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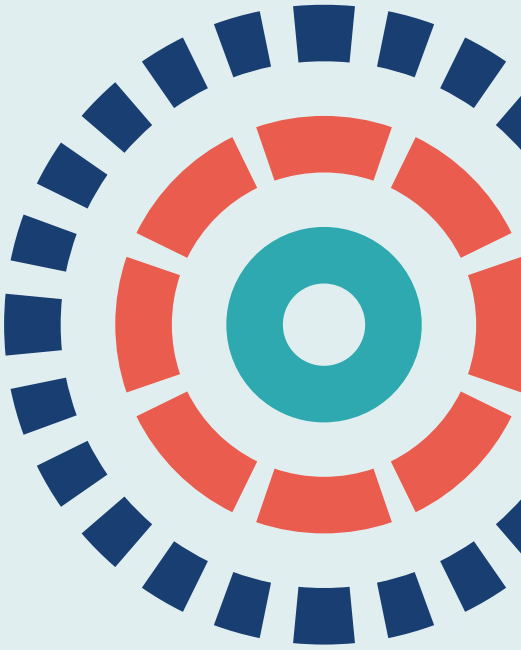

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This report

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Abstract

The effect of statins on muscle symptoms in primary care: the StatinWISE series of 200 N-of-1 RCTs

Emily Herrett[1], Elizabeth Williamson[2], Kieran Brack[3], Alexander Perkins[4], Andrew Thayne[4], Haleema Shakur-Still[4], Ian Roberts[4], Danielle Prowse[4], Danielle Beaumont[4], Zahra Jamal[4], Ben Goldacre[5], Tjeerd van Staa[6], Thomas M MacDonald[7], Jane Armitage[8], Michael Moore[9], Maurice Hoffman[10] and Liam Smeeth[1*]

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Background: Uncertainty persists about whether or not statins cause symptomatic muscle adverse effects (e.g. pain, stiffness and weakness) in the absence of severe myositis.

Objectives: To establish the effect of statins on all muscle symptoms, and the effect of statins on muscle symptoms that are perceived to be statin related.

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

Setting: Participants were recruited from 50 general practices in England and Wales.

Participants: Patients who were considering discontinuing statin use and those who had discontinued statin use in the last 3 years because of perceived muscle symptoms.

Interventions: Participants were randomised to a sequence of six 2-month treatment periods during which they received 20 mg of atorvastatin daily or a matched placebo.

Main outcome measures: The primary outcome was self-reported muscle symptoms rated using a visual analogue scale on the last week of each treatment period. Secondary outcomes included the participant's belief about the cause of their muscle symptoms, the site of muscle symptoms, how the muscle symptoms affected the participant, any other symptoms they experienced, adherence to medication, the participant's decision about statin treatment following the trial, and whether or not they found their own trial result helpful.

Results: A total of 151 out of 200 (75.5%) randomised participants provided one or more visual analogue scale measurements in a placebo period and one or more measurements in a statin period, and were included in the primary analysis. There was no evidence of a difference in muscle symptom scores between statin and placebo periods (mean difference statin minus placebo −0.11, 95% confidence interval −0.36 to 0.14; $p = 0.398$). Withdrawals, adherence and missing data were similar during the statin periods and the placebo periods.

Conclusions: Among people who previously reported severe muscle symptoms while taking statins, this series of randomised N-of-1 trials found no overall effect of statins on muscle symptoms compared with the placebo. The slight difference in withdrawals due to muscle symptoms suggests that statins may contribute to symptoms in a small number of patients. The results are generalisable to patients who are considering discontinuing or have already discontinued statins because of muscle symptoms, and who are willing to re-challenge or participate in their own N-of-1 trial.

Future work: We recommend that additional statins and doses are explored using N-of-1 trials. More broadly, N-of-1 trials present a useful tool for exploring transient symptoms with other medications.

Limitations: This study used 20-mg doses of atorvastatin only. Furthermore, a dropout rate of 43% was observed, but this was accounted for in the power calculations.

Trial registration: Current Controlled Trials ISRCTN30952488 and EudraCT 2016-000141-31.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 16. See the NIHR Journals Library website for further project information.

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List of abbreviations

app	application
CI	confidence interval
CTU	clinical trials unit
CVD	cardiovascular disease
EDC	electronic data capture
GP	general practitioner
HTA	Health Technology Assessment
IQR	interquartile range
IT	information technology
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OR	odds ratio
PI	principal investigator
SD	standard deviation
StatinWISE	Statin Web-based Investigation of Side Effects
VAS	visual analogue scale

Plain English summary

Statins are one of the most commonly prescribed drugs in the UK. There is strong evidence that they are effective in safely reducing heart disease; however, there is some doubt about whether or not statins cause muscle pain, stiffness or weakness. This research has been carried out to understand the effect of statins on muscle symptoms.

To answer our question, we asked 200 volunteers from across England and Wales to participate in the study. Patients who joined the study either had recently stopped taking statins because of muscle symptoms or were considering stopping because of muscle symptoms. Patients who participated were randomly assigned to a sequence of six 2-month treatment periods during which they received either statins or a placebo. Neither patients nor their general practitioner knew which tablet they were receiving. This helped to reduce bias in the data. At the end of each treatment period, patients were asked to report any muscle symptoms, or any other symptoms, that they experienced.

