daily dose and unit																								
1.																										
27. Consent to participate in genetic study? YES/NO																										
27a. Blood sample taken? YES/NO		27b. Blood shipment reference:																								
RANDOMISATION DATA																										
28. Is patient fully eligible? YES/NO																										
29a. Date of Randomisation?		29b. Time of Randomisation? (24 hour clock)																								
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31. Method of data collection chosen?																										
(a) Online system (b) Mobile application		31a. App successfully installed?																								
(c) Phone call (d) Paper CRFs		YES/NO																								
		32. Training provided on method chosen?																								
		YES/NO																								
33. Form completed by:		34. Date:																								

This data should be collected directly onto the online trial database (detail in your study file). If you are unable to enter this data, call 0207 299 4684

Appendix 3: StatinWISE End of Trial data form



End of Trial Form (Month 15) / Early Withdrawal

1. Did the patient complete -the Trial to Month 15?



YES
<p>A.1. Has the Research Nurse/GP spoken to the patient to discuss their individual results? (i) YES (ia) Date seen: : _____ dd/mm/yyyy (ii) NO – (please arrange an appointment). (iia) Date of appointment: _____ dd/mm/yyyy</p>
<p>A.2. Has the patient seen his/her GP since end of Treatment Period 6? (i) YES (ii) NO (please remind the patient to book an appointment) (iia) Date reminder done: _____ dd/mm/yyyy</p>
<p>A.3. Has the patient been given a statin prescription in the 12 weeks since Treatment Period 6 ended? (i) YES (ia) Name of Statin: _____ (ib) Dose of statin: _____ (ic) Date of issue of prescription: _____ (ii) NO (iia) If no statin has been prescribed, does the patient intend on re-starting long term statin therapy? YES/NO/Don't know</p>
<p>A.4. Has the patient found their own trial results helpful to reach the decision as to whether to continue statin use? YES/NO</p>

NO
<p>B.1. Please tick reason why the patient did not complete the trial: <input type="checkbox"/> Lost to follow-up <input type="checkbox"/> Early withdrawal <input type="checkbox"/> Death</p>
<p>B.2. Lost to follow-up: Date of last contact with patient? _____ Dd/mm/yyyy</p>
<p>B.3. If Early withdrawal, give reason: a. withdrawal of informed consent b. intolerable muscle symptoms* c. clinical concern* d. other* *: please enter details here: _____ _____</p>
<p>B.4. Has the patient contacted their GP to discuss reason for withdrawal? (i) YES (ia) Date seen: : _____ dd/mm/yyyy (ii) NO – (advise patient to contact GP).</p>
<p>B.5. Has the Research Nurse/GP spoken to the patient to discuss their individual results? (i) YES (ia) Date seen: : _____ dd/mm/yyyy (ii) NO – (please arrange an appointment). (iia) Date of appointment: _____ dd/mm/yyyy</p>
<p>B.6. Death _____ B.6.a. Date of death: _____ dd/mm/yyyy</p>
<p>B.6.b Cause of death (either autopsy report or clinical judgement if autopsy not available): _____</p>
<p>B.6.c. Date SAE form completed: _____ dd/mm/yyyy (if applicable)</p>

C.1. This form was completed by: _____ Date: dd/mm/yyyy

Appendix 4: StatinWISE Patient questionnaire



INSTRUCTIONS

This questionnaire is to be filled out once every two months (on day 56). We will remind you one day before it is due. Please answer all questions. If you need any help to complete the form. Please call our Freephone number 08000 147410 or email the study team: statinwise@lshtm.ac.uk.

PART 1: ADHERENCE TO MEDICATION

Step 1 (all participants):

Q1. How would you best describe your use of study medication in the past two months? (Please choose one of the following options)

- I didn't take my study medication at all
- I took my study medication on some days
- I took my study medication on most days, but missed an occasional dose
- I took my study medications every day

Step 2 (appears if the participant chooses "I didn't take my study medication at all", or "I took my study medication on some days"):

Q2. What was the reason that you didn't take your study medication every day in the past two months? (please tick all that apply)

- I forgot to take my study medication

Ticking the above will prompt the following option, if ticked, the trial team will action:

- Would you like a daily reminder sent to you via email/push notification

- I was prescribed another medication and my doctor told me to stop taking my study medication

Ticking the above will prompt an alert for the trial team to contact surgery for details and consider withdrawal from study

- My doctor recommended that I stop taking study medication because of muscle symptoms

Ticking the above will prompt an alert for the trial team to contact surgery for details

- I decided to stop taking study medication because of muscle symptoms

Ticking the above will prompt an alert for the patient to contact the GP for advice

- I didn't want to take my study medication

Ticking the above will prompt the following option, if ticked NO, the trial team will arrange for end of trial:

Do you still wish to participate in the trial: Yes No

- Other (please specify)

(free text)

1
2 **PART 2: EXPLORING SYMPTOMS IN THE PAST TWO MONTHS**
3

- 4 1. *(all participants)*: In the last two months, have you experienced muscle symptoms, e.g. muscle pain or weakness?
5
6 Yes
7 No
8
-

- 9
10 2. *(appears if the participant ticks yes for Question 1)*: Do you think these muscle symptoms are related to your study
11 medication?
12
13 Yes
14 No
15 Don't know
16
17
-