The key result of this work is that patients reported no difference, on average, in their muscle symptoms between periods of taking a statin and periods of taking a placebo. We also assessed the impact on the patient's quality of life by looking at how statins affected the following areas: general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. As with muscle symptoms, there was no evidence of a difference between statin and placebo periods. The majority of patients who finished the trial decided to continue using statins after the trial. Future research should be carried out to assess different statin doses, as higher doses are often used following a heart attack. In addition, further work is needed to see how the approach we used could be adopted into everyday clinical care.

Scientific summary

Background

Statins effectively reduce cardiovascular disease in primary and secondary prevention among men and women across all age groups. Meta-analyses have demonstrated the safety of statins; however, uncertainty persists about whether or not statins cause symptomatic muscle adverse effects in the absence of myopathy. Many people strongly believe that statins commonly cause muscle symptoms, such as stiffness, pain and weakness. This has been driven by unblinded observational studies and exacerbated by media reports worldwide. Because some patients think that their muscle symptoms are caused by statins, discontinuation is common, which leads to increased cardiovascular disease mortality and a substantial public health burden.

Objective

Our aims were to establish (1) the effect of statins on all muscle symptoms and (2) the effect of statins on muscle symptoms that are perceived to be statin related.

Methods

We conducted a series of 200 double-blinded, placebo-controlled N-of-1 trials in UK primary care. We recruited patients who were considering discontinuing statin use and those who had discontinued in the last 3 years because of perceived muscle symptoms.

Participants were randomly assigned to a sequence of six 2-month treatment periods during which they received 20 mg of atorvastatin daily or a matched placebo. The trial treatment packs were posted to patients prior to the start of each treatment period. Patients, general practice staff and trial staff were blind to allocation in each treatment period.

The primary outcome was self-reported muscle symptoms, defined as pain, weakness, tenderness, stiffness or cramp to the body of any intensity. On the last week of each treatment period, participants rated their muscle symptoms on a visual analogue scale (0 = no symptoms, 10 = worst possible symptoms) online, over the telephone, using a mobile phone application or on paper.

Secondary outcomes were collected on the last day of each treatment period and included binary measures for experience of muscle symptoms and attribution of symptoms to the study medication, site of muscle symptoms, visual analogue scale scores 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 believed were attributable to the study medication. Adherence to study medication was self-reported and verified by a drug accountability count of returned treatment packs containing the trial medication.

At the end of their trial, each participant was provided with a summary of their symptom data during the statin periods and the placebo periods. Three months after the end of the final treatment period, we asked the participants if they intended to continue or cease statin treatment. All participants were asked if they found the trial useful in making a decision about future statin use, and we determined the relationship between this decision and the participant's primary outcome.

The primary analysis aggregated data from all participants' muscle symptom scores, comparing statin with placebo periods.

Results

Two hundred patients were recruited between December 2016 and April 2018. The median age was 69.5 years (interquartile range 63–76 years) and 115 (57.5%) were male. Fourteen participants (7.0%) were current smokers, 105 (52.5%) were ex-smokers, 33 (16.5%) had diabetes and 140 (70.0%) had a history of cardiovascular disease. The mean total cholesterol level was 5.4 mmol/l (standard deviation 1.4 mmol/l).

Primary outcome

A total of 151 out of 200 (75.5%) randomised participants provided one or more visual analogue scale measurements in a placebo period and one or more in a statin period, and are therefore included in the primary analysis. A total of 86 (43.0%) participants did not complete the whole trial (two died, four were lost to follow-up and 80 withdrew).

There was no evidence of a difference in aggregated muscle symptom scores between statin and placebo periods (mean difference statin minus placebo –0.11, 95% confidence interval –0.36 to 0.14; $p = 0.398$).

Secondary outcomes

Among the 152 patients who contributed at least one secondary outcome measurement in a placebo period and one in a statin period (note that one additional participant provided secondary outcome data compared with primary outcome data), there was no evidence of an effect of statins on muscle symptoms overall (odds ratio 1.11, 99% confidence interval 0.62 to 1.99), nor was there evidence of an effect of statins when restricting to muscle symptoms that could not be attributed to another cause (odds ratio 1.22, 99% confidence interval 0.77 to 1.94). Of the other secondary outcomes (e.g. general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life), there was no evidence of a difference in symptom scores between the statin and placebo periods.

Adherence to the study medication was high, with the proportion of participants reporting taking their study medication 'every day' or 'most days' being at least 80% during each period, among participants who had not yet withdrawn.

Of the 114 patients who completed the full six treatment periods, 113 received their results during an end-of-trial discussion with their general practitioner or research nurse (56.5% of randomised participants) (one participant did not attend). At 15 months, 58 (51.3%) of these 113 participants had a prescription for statins, 74 (65.5%) said that they intended to resume statins or had already done so, and 99 participants (87.6%) said that their trial had been helpful.

Conclusions

The evidence from StatinWISE (Statin Web-based Investigation of Side Effects) suggests that, on re-challenge among patients who have previously experienced muscle symptoms that they attribute to statins, 20 mg of atorvastatin (Lipitor, Pfizer) has no effect on muscle symptoms at the population level.

Among individual patients, a majority of those completing the trial decided to restart statins. Therefore, the N-of-1 trial design could be a useful method of encouraging patients to find out whether or not statins are causing their pain and guide individual therapy.

Implications for practice

The evidence from our series of N-of-1 trials suggests that this methodology could be a useful tool to aid decision-making about future statin use, and could encourage patients to find out whether or not statins are causing their symptoms.

General practitioners who are managing patients who believe that they are experiencing muscle symptoms because of their statin use should be aware that the majority of StatinWISE participants did not experience a difference in symptoms between the statin and the placebo periods.

Recommendations for future research

1. We would recommend that series of N-of-1 trials be undertaken for other types of statins, higher dosages and non-muscle symptoms that are frequently attributed to statins. In particular, we would recommend this methodology among patients with existing cardiovascular disease who require higher doses of statin than tested in our series of N-of-1 trials.
2. We would recommend that N-of-1 trials could be used in the context of transient symptoms that occur during use of other medications.

Trial registration

This trial is registered as ISRCTN30952488 and EudraCT 2016-000141-31.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 16. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Background

Statins effectively reduce cardiovascular disease (CVD) in primary and secondary prevention among men and women across all age groups.[2,3] Meta-analyses have demonstrated the safety of statins.[4] Although severe adverse effects are rare, statins are known to be associated with a small increase in the risk of myopathy (absolute excess risk 1 case per 10,000 people treated per year), which can progress to more severe rhabdomyolysis (0.2 cases per 10,000 people treated per year).[4] Although the association between statins and these severe muscle disorders is well characterised, uncertainty persists about less severe muscle symptoms. Many people strongly believe that statins commonly cause muscle symptoms such as stiffness, pain and weakness.[5–7]

This perception has been driven by unblinded observational studies[7,8] and exacerbated by media reports worldwide.[9–11] The lack of blinding in observational studies means that patients taking a medication expect to experience adverse effects[12] 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. Because some patients think that their muscle symptoms are caused by statins, discontinuation is common,[7–11,13] which leads to increased CVD and mortality[14] and a substantial public health burden.

Previous research on statins and myalgia

In the ODYSSEY ALTERNATIVE trial,[15] statin-'intolerant' patients initially underwent a double-blind 4-week phase in which they received placebo. Interestingly, during this time, 7% dropped out because of myalgia. In the main phase of this three-arm trial [alirocumab (Praulent, Regeneron and Sanofi) vs. ezetimibe (Ezetrol, Merck Sharp and Dohme) vs. atorvastatin], rates of adverse events were the same across all groups, at roughly 80%, but dropped to 55% among the alirocumab patients when unblinded.[15] Therefore, in some trials of statins, expectation of adverse effects among both the placebo and the 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.[16]

There have also been two other important criticisms of the existing randomised controlled trial evidence. First, not all trials have collected data on subjective symptoms and recording may be inconsistent because of the definitions used. Studies have shown that adverse events are rarely fully presented in journal publications.[17] Second, although there have been trials among specific vulnerable patient groups,[18–20] there is a perception that trial participants do not reflect the populations taking statins in routine care.

Need for trial

For any patient in routine clinical care, it is not easy for the clinician or patient to determine reliably whether or not muscle symptoms are caused by statins, despite available guidance and support.[21–23] There is currently no diagnostic tool that allows clinicians to empirically evaluate whether symptoms reported by an individual statin user are caused by the statin itself or by the 'nocebo' effect.

This creates a barrier to patients receiving the benefits of CVD prevention from statins. One way of overcoming this barrier is to undertake blinded N-of-1 trials among individual patients who are experiencing symptoms during statin use. N-of-1 trials are a type of randomised trial in individual patients[24] and can provide further information to determine the best course of action for each individual. The trial addresses some of the criticisms of previous evidence. The trial will focus on muscle symptoms as a primary outcome, it will be blinded and placebo controlled to minimise bias and the sequence of statin and placebo treatments will be randomised to avoid confounding. When the results of a number of N-of-1 individuals are combined in analysis, the result can be used to demonstrate the overall effect of a treatment.

Using a series of N-of-1 trials comparing statin with placebo, StatinWISE (Statin Web-based Investigation of Side Effects) will seek to establish (1) the effect of statins on all muscle symptoms and (2) the effect of statins on muscle symptoms that are perceived to be statin related. The results of this work has also been published in the *BMJ*.[1]

Chapter 2 Methods

Study design

The trial protocol has been previously published[25] and parts of the published article are reproduced throughout this report. This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

StatinWISE was a series of randomised, double-blind, placebo-controlled N-of-1 trials. The overall duration of the trial was 1 year for each participant and comprised six 2-month treatment periods (three of placebo and three of active treatment) in a randomly allocated order (*Figure 1*).