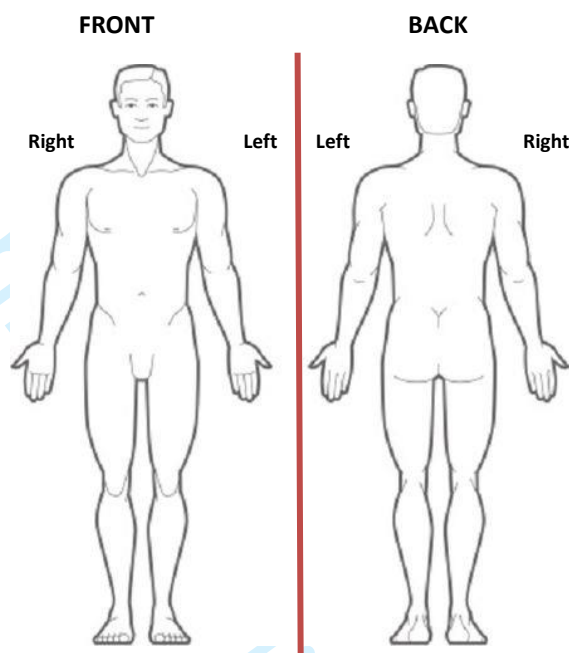
- 18
19 3. *(appears if the participant ticks no for Question 2)*: What do you think may have caused these muscle symptoms?
20 *(free text)*
21
22
23 Don't know
24
-

- 25
26 4. *(appears if the participant ticks yes for Question 1)*: Indicate with a cross (x) on the scale the number that
27 describes how, during the last two months, pain has interfered with your:
28 a. General activity
29 b. Mood
30 c. Walking ability
31 d. Normal work (includes both work outside the home and housework)
32 e. Relations with other people
33 f. Sleep
34 g. Enjoyment of life
35

36 *For each of (a) to (g), the following scale will appear:*



- 1
2 5. (appears if the participant ticks yes for Question 1): **On the diagram, tap to highlight the area that hurts the most.**
3 (Paper form will read: 'On the diagram, put an X on the area that hurts the most.')



- 29
30
31 More than one area

32
33 The body will be divided into the following locations and answers should be categorized depending where the participant
34 taps. For paper forms, the location given by X marked on the body will be entered into the web or app version at data
35 entry. Locations: head and neck/upper limbs/lower limbs/trunk.

- 36
37
38
39
40 6. (All participants): **In the last two months, have you experienced any other symptom that you think is associated
41 with your study medication?**

- 42 Yes (please specify)

43 (free text)

- 44 No

- 45 Don't know

46
47
48 **PART 3: ADVERSE EVENTS**

- 49
50 1. (All participants): **Have you been admitted to hospital in the last two months?**

- 51 Yes

- 52 No

- 53
54 2. (Appears if the participant ticks yes for Question 1): **What was the reason for your admission to hospital?**




55
56 (free text)

StatinWISE VAS Pain Scale data form, Version 1.0, 23/05/2016

Appendix 5: StatinWISE VAS Pain Scale data form



You will be asked to complete this form each day during the last seven days of each two-month treatment period.

Day	Daily symptoms report		
1	1. Did you take study medication yesterday? No <input type="checkbox"/> Yes <input type="checkbox"/> ↓ 2. Did you experience muscle symptoms today? No <input type="checkbox"/> Yes <input type="checkbox"/> <i>If yes:</i>		3: Please indicate severity of muscle symptoms you experienced today.  0 1 2 3 4 5 6 7 8 9 10 No symptoms Moderate symptoms Worst possible symptoms
2	1. Did you take study medication yesterday? No <input type="checkbox"/> Yes <input type="checkbox"/> ↓ 2. Did you experience muscle symptoms today? No <input type="checkbox"/> Yes <input type="checkbox"/> <i>If yes:</i>		3: Please indicate severity of muscle symptoms you experienced today.  0 1 2 3 4 5 6 7 8 9 10 No symptoms Moderate symptoms Worst possible symptoms
3	1. Did you take study medication yesterday? No <input type="checkbox"/> Yes <input type="checkbox"/> ↓ 2. Did you experience muscle symptoms today? No <input type="checkbox"/> Yes <input type="checkbox"/> <i>If yes:</i>		3: Please indicate severity of muscle symptoms you experienced today.  0 1 2 3 4 5 6 7 8 9 10 No symptoms Moderate symptoms Worst possible symptoms

4

1. Did you take study medication yesterday? No Yes

2. Did you experience muscle symptoms today? No Yes
If yes:

3: Please indicate severity of muscle symptoms you experienced today.

5

1. Did you take study medication yesterday? No Yes

2. Did you experience muscle symptoms today? No Yes
If yes:

3: Please indicate severity of muscle symptoms you experienced today.

6

1. Did you take study medication yesterday? No Yes

2. Did you experience muscle symptoms today? No Yes
If yes:

3: Please indicate severity of muscle symptoms you experienced today.

7

1. Did you take study medication yesterday? No Yes

If yes: ↓

2. Did you experience muscle symptoms today? No Yes
If yes:

3: Please indicate severity of muscle symptoms you experienced today.

StatinWISE Patient Information Sheet, Version 2.0, 27/06/2017

Appendix 6: StatinWISE Patient Information Sheet

IRAS project ID: 197990

Site contact info and logo



StatinWISE: Investigation of STATIN Side Effects



INFORMATION FOR PATIENTS

We invite you to take part in a research study called StatinWISE

- Before you decide whether 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 this information carefully and discuss it with friends or relatives if you wish
- You are encouraged to ask any questions you wish, before, during or after the study
- You are entirely free to decide whether or not to take part in this trial. If you choose not to take part, the care you are given by your GP will not be affected
- If there is anything that is not clear, or if you would like more information, please telephone the StatinWISE Research Nurse on [insert details]

Important things that you need to know

- We want to find out whether statins are the cause of muscle symptoms
- There will be only one visit to your GP practice as the study is done by phone or by the web
- The study treatment is posted directly to you and will fit through your letterbox
- At the end of the study, you will get personalised results so you can see if your own muscle symptoms are caused by statins
- You can stop taking part in the study at any time
- Support will be given to you throughout the study

Contents

1. Why are we doing this study?
2. Why have I been asked to take part?
3. What will happen if I take part?
4. What are the possible benefits of taking part in the study?
5. What are the possible risks of taking part in the study?
6. What if I don't want to be part of this study anymore?
7. What happens if I experience side effects?
8. Will my participation in the study be kept private?
9. Who can I contact to join the trial, ask questions or contact if I have a problem?
10. What else do you need to know?