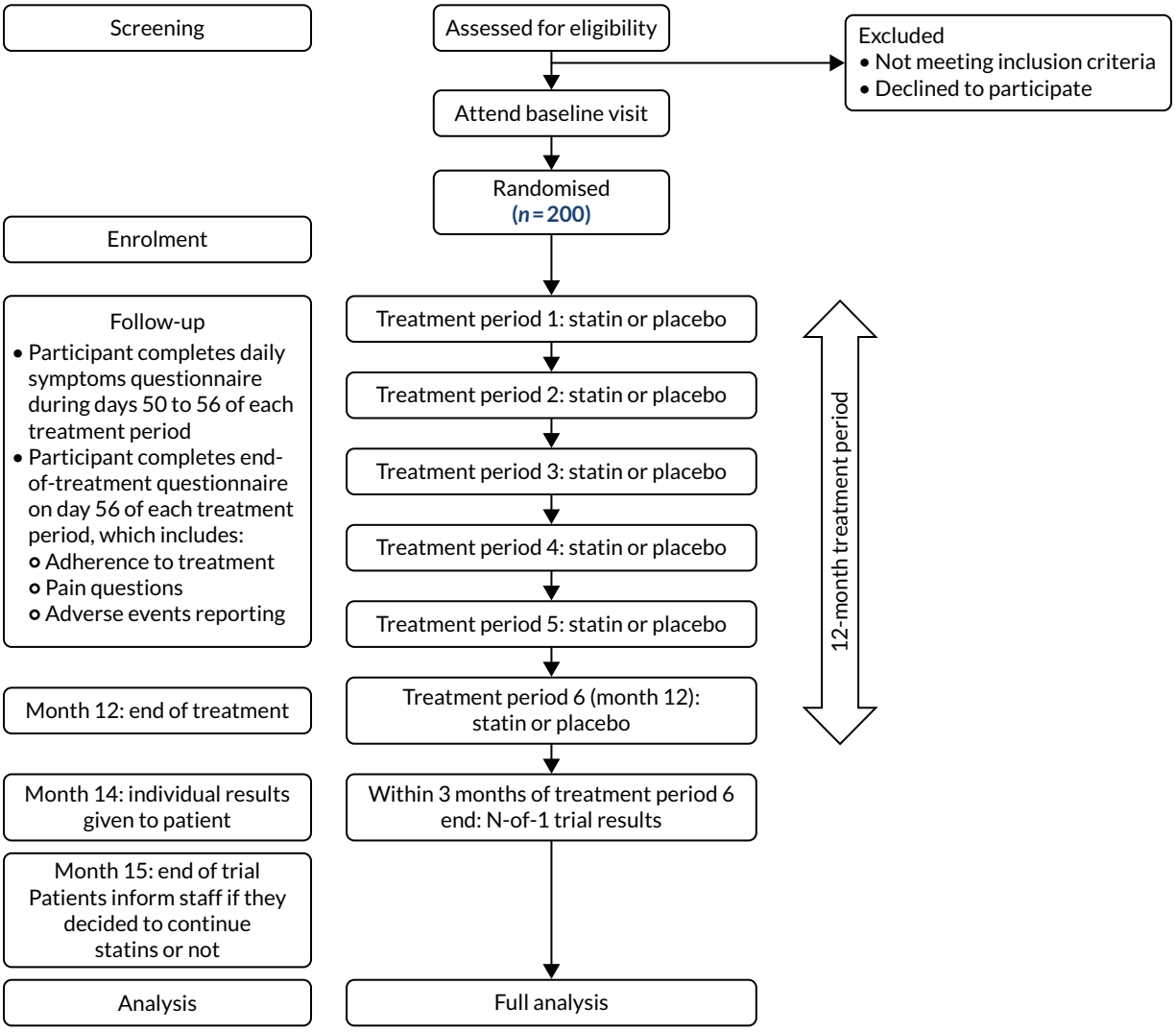

FIGURE 1 The trial overview. This figure has been reproduced from Herrett *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Study participants

Participants were recruited from general practices in England and Wales and either were considering discontinuation of their statin because of muscle symptoms or they had stopped taking a statin in the last 3 years because of muscle symptoms.

The inclusion and exclusion criteria for patient eligibility were as follows.

Inclusion criteria

- Adults (aged $\geq$ 16 years).
- Registered in a participating general practice.
- Previously prescribed statin treatment in the last 3 years.
- Stopped or considering stopping statin treatment because of muscle symptoms.
- Provided fully informed consent.

Exclusion criteria

- Any previously documented serum alanine aminotransferase levels at or above three times the upper limit of normal.
- Have persistent, generalised, unexplained muscle pain (whether or not this was associated with statin use) and have creatinine kinase levels greater than five times the upper limit of normal.
- Any contraindications listed in the summary of product characteristics for 20 mg of atorvastatin (see *Appendix 2*).
- Should not participate in the trial in the opinion of the general practitioner (GP).

Procedures

The trial treatment consisted of once-daily oral administration of 20-mg atorvastatin capsules, which was compared with a matching placebo (microcrystalline cellulose). The treatment phase of the trial consisted of six treatment periods of 8 weeks' duration each (i.e. 56 daily capsules). During each treatment period participants received 20 mg of atorvastatin or placebo. A blinded placebo, identical in size, colour, smell and packaging to the active statin, was chosen to prevent knowledge of treatment from affecting symptom scores.

All treatment packs were stored in a temperature-monitored room with temperature-controlled refrigeration units at the London School of Hygiene & Tropical Medicine. Each 8-week supply of allocated treatment was posted to the patient by the trial team. Patients were contacted to ensure that they had received the correct treatment pack and to confirm the date when they would start the new treatment period. Alternatively, patients could access the trial electronic data capture (EDC) system themselves and enter their treatment pack number and start date.

The start date that was entered into the EDC system was used to calculate the dates for data collection for that treatment period. Reminder notifications for sending the next treatment pack were also generated by the EDC system, and the next treatment pack would be sent by the trial team. Patients were provided with prepaid stamped envelopes to return each treatment pack once completed. Patients were also given written instructions (included on the inside of the treatment pack) on how to take the study medication. A freephone telephone number was provided for patients to call if they had any questions.

Patients were asked to take one capsule orally once daily at a time of day that was convenient to them, and to try to take it at a similar time each day. If patients suffered any difficulties when taking the capsules, changing the time of the day that the medication was taken was an initial option offered

to them. Stopping the medication with a short treatment break was also offered to patients if they were experiencing any adverse symptoms. Patients were advised to consult their GP if symptoms persisted.