1. Why are we doing this study?

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.

2. Why have I been asked to take part?

You have been invited to take part because you have been prescribed a statin which you have either stopped taking within the last 3 years, or you are considering stopping, due to muscle related side-effects. Your GP thinks you are eligible and has invited you to take part. It is up to you to decide if you wish to take part or not.

3. What will happen if I take part?

Everyone taking part will have agreed to do so voluntarily, knowing the study involves:

- Most people will need a blood test, but this will only be once.
- 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.
- 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.
- Completing 6 short questionnaires on your muscle symptoms every 2 months. There are a few ways in which you can choose to complete the questionnaires; via the web, verbally over the phone, mobile phone app or conventional paper form.
- At the end of 12 months, there will be one phone call or face-to-face appointment with your GP or Research Nurse to discuss your own results based on the information you provided in your questionnaires. You can also 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.

Study Timeline:



4. What are the possible benefits of taking part in the study?

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.

5. What are the possible risks of taking part in the study?

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.

6. What if I don't want to be part of this study anymore?

You can withdraw from the study at any time. We hope that you will let us use the information we have collected up to that point, but if you do not want us to use it please tell the Research Nurse or your GP.

7. What happens if I experience side effects?

You will be given an alert card when you join the study. If you experience any bad side effects, and wish to stop the medications, you should tell your GP. Your GP will continue to give you the best available care if there are any problems. If your GP decides you should not take part in the study for any reason, s/he can also withdraw you from the study.

8. Will my participation in the study be kept private?

The only people who are allowed to look at the information will be the team responsible for the study at the London School of Hygiene & Tropical Medicine and regulatory authorities who check that the study is being carried out properly. The GP Practice will need to share your personal information (name, address, phone number and email address) with the London School of Hygiene & Tropical Medicine so that they can send you the study treatment and help you with completing the questionnaires. All information collected about you will be kept private and used in strict confidence by the people working on the study.

We will publish the study results in a medical journal so that other doctors can benefit from the knowledge. Your personal information will not be included in the study report and there is no way that you can be identified. The study data, without any personal information, will be made available to researchers worldwide so that it can be used to improve medical knowledge and patient care.

9. Who can I contact to join the trial, ask questions or contact if I have a problem?

If you would like to join the study, you can complete the reply slip enclosed and return it in the freepost envelope provided. The Research Nurse at your GP Practice will then contact you to arrange an appointment. Otherwise you can call your GP Practice on [insert details] to arrange an appointment.

If you have any questions or concerns about the study, you should ask to speak with the study doctors or Research Nurses who will do their best to answer your questions. Your GP and Research Nurse can be contacted as follows:

Name	Personalise for each site
Address	
Phone Number	
Email	

10. What else do you need to know?

- The study is organised by the London School of Hygiene & Tropical Medicine and is funded by the Department of Health.
- The lead study doctor is a GP Professor Liam Smeeth at the London School of Hygiene and Tropical Medicine.
- In the unlikely event of you being harmed as a result of taking part in the study, the London School of Hygiene & Tropical Medicine would be responsible for claims for any non-negligent harm suffered as a result of participating in the study. You would retain the same rights of care as any other patient treated in the National Health Service.
- If you have any complaints about the StatinWISE study, please contact your GP Practice Manager.
- To protect your rights and well-being, all research conducted in the NHS is reviewed by an independent group of people called a Research Ethics Committee. Southampton Research Ethics Committee have given favorable ethical opinion for the study. The study has been reviewed, and approved, by the Medicines and Healthcare products Regulatory Agency who regulate clinical trials in the UK.
- If you would like to have a summary of the results of this study when it has ended, please let the Research Nurse know.

To contact the Clinical Trials Unit at London School of Hygiene & Tropical Medicine:

e-mail: statinwise@lshtm.ac.uk

Freephone: 0800 014 7410

Post: StatinWISE study, LSHTM, Room 180, Keppel Street, London WC1E 7HT.

1
2 *StatinWISE Patient Information Sheet, Optional Genetic Study, Version 1.0, 27/06/2017*
3
4

5 **Site contact info and logo**
6

7 **Appendix 6A: StatinWISE Patient Information Sheet – Optional Genetic Study**

8 IRAS Project ID: 197990
9



18 **Web-based Investigation of STATIN Side Effects**

19
20
21
22 **INVITATION TO TAKE PART IN AN OPTIONAL**
23 **GENETIC STUDY FOR StatinWISE**
24
25
26
27

28 A randomised clinical trial to assess if atorvastatin treatment
29 causes more muscle symptoms than placebo
30
31
32

33
34 Thank you for taking part in StatinWISE
35

36 Before you decide whether to take part in this optional genetic study, it is
37 important for you to understand why the research is being done and what
38 is involved. Please take time to read the information carefully and discuss it
39 with friends or relatives if you wish. You are entirely free to decide whether
40 or not to take part in this optional blood sample study. There are no extra
41 visits to take part in this study. If you choose not to take part, the care you
42 are given by your GP will not be affected.
43
44
45
46

47 If anything is unclear, or if you would like more information, please
48 telephone the StatinWISE Research Nurse on **[insert details]**
49

50
51 *StatinWISE is coordinated by the London School of Hygiene & Tropical Medicine Clinical Trials Unit and funded by the*
52 *National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme*
53
54
55
56
57
58
59
60



Web-based Investigation of **STATIN** Side Effects

1. Why are we doing this optional genetic study

The link between taking statins and aches and pains is not fully understood, but may be linked to underlying genetic markers. This study aims to determine whether muscle pain considered to be due to statins is associated with genetic markers. Knowing this association may direct future medical management of using statins.