Adherence to the study was monitored as part of the data collection. Monitoring returned packs for drug accountability against the reported data collection was also undertaken.

Dose selection

Atorvastatin is recommended by the current National Institute for Health and Care Excellence (NICE) guidelines for lipid modification,[26] and 20 mg is the recommended dose for primary prevention of CVD. Atorvastatin is also recommended by NICE for secondary prevention;[26] for patients with a high risk of adverse events (our patient population), a dose of < 80 mg is recommended.

Outcome measures

The primary outcome was self-reported muscle symptoms, defined as pain, weakness, tenderness, stiffness or cramp to the body of any intensity. The primary outcome was measured each day using a validated visual analogue scale (VAS) (range 0 to 10 cm)[27] for the last 7 days of each treatment period. We aimed to collect symptoms using a web-based database or mobile phone app (application), but our patient representatives recommended that participants should also be permitted to submit their scores over the telephone or by paper questionnaire. Participants reporting by telephone were asked to score their symptoms on an analogue severity scale and, thus, did not use a VAS. Measuring symptoms during only the last week of each 2-month treatment period was designed to avoid any carryover effect.

Secondary outcomes were collected on the last day of each 2-month treatment period. These included whether or not patients reported that they believed their symptoms were caused by the study medication, the site of muscle symptoms and VAS scores 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 patient believes were attributed to the study medication. Adherence to study medication was self-reported and verified by a count of returned treatment packs containing the trial medication. Three months after the end of the final treatment period, we determined if the participant continued or ceased statin treatment and the relationship to their primary outcome, as well as whether or not patients found their own trial result helpful in making the decision about future statin use.

Number of participants needed

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

Power calculations

Our power calculation was performed via simulation.[28] Data were generated under the proposed study design using the parameters detailed below. The generated data were analysed following the proposed primary analysis. The empirical power was determined as the proportion of such generated samples in which the p-value was < 0.05.

Minimum clinically significant difference in visual analogue scale pain score (10 mm, i.e. 1 unit)

This value was chosen to represent the smallest VAS change in pain that 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 setting[29–32] both concluded that the smallest change in VAS pain score corresponding to 'a little more' or 'a little less' pain was 13 mm, with 95% confidence intervals (CIs) of 10 to 17 mm and 10 to 16 mm, respectively. We took the lower limit of the CI to represent the smallest change likely to be perceived as beneficial.

Within- and between-participant variability in visual analogue scale 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 effects[33] (data obtained by approximation from figures presented in Breivik *et al.*[33]). These variance components can be poorly estimated; therefore, we took values from the higher end of the CIs, giving conservative estimates of these components.

Sample size

A sample size of 64 participants provides approximately 90% power to detect a treatment effect of at least 10 mm, 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 because of factors other than randomised treatment, e.g. seasonal, activity related), variability in individual statin effects across patients, imperfect adherence to the assigned treatment and potential non-normality of the distribution of VAS pain scores were investigated by further detailed simulations. 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 $\geq$ 90% power across a plausible range of these potential effects; thus, we determined that a final sample size of 200 was required.

Multiple testing

Rather than making formal adjustments for multiple testing, we follow an approach advocated by Pocock[34] of clearly specifying our primary analysis (which provides a single test for treatment effect), while explicitly presenting and interpreting all other tests as secondary analyses.

Power for individual N-of-1 trials

To increase the statistical power for the analysis of individual N-of-1 trials, we asked participants to report symptoms daily in the last week of each period, rather than once per period. Full adherence throughout the trial would provide between 55% and 70% power to detect effects of $\geq$ 10 mm for individual treatment comparisons.

Estimates of recruitment and retention rates

We anticipated that some patients will not provide complete data in each treatment period, and that some would not complete their 12-month follow-up. By designing this study as a series of N-of-1 trials, which offer individual participant benefit in the form of an individualised estimate of effect, we hoped to minimise this type of dropout. However, we accounted for this in our sample size calculation by allowing for 40% loss to follow-up.

Randomisation and masking

Randomisation codes were generated and held securely by the clinical trials unit (CTU) information technology (IT) team at the London School of Hygiene & Tropical Medicine, which was independent of

the StatinWISE trial management team, maintaining the blinded processes. Eight treatment sequences were defined (*Table 1*) and given an equal corresponding range of values between 0 and 1. Then, a series of random numbers between 0 and 1 were generated and matched to a treatment sequence, producing the randomisation list. The codes were made available to a Good Manufacturing Practice-certified clinical trial supply company (Sharp Clinical Services, Rhymney, UK) for the treatment packs to be manufactured in accordance with the randomisation list that was established in sequence from 1001 to 1200 in the EDC system.

Patients were randomly allocated to receive a sequence of blinded placebo or atorvastatin treatment by the research nurse/general practice trial team and entered into the EDC system and associated with a treatment sequence allocation. Treatment blocks were stratified to ensure that (1) all participants received one period of statin and placebo in their first two treatment periods (in a random order) and (2) no participant would be allocated to three sequential periods of the same treatment. Treatments were therefore allocated in three paired blocks (statin–placebo or placebo–statin) of treatment, with patients completing six treatment periods of 8 weeks' duration each (i.e. 56 daily capsules). Each individual was randomly allocated (with equal probability) to one of the eight sequences (see *Table 1*).

Atorvastatin and the placebo were in capsule form and identical in appearance. DBcaps® capsules (Capsugel®, Morristown, NJ, USA), which have a unique locking mechanism to help with assuring the integrity of the blind, were used for overencapsulation of both the atorvastatin and the placebo treatments. The treatment packs were packaged in boxes of six, in line with the eight sequence options as per the randomisation code. Patients were recruited and allocated a sequence in order of entry on to the EDC system (see *Table 1*). Patients, general practice staff and trial staff were blind to the allocation in each period.

A visually matched placebo was chosen as an appropriate comparator for two reasons. First, patient expectation of symptoms when on statins is likely to affect their experience of symptoms. A placebo control should minimise bias arising from knowledge of allocation. Second, withholding statin treatment from patients during placebo treatment periods is justified because the trial recruited patients who had recently stopped using statins (and, therefore, were not currently receiving any benefit from statins) and those who wished to discontinue. If patients in the trial tolerate the active treatment periods with few symptoms, then this trial is likely to increase their use of statins in the long term.

TABLE 1 The treatment sequences in StatinWISE

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

P, placebo; S, statin.

Data collection

This trial was co-ordinated from the CTU at the London School of Hygiene & Tropical Medicine and conducted at GP practices in England and Wales.

Baseline data were collected and entered online to the trial database provided by the London School of Hygiene & Tropical Medicine CTU. Follow-up data were collected directly from each patient at the end of each 2-month period.

Patients were allowed to choose the method of data collection that was most suitable for them from the following:

- Bespoke mobile phone app that required patients to use their own smartphone.
- Online database using a computer, mobile phone or tablet.
- Paper forms that they received by post at the same time as their trial treatment and that they could complete themselves or with the help of a trial team member by telephone if they so requested. Trial staff would telephone the patient on each data collection day and complete the questionnaire based on the patient's answers.

A sensitivity analysis was performed to assess any evidence of symptom scores varying between participants using different data collection methods.

For patients with a smartphone who chose to submit outcome data using the trial's bespoke mobile app, the GP, principal investigator (PI) or research nurse helped the patient to install and set up the app. The GP, PI or research nurse also gave a demonstration to ensure that the patient understood how to use it. Each GP, PI or research nurse had access to the internet so that the patient could download the app without using their own mobile network (ensuring that download of the app was free of charge to the patient).

The GP or research nurse also showed the patient how to complete the symptoms data for the baseline form using their preferred method. Any questions were addressed at this stage. Once baseline procedures were completed and the patient was confirmed as being eligible and consented, the patient would then be allocated to a randomly selected sequence of treatments.

A screening log was 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 remained at the relevant research site and only anonymised information regarding number of screened patients and number and reasons for screen failure was shared with the CTU.

Data outlined on only the baseline, follow-up, end-of-trial and adverse events data forms were collected as part of the trial database.

Treatment phase follow-up data

In the seventh week of each treatment period, patients received reminders (format agreed at baseline) to alert them that follow-up data collection was approaching. During the eighth week of each treatment period, the patient questionnaire and VAS pain scale forms were completed by the patient. Patients could choose to receive daily reminders on each day that their data were due to be collected. Non-responders would automatically receive a reminder from the trial team 24 hours after the due date.

End-of-trial data

During the seventh week of treatment period 6, the GP, PI or research nurse contacted patients to thank them for their participation so far and to inform them that this was the last treatment period

and inform them that they, together with their GP, the PI and research nurse, would receive their individual results at the beginning of month 14. The research nurse and patient arranged a telephone or face-to-face appointment to discuss the individual results during month 14. The research nurse also informed patients, that if they wanted to continue taking a statin without a break, they should arrange a separate clinical appointment with their GP prior to the end of the treatment period.

At month 15, trial staff contacted the patient to document their decision on future statin use and whether or not the results helped them to reach this decision. This was the last data collection point of the trial.

Throughout the trial, continued patient care was at the discretion of the patient's GP. In primary care, the patient was recorded as having an ongoing statin prescription.

Where treatment with an interacting drug was needed and the duration was expected to be less than 1-month, the patient was be asked to stop the trial treatment for that period.

If treatment with an interacting drug was needed and was expected to be for more than 1 month, the patient was asked to withdraw from study treatment completely.

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

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

Patients reporting intolerable symptoms

The GP remained the first point of contact for patients during the trial for their care. Intolerable muscle symptoms were to be reported to the GP, who provided clinical care as directed by the appropriate NICE guidelines. *Figure 2* shows the decision-making pathway for the GP and the patient in the case of patients reporting intolerable symptoms.

If patients experienced intolerable muscle symptoms and who did not want to be withdrawn early from the trial, the GP was asked to confirm that the patient still met the trial eligibility criteria. Patients who continued to meet the eligibility criteria could be offered the following options by the GP, depending on the GP's clinical judgement:

- continue with 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.

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

Early withdrawal of patients from the trial

Patients were free to change their minds about participation at any time. We advised that the patient see their GP to discuss future routine care. GPs were able to withdraw a patient at any time if clinical concerns arose or if the patient presented with any reason to stop atorvastatin as described in the summary of product characteristics for 20 mg of atorvastatin (see *Appendix 2*). In each case, an end-of-trial form was completed.