2. Why have I been asked to take part?

You have been asked to participate because you are taking part on StatinWISE. It is up to you to decide if you wish to participate or not. If you do not want to take part, your participation on StatinWISE will not change, neither will your future medical care be affected.

3. What will happen if I take part?

- Your GP practice research nurse will take one small (9mls, 2 teaspoons) blood sample
- Your sample will be labelled only with a trial identification number and sent to a laboratory at the University of Liverpool for analysis without any of your personal information.

4. What are the possible benefits of taking part in the study?

This optional study will allow scientists to understand if muscle symptoms experienced with statins are influenced by people's genes. The blood sample you give can be used also for other research studies. This may help direct future medical management of the use of statins.

5. What are the possible risks of taking part in the study?

It is very rare for a blood test to result in any serious complications. Risks associated with this test are no different to any regular blood test that you will have as part of routine clinical care. You may experience bruising as a result of taking the blood.

6. Will my participation in the study be kept private?

The only people who are allowed to look at your personal information will be the team responsible for the study at the London School of Hygiene & Tropical Medicine and regulatory authorities who check that the study is being carried out properly. The GP Practice will **not** share your personal information with the genetics laboratory. The results of the genetic analysis will not be shared with you, your GP or the StatinWISE team.

To contact the Clinical Trials Unit at London School of Hygiene & Tropical Medicine:

e-mail: statinwise@lshtm.ac.uk

Freephone: 0800 014 7410

Post: StatinWISE study, LSHTM, Room 180, Keppel Street, London WC1E 7HT.

1
2 *StatinWISE Informed Consent Form, Optional Genetic Study, Version 1.0, 27/06/2017*

3 IRAS project ID: 197990

4 **Appendix 7A StatinWISE Informed Consent Form – Optional Genetic**
5 **Study**



6
7
8 **Name of Principal Investigator:**
9

10 11 12	1. Patient Initials			2. Patient Screening ID				-				3. Site ID			
----------------	---------------------	--	--	-------------------------	--	--	--	---	--	--	--	------------	--	--	--

15 16	Statement - <u>Optional blood sample</u>	Please initial each box
17 18 19 20	I understand that my blood sample will not contain any of my personal information and will be stored at the University of Liverpool.	
21 22 23	I give permission for my blood sample to be used in the future ethically approved research projects.	
24 25	I agree to have a blood sample taken for genetic analysis.	

27 28 29			
----------------	--	--	--

30 Printed name of participant

Signature of participant

Date

31
32 I confirm that I have explained the study information accurately to, and was understood to the best of my knowledge by, the
33 participant and that he/she has freely given their consent to participate.
34

35 36 37			
----------------	--	--	--

38 Printed name of person obtaining consent

Signature of person obtaining consent

Date

39
40 *1 copy of participant, 1 for investigator file and 1 for medical notes.*
41
42
43
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Appendix 8: Summary of Product Characteristics for Atorvastatin 20 mg tablets

1 NAME OF THE MEDICINAL PRODUCT

Atorvastatin 20 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 20 mg atorvastatin (as atorvastatin calcium)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, elliptic, biconvex and smooth film-coated tablets. The dimensions of each tablet are approximately 12.5 mm x 6.6 mm.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypercholesterolaemia

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non pharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Prevention of cardiovascular disease

Prevention of cardiovascular events in patients estimated to have a high risk for a first cardiovascular event (see section 5.1), as an adjunct to correction of other risk factors.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin.

The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.

The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia The majority of patients are controlled with atorvastatin 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous familial hypercholesterolaemia

Patients should be started with atorvastatin 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia

Only limited data are available (see section 5.1).

The dose of atorvastatin in patients with homozygous familial hypercholesterolaemia is 10 to 80 mg daily (see section 5.1). Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Prevention of cardiovascular disease

In the primary prevention trials the dose was 10 mg/day. Higher dosages may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

Renal impairment

No adjustment of dose is required (see section 4.4).

Hepatic impairment

Atorvastatin should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). Atorvastatin is contraindicated in patients with active liver disease (see section 4.3).

Use in the elderly

Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.

Paediatric use

Hypercholesterolaemia:

Paediatric use should only be carried out by physicians experienced in the treatment of paediatric hyperlipidaemia and patients should be re-evaluated on a regular basis to assess progress.

For patients aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day with titration up to 20 mg per day. Titration should be conducted according to the individual response and tolerability in paediatric patients. Safety information for paediatric patients treated with doses above 20 mg, corresponding to about 0.5 mg/kg, is limited.

1
2 There is limited experience in children between 6-10 years of age (see section 5.1). Atorvastatin is not
3 indicated in the treatment of patients below the age of 10 years.