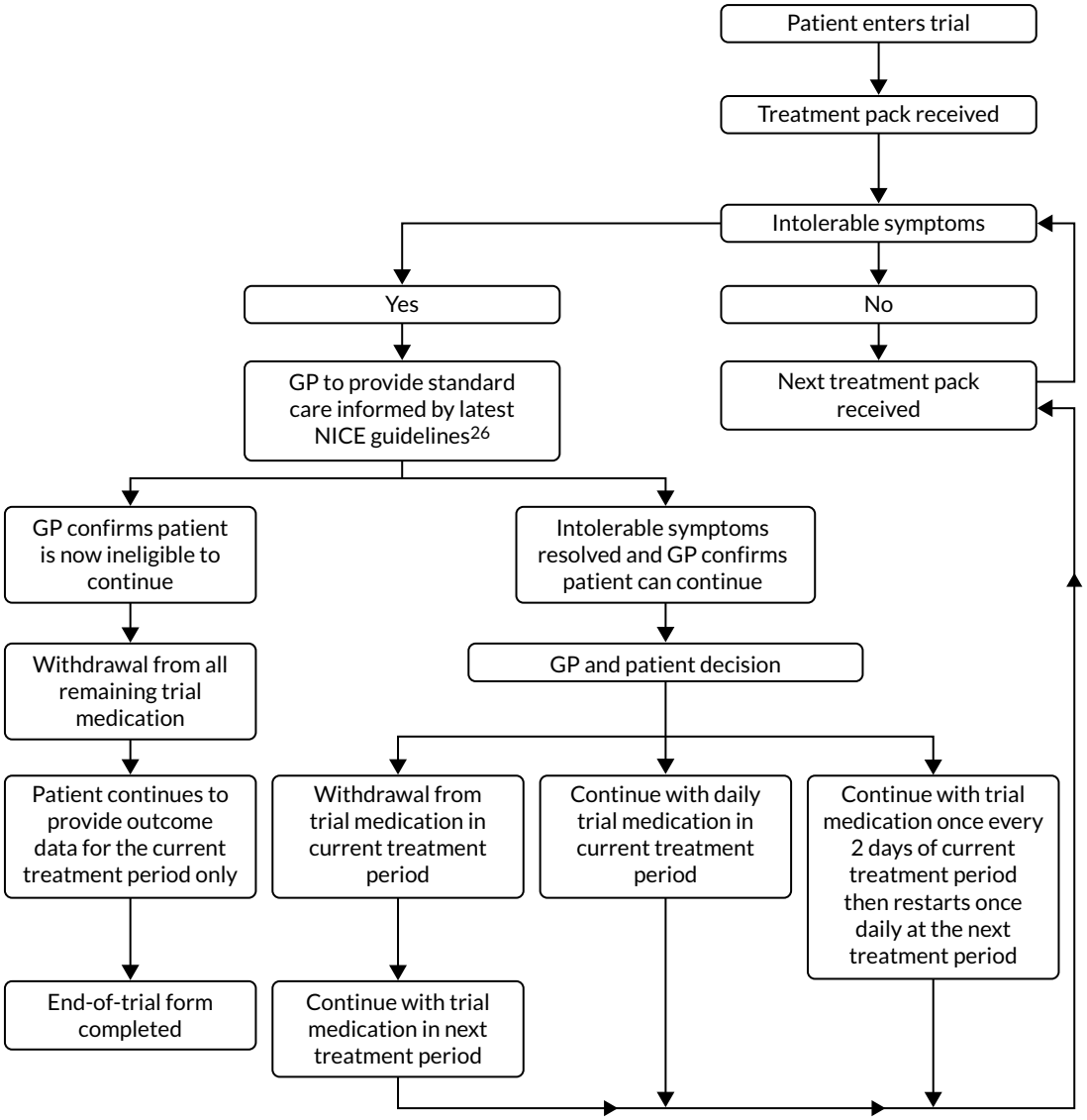

FIGURE 2 Intolerable symptoms pathway. Note that withdrawal from the trial at any time is possible (the patient should visit their GP and complete a withdrawal form). This figure has been reproduced from Herrett *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Statistical methods

Full details of the statistical analysis methods and the plan can be found on the project page (www.journalslibrary.nihr.ac.uk/programmes/hta/1449159/#/documentation; accessed May 2020).

Individual N-of-1 trials

At the end of the trial, patients were shown numerical and graphical summaries of their individual data in relation to their statin and placebo periods, and were asked if this was helpful and whether or not they would restart a statin. See the project page for an example of a personalised results document (www.journalslibrary.nihr.ac.uk/programmes/hta/1449159/#/documentation; accessed May 2020).

Combined analysis of N-of-1 trials

To estimate the population-average estimate of the trial treatment on VAS muscle symptom scores, data from each N-of-1 trial were aggregated. The primary analysis included all patients who provided

a daily VAS symptom score at least once during a treatment period with the statin and at least once during a treatment period with placebo. The primary analysis was a linear mixed model for VAS muscle symptom scores with random effects for participant and treatment. Residual errors were modelled using a first-order auto-regressive error structure within each treatment period to account for correlation between the seven daily measurements, with robust standard errors to account for non-normality of the VAS scores. Although VAS muscle symptom scores are not normally distributed, analysing such data using normal-based methods is likely to be a sufficiently robust approach.[27] All tests were two-sided, with a p-value of < 0.05 being considered as statistically significant.

Period effects and robustness of conclusions to the correlation structure of residual errors were explored in a sensitivity analysis. The length of treatment periods in our study was chosen so that carryover effects would be avoided.