4
5 Other pharmaceutical forms/strengths may be more appropriate for this population.
6

7 Method of administration

8
9
10 Atorvastatin is for oral administration. Each daily dose of atorvastatin is given all at once and may be given at
11 any time of day with or without food.
12

13 14 **4.3 CONTRAINDICATIONS**

15
16 Atorvastatin is contraindicated in patients:

- 17 • with hypersensitivity to the active substance or to any of the excipients of this medicinal product
- 18 • with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3
- 19 times the upper limit of normal
- 20 • during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate
- 21 contraceptive measures (see section 4.6).
22

23 24 25 **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

26 Liver effects

27
28 Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients
29 who develop any signs or symptoms suggestive of liver injury should have liver function tests performed.
30 Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve.
31 Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction
32 of dose or withdrawal of atorvastatin is recommended (see section 4.8).
33

34
35 Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have
36 a history of liver disease.
37

38
39 Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) In a *post-hoc* analysis of stroke
40 subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack
41 (TIA) there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared
42 to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar
43 infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and
44 benefits of atorvastatin 80 mg is uncertain, and the potential risk of haemorrhagic stroke should be carefully
45 considered before initiating treatment (see section 5.1). Immune-mediated necrotizing myopathy (IMNM)
46 There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after
47 treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and
48 elevated serum creatine kinase, which persist despite discontinuation of statin treatment.
49

50 Skeletal muscle effects

51 Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and
52 cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening
53 condition characterised by markedly elevated creatine kinase (CK) levels (>10 times ULN), myoglobinaemia
54 and myoglobinuria which may lead to renal failure.
55

56 *Before the treatment*

57 Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK
58 level should be measured before starting statin treatment in the following situations:

- 59 – Renal impairment
- 60 – Hypothyroidism

- 1 – Personal or familial history of hereditary muscular disorders
- 2
- 3 – Previous history of muscular toxicity with a statin or fibrate
- 4
- 5 – Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- 6 – In the elderly (age >70 years), the necessity of such measurement should be considered, according to the
- 7 presence of other pre-disposing factors for rhabdomyolysis.
- 8 – Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and
- 9 special populations including genetic subpopulations (see section 5.2)

10 In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical
11 monitoring is recommended.

12
13
14 If CK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started.

15 16 *Creatine kinase measurement*

17 Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible
18 alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly
19 elevated at baseline (>5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the
20 results.

21 22 *Whilst on treatment*

- 23 – Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied
- 24 by malaise or fever.
- 25 – If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should
- 26 be measured. If these levels are found to be significantly elevated (>5 times ULN), treatment should
- 27 be stopped.
- 28 – If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5 x
- 29 ULN, treatment discontinuation should be considered.
- 30 – If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction
- 31 of an alternative statin may be considered at the lowest dose and with close monitoring.
- 32 – Atorvastatin must be discontinued if clinically significant elevation of CK levels (>10 x ULN) occur, or
- 33 if rhabdomyolysis is diagnosed or suspected.
- 34
- 35

36 Concomitant treatment with other medicinal products

37 Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal
38 products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or
39 transport proteins (e.g.
40 ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole,
41 posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc).
42 The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid
43 derivatives, erythromycin, niacin and ezetimibe. If possible, alternative (noninteracting) therapies should be
44 considered instead of these medicinal products.

45
46 In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the
47 risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products
48 that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended.
49 In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered
50 and appropriate clinical monitoring of these patients is recommended (see section 4.5).

51
52
53 The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of
54 atorvastatin may be considered during fusidic acid therapy (see section 4.5).

55 56 Interstitial lung disease

57 Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term
58 therapy (see section 4.8). Presenting features can include dyspnoea, non productive cough and deterioration in
59 general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung
60 disease, statin therapy should be discontinued.

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Paediatric use

Developmental safety in the paediatric population has not been established (see section 4.8).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effect of co-administered medicinal products on atorvastatin

Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivatives and ezetimibe (see section 4.4).

CYP3A4 inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Coadministration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where coadministration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

CYP3A4 inducers

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport protein inhibitors

Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).

Gemfibrozil / fibric acid derivatives

1
2 The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The
3 risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If
4 concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic
5 objective should be used and the patients should be appropriately monitored (see section 4.4).
6

7 Ezetimibe

8 The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of
9 these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate
10 clinical monitoring of these patients is recommended.
11

12 Colestipol

13 Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol
14 was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol
15 were co-administered than when either medicinal product was given alone.
16

17 Fusidic acid

18 Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle
19 related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin
20 and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely
21 monitored and temporary suspension of atorvastatin treatment may be appropriate.
22
23

24 Effect of atorvastatin on co-administered medicinal products

25 Digoxin

26 When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin
27 concentrations increased slightly. Patients taking digoxin should be monitored appropriately.
28
29

30 Oral contraceptives

31 Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of
32 norethindrone and ethinyl oestradiol.
33

34 Warfarin

35 In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily
36 with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of
37 dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of
38 clinically significant anticoagulant interactions have been reported, prothrombin time should be determined
39 before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early
40 therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has
41 been documented, prothrombin times can be monitored at the intervals usually recommended for patients on
42 coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be
43 repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in
44 patients not taking anticoagulants.
45
46
47

48 Paediatric population

49 Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric
50 population is not known. The above mentioned interactions for adults and the warnings in section 4.4 should
51 be taken into account for the paediatric population.
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Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC*	Clinical Recommendation**
Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	↑ 9.4 fold	In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	↑ 8.7 fold	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	↑ 5.9 fold	In cases where coadministration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	↑ 4.4 fold	
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 5-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	↑ 3.9 fold	In cases where coadministration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	↑ 3.3 fold	
Itraconazole 200 mg OD, 4 days	40 mg SD	↑ 3.3 fold	
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	↑ 2.5 fold	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	↑ 2.3 fold	
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	↑ 1.7 fold***	
			No specific recommendation

Grapefruit Juice, 240 mL OD ****	40 mg, SD	↑ 37%	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	↑ 51%	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%***	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	↑ 18%	No specific recommendation.
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 4 weeks	↓ less than 1%***	No specific recommendation.
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks	10 mg OD for 4 weeks	↓ 35%***	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	↓ 41%	No specific recommendation.
Rifampin 600 mg OD, 7 days (coadministered)	40 mg SD	↑ 30%	If co-administration cannot be avoided, simultaneous coadministration of atorvastatin with rifampin is recommended, with clinical monitoring.
Rifampin 600 mg OD, 5 days (doses separated)	40 mg SD	↓ 80%	
Gemfibrozil 600 mg BID, 7 days	40mg SD	↑ 35%	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40mg SD	↑ 3%	Lower starting dose and clinical monitoring of these patients is recommended.

* Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

** See sections 4.4 and 4.5 for clinical significance.

*** Total atorvastatin equivalent activity

**** Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).

Increase is indicated as “↑”, decrease as “↓”

OD = once daily; SD = single dose; BID = twice daily; QID = four times daily

Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products

Atorvastatin and dosing regimen	Co-administered medicinal product		
	Medicinal product/Dose (mg)	Change in AUC*	Clinical Recommendation
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	↑ 15%	Patients taking digoxin should be monitored appropriately.
40 mg OD for 22 days	Oral contraceptive OD, 2 months - norethindrone 1 mg - ethinyl estradiol 35 µg	↑ 28% ↑ 19%	No specific recommendation.
80 mg OD for 15 days	** Phenazone, 600 mg SD	↑ 3%	No specific recommendation.

* Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)

** Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

Increase is indicated as “↑”, decrease as “↓”

OD = once daily; SD = single dose

4.6 PREGNANCY AND LACTATION

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3).

Pregnancy

Atorvastatin is contraindicated during pregnancy (see section 4.3). Safety in pregnancy woman has not been established (see section 4.3). No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction (see section 5.3).

Maternal treatment with atorvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

For these reasons, atorvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with atorvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3.)

Breastfeeding

It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk (see section 5.3). Because of the potential for serious adverse reactions, women taking atorvastatin should not breast-feed their infants (see section 4.3). Atorvastatin is contraindicated during breastfeeding (see section 4.3).

Fertility

In animal studies atorvastatin had no effect on male or female fertility (see section 5.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Atorvastatin has negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for atorvastatin.

Estimated frequencies of reactions are ranked according to the following convention: common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

Infections and infestations

Common: | nasopharyngitis.

Blood and lymphatic system disorders

Rare: | thrombocytopenia.

Immune system disorders

Common: | allergic reactions

Very rare: | anaphylaxis

Metabolism and nutrition disorders

Common: | hyperglycaemia

Uncommon: | hypoglycaemia, weight gain, anorexia

Psychiatric disorders

Uncommon: | nightmare, insomnia

Nervous system disorders

Common: | headache

Uncommon: | dizziness, paraesthesia, hypoaesthesia, dysgeusia, amnesia

Rare: | peripheral neuropathy

Eye disorders

Uncommon: | vision blurred

Rare: | visual disturbance

Ear and labyrinth disorders

Uncommon: | tinnitus

Very rare: | hearing loss

Respiratory, thoracic and mediastinal disorders

Common: | pharyngolaryngeal pain, epistaxis

Gastrointestinal disorders

Common: | constipation, flatulence, dyspepsia, nausea, diarrhoea

Uncommon: | vomiting, abdominal pain upper and lower, eructation, pancreatitis

Hepatobiliary disorders

Uncommon: | Hepatitis

Rare: | cholestasis

Very rare: | hepatic failure

Skin and subcutaneous tissue disorders

Uncommon: | urticaria, skin rash, pruritus, alopecia

Rare: | angioneurotic oedema, dermatitis, bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Common: | myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain

Uncommon: | neck pain, muscle fatigue

Rare: | myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture

Not known: | immune-mediated necrotizing myopathy (see section 4.4)

Reproductive system and breast disorders

Very Rare: | gynaecomastia

General disorders and administration site conditions

Uncommon: | malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.

Investigations

Common: | liver function test abnormal, blood creatine kinase increased

Uncommon: | white blood cells urine positive

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (>3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose-related and were reversible in all patients.

Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin-treated patients (see section 4.4).

The following adverse events have been reported with some statins:

- Sexual dysfunction
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30 kg/m², raised triglycerides, history of hypertension).

Paediatric Population

The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.

Nervous system disorders

Common: Headache

Gastrointestinal disorders

Common: Abdominal pain

Investigations

Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the Yellow Card Scheme at:

www.mhra.gov.uk/yellowcard

By reporting side effects you can help provide more information on the safety of this medicine.

4.9 OVERDOSE

Specific treatment is not available for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA reductase inhibitors
ATC code: C10A A05

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the ratelimiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutarylcoenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering agents.

Atorvastatin has been shown to reduce concentrations of total-C (30%-46%), LDL-C (41%-61%), apolipoprotein B (34%-50%), and triglycerides (14%-33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose-response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, non-familial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce the risk for cardiovascular events and cardiovascular mortality.

Homozygous familial hypercholesterolaemia

In a multicenter 8 week open-label compassionate-use study with an optional extension phase of variable length, 335 patients were enrolled, 89 of which were identified as homozygous familial hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDL-C was approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid- Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomised, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

1
2
3 The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4%
4 (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to
5 pravastatin the effects of atorvastatin were statistically significant (p=0.02). The effect of intensive lipid
6 lowering on cardiovascular endpoints (e. g. need for revascularisation, non fatal myocardial infarction,
7 coronary death) was not investigated in this study.
8

9
10 In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L \pm 0.8 (78.9 mg/dl \pm 30) from baseline
11 3.89 mmol/l \pm 0.7 (150 mg/dl \pm 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85
12 mmol/l \pm 0.7 (110 mg/dl \pm 26) from baseline 3.89 mmol/l \pm 0.7 (150 mg/dl \pm 26) (p<0.0001). Atorvastatin also
13 significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20%
14 (pravastatin: -6.8%, p<0.0009), and mean apolipoprotein B by 39.1% (pravastatin: -22.0%, p<0.0001).
15 Atorvastatin increased mean HDL-C by 2.9% (pravastatin: +5.6%, p=NS). There was a 36.4% mean reduction
16 in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).
17

18 Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower
19 dose strengths.
20

21 The safety and tolerability profiles of the two treatment groups were comparable.
22

23 The effect of intensive lipid lowering on major cardiovascular endpoints was not investigated in this study.
24 Therefore, the clinical significance of these imaging results with regard to the primary and secondary
25 prevention of cardiovascular events is unknown.
26

27 Acute coronary syndrome

28 In the MIRACL study, atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo
29 n=1,548) with an acute coronary syndrome (non Qwave MI or unstable angina). Treatment was initiated during
30 the acute phase after hospital admission and lasted for a period of 16 weeks. Treatment with atorvastatin 80
31 mg/day increased the time to occurrence of the combined primary endpoint, defined as death from any cause,
32 nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischaemia requiring
33 hospitalization, indicating a risk reduction by 16% (p=0.048). This was mainly due to a 26% reduction in
34 rehospitalisation for angina pectoris with evidence of myocardial ischaemia (p=0.018). The other secondary
35 endpoints did not reach statistical significance on their own (overall: Placebo: 22.2%, Atorvastatin: 22.4%).
36
37

38 The safety profile of atorvastatin in the MIRACL study was consistent with what is described in section 4.8.
39

40 Prevention of cardiovascular disease

41
42 The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomised, double-
43 blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm
44 (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or
45 treatment for angina, and with TC levels \leq 6.5 mmol/L (251 mg/dL). All patients had at least 3 of the
46 predefined cardiovascular risk factors: male gender, age \geq 55 years, smoking, diabetes, history of CHD in a
47 first-degree relative, TC:HDL-C $>$ 6, peripheral vascular disease, left ventricular hypertrophy, prior
48 cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were
49 estimated to have a high risk for a first cardiovascular event.
50
51

52
53 Patients were treated with antihypertensive therapy (either amlodipine or atenololbased regimen) and either
54 atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).
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The absolute and relative risk reduction effect of atorvastatin was as follows:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹(%)</i>	<i>P value</i>
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events and revascularisation procedures	20%	389 vs. 483	1.9%	0.0008
Total coronary events	29%	178 vs 247	1.4%	0.0006

¹ Based on difference in crude events rates occurring over a median follow-up of 3.3 years. CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, $p=0.17$ and 74 vs. 82 events, $p=0.51$). In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non-fatal MI) was significantly reduced by atorvastatin in patients treated with amlodipine (HR 0.47 (0.32-0.69), $p=0.00008$), but not in those treated with atenolol (HR 0.83 (0.59-1.17), $p=0.287$).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomised, double-blind, multicentre, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 4.14 mmol/L (160 mg/dL) and TG ≤ 6.78 mmol/L (600 mg/dL). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

Patients were treated with either atorvastatin 10 mg daily ($n=1,428$) or placebo ($n=1,410$) for a median follow-up of 3.9 years.

The absolute and relative risk reduction effect of atorvastatin was as follows:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs. 64	1.9%	0.0070
Strokes (fatal and non-fatal)	48%	21 vs 39	1.3%	0.0163

¹ Based on difference in crude events rates occurring over a median follow-up of 3.9 years.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, $p=0.0592$).

Recurrent stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4,731 patients who had a stroke or transient ischaemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years) and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (HR 0.85; 95% CI, 0.72-1.00; $p=0.05$ or 0.84; 95% CI, 0.71-0.99; $p=0.03$ after adjustment for baseline factors) compared to placebo. All-cause mortality was 9.1% (216/2,365) for atorvastatin versus 8.9% (211/2,366) for placebo.

In a *post-hoc* analysis, atorvastatin 80 mg reduced the incidence of ischaemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%, $p=0.01$) and increased the incidence of haemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 1.4%, $p=0.02$) compared to placebo.

- The risk of haemorrhagic stroke was increased in patients who entered the study with prior haemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57) and the risk of ischaemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).
- The risk of haemorrhagic stroke was increased in patients who entered the study with prior lacunar infarct (20/708 for atorvastatin versus 4/701 for placebo; HR 4.99; 95% CI, 1.71-14.61), but the risk of ischaemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95% CI, 0.57-1.02). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive atorvastatin 80 mg/day.

All-cause mortality was 15.6% (7/45) for atorvastatin versus 10.4% (5/48) in the subgroup of patients with prior haemorrhagic stroke. All-cause mortality was 10.9% (77/708) for atorvastatin versus 9.1% (64/701) for placebo in the subgroup of patients with prior lacunar infarct.

Paediatric Population

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 6-17 years old

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of atorvastatin was conducted in children and adolescents with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL-C ≥ 4 mmol/L. A total of 39 children and adolescents, 6 to 17 years of age, were enrolled. Cohort A included 15 children, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 children, 10 to 17 years of age and at Tanner Stage ≥ 2 .

The initial dose of atorvastatin was 5 mg daily of a chewable tablet in Cohort A and 10 mg daily of a tablet formulation in Cohort B. The atorvastatin dose was permitted to be doubled if a subject had not attained target LDL-C of < 3.35 mmol/L at Week 4 and if atorvastatin was well tolerated.

Mean values for LDL-C, TC, VLDL-C, and Apo B decreased by Week 2 among all subjects. For subjects whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first assessment, after dose escalation. The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether subjects remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures.

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 10-17 years old

In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (FH) or severe hypercholesterolaemia were randomised to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks.. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 3.36 mmol/l. Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase. The mean achieved LDL-C value was 3.38 mmol/l (range: 1.81-6.26 mmol/l) in the atorvastatin group compared to 5.91 mmol/l (range: 3.93-9.96 mmol/l) in the placebo group during the 26-week double-blind phase.

An additional paediatric study of atorvastatin versus colestipol in patients with hypercholesterolaemia aged 10-18 years demonstrated that atorvastatin (N=25) caused a significant reduction in LDL-C at week 26 ($p<0.05$) compared with colestipol (N=31).

A compassionate use study in patients with severe hypercholesterolaemia (including homozygous hypercholesterolaemia) included 46 paediatric patients treated with atorvastatin titrated according to response (some subjects received 80 mg atorvastatin per day). The study lasted 3 years: LDL-cholesterol was lowered by 36%.

The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

The European Medicines Agency has waived the obligation to submit the results of studies with atorvastatin in children aged 0 to less than 6 years in the treatment of heterozygous hypercholesterolaemia and in children aged 0 to less than 18 years in the treatment of homozygous familial hypercholesterolaemia, combined (mixed) hypercholesterolaemia, primary hypercholesterolaemia and in the prevention of cardiovascular events (see section 4.2 for information on paediatric use).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism

Distribution

Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is $\geq 98\%$ bound to plasma proteins.

Metabolism

Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolised via glucuronidation. *In vitro*, inhibition of HMGCoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Excretion

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Special populations

- Elderly: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.
- Paediatric: In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥ 2 (N=24) paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C ≥ 4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.
- Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (women: approximately 20% higher for C_{max} and approximately 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
- Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.
- Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approximately 16-fold in C_{max} and approximately 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).
- SLOC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

5.3 PRECLINICAL SAFETY DATA

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC_{0-24h} reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Microcrystalline cellulose
Sodium carbonate anhydrous Maltose
Croscarmellose sodium
Magnesium stearate

Film-coating

Hypromellose (E464)
Hydroxypropylcellulose
Triethyl citrate (E1505)
Polysorbate 80
Titanium dioxide (E171).

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

Aluminium-aluminium blisters.

Atorvastatin 20 mg Film-coated Tablets are available in pack sizes of 7, 10, 14, 15, 20, 28, 30, 50, 50x1, 56, 60, 84, 90, 98, 100 or 200 tablets.

High density polyethylene bottle with a polypropylene cap provided with a compartment for desiccant.

Atorvastatin 20 mg Film-coated Tablets is available in pack sizes of 50, 100 tablets and as multipack containing 100 tablets (2 bottles of 50 tablets)

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

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3 Any unused product or waste should be disposed of in accordance with local requirements.
4

5 **7 MARKETING AUTHORISATION HOLDER**

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7
8 TEVA UK Limited
9 Brampton Road,
10 Hampden Park,
11 Eastbourne,
12 East Sussex BN22 9AG
13 UNITED KINGDOM
14

15 **8 MARKETING AUTHORISATION NUMBER(S)**

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18 PL 00289/1290
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20 **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE 21 AUTHORISATION**

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25 03/08/2010
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27 **10 DATE OF REVISION OF THE TEXT**

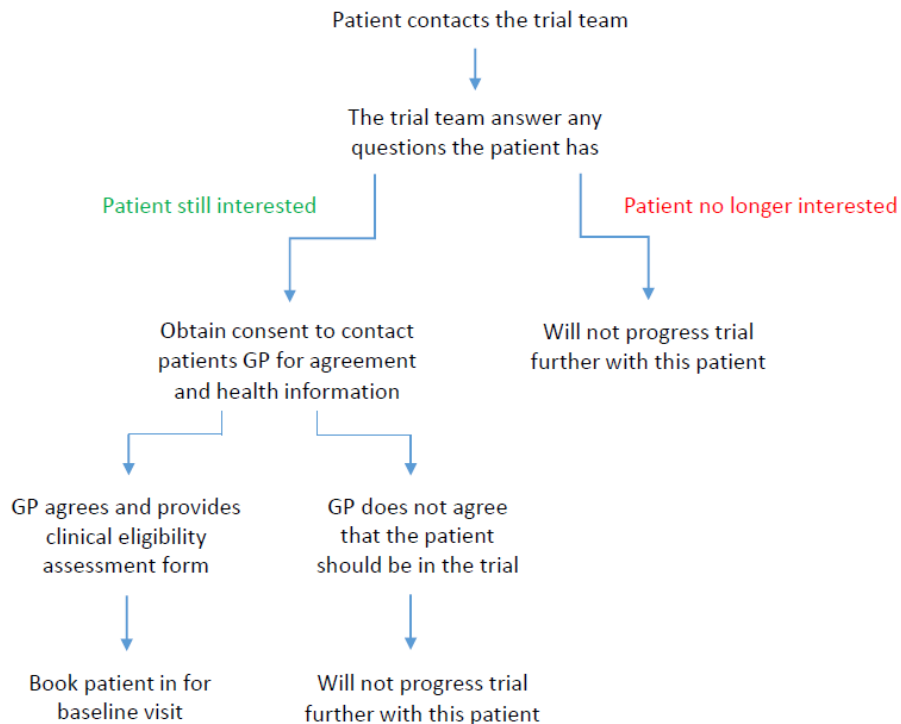
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StatinWISE Patient Recruitment Pathway, FINAL Version 1.0, 23 May 2017

Appendix 9: StatinWISE Patient Recruitment Pathway

IRAS: 197990

Diagram illustrating communication pathway following patient initiated contact



Recruitment Pathway_FINAL Version 1.0, 23 May 2017

View Only

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