Secondary analyses

The single binary measure of whether or not the participant reported having muscle symptoms during that treatment period was assessed using a logistic mixed model with random participant and treatment effects. This binary measure was then combined with the follow-up question pertaining to attribution, to obtain a single binary measure of whether or not the participant reported having muscle symptoms that they attributed to the study medication, and was analysed using a logistic mixed model with random participant and treatment effects. We also repeated the primary analysis, setting patients' pain scores to zero if they reported that their symptoms had a non-statin-related cause.

Secondary outcomes measured using VASs relating to the impact of the statin on other aspects of life were analysed in a similar manner to the primary outcome, omitting the auto-regressive correlation structure because these secondary outcomes were measured once per treatment period. Whether or not the excess muscle symptoms (if any) that were experienced during treatment periods with the statin appeared to be concentrated in multiple sites was investigated.

Graphical and descriptive summaries were used to explore how discontinuation and adherence related to the statin and placebo periods. Linear mixed models for continuous measures of adherence with random participant and treatment effects were fitted.

We related the patients' decision regarding future statin use, and whether or not the participant found their own result helpful in making their subsequent treatment decisions, to their individual estimated effect of the statin.

Protocol changes

Prior to any patients being randomised to the trial, an addition was made to the exclusion criteria: excluding any patients with any contraindications to the summary of product characteristics for 20 mg of atorvastatin.

Adverse events were also changed to be reported if they met the outlined criteria for a serious adverse event on the protocol, and not only those resulting in a hospitalisation/death.

After an initial slow period of recruitment, an advertising campaign was launched to promote the trial in GP practices. Patients could contact the CTU at the London School of Hygiene & Tropical Medicine directly, expressing their interest in participating. They would then be sent a letter requesting their GP's details. The CTU would then contact the GP for confirmation of the patient's suitability for the trial. Patients would then be screened at William Harvey Heart Centre at Barts and The London School of Medicine and Dentistry, Queen Mary University of London. The recruitment pathway for the trial was subsequently updated to incorporate this process, as well as amendments made to the patient

information sheet. However, only one patient was recruited via this pathway. The recruitment period was also extended after recruitment began, although working to the same sample size.

The consent form was also amended so that consent to participate in the optional genetic study was captured on a separate form to that of consent to participate in the trial itself.

Patient and public involvement

Three patient representatives were on the Trial Steering Committee (see *Appendix 1*). A StatinWISE patient involvement group provided feedback on the trial design, patient information sheet and data collection tools. Their input and views shaped aspects of the design, specifically around the logistics of drug postage and return, the drug packaging, the phrasing of questions for the outcome measures, the format of the data collection tools that were patient facing, and the content and wording of the patient information sheet. The group continued to be involved throughout the course of the trial, including providing substantial input into the individual participants' results feedback document. Patient representatives also provided active input into the interpretation of the results and their presentation. They will also play an important role in designing materials for dissemination.

Approvals

StatinWISE was given a favourable opinion by the South Central Hampshire Research Ethics Committee (16/SC/0324) and regulatory approval (17072/0009/001-0001).

Role of the funding source

The trial was funded by the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme. The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The writing committee had full access to all data in the study and had final responsibility for the decision to submit for publication.

Chapter 3 Main results

Recruitment and participant flow

Two hundred patients were recruited between December 2016 and April 2018. The first patient was enrolled on 20 December 2016 and the last patient's last follow-up took place on 5 July 2019.

Baseline data

The median age was 69.5 years [interquartile range (IQR) 63–76 years] and 115 (57.5%) participants were male (*Table 2*). Fourteen participants (7.0%) were current smokers, 105 (52.5%) were ex-smokers, 33 (16.5%) had diabetes and 140 (70.0%) had a history of CVD. The mean total cholesterol level was 5.4 mmol/l [standard deviation (SD) 1.4 mmol/l].

Table 3 shows the numbers of participants allocated to each sequence of treatment over the six trial periods.

TABLE 2 Baseline characteristics

Characteristic	Frequency	%
Total patients	200	100
Age (years)		
Mean (SD)	69.1 (9.5)	
Age category (years)		
35–49	7	3.5
50–64	49	24.5
65–79	115	57.5
≥ 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

continued

TABLE 2 Baseline characteristics (*continued*)

Characteristic	Frequency	%
CVD history		
No	60	30
Yes	140	70
Cholesterol level (mmol/l)[a]		
Median (25th, 75th percentile)	5.3 (4.4, 6.2)	
QRISK2® (ClinRisk Ltd, Leeds, UK) score for participants with no history of CVD		
Median (25th, 75th percentile)	18.3 (9.6, 28.8)	

SD, standard deviation.
a One value missing.

TABLE 3 Frequency of different treatment sequences in the trial

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

P, placebo; S, statin. Treatment sequences in StatinWISE.

Data collection methods

Table 4 shows the details of the method chosen to collect outcome data. Around half of the participants chose to collect data using the paper form. A total of 88 participants (44%) chose to fill in the online form and 17 participants (8.5%) submitted data by telephone.

Numbers analysed

Figure 3 describes participant flow through the trial. A total of 151 out of 200 (75.5%) randomised participants provided one or more VAS measurements in a placebo period and one or more in a statin period and are therefore included in the primary analysis. A total of 86 (43.0%) participants did not complete the whole trial (two died, four were lost to follow-up and 80 withdrew).

TABLE 4 Data collection method chosen

Collection method	Frequency ($n = 200$)	%
Mobile app	2	1.0
Online	88	44.0
Paper	93	46.5
Telephone	17	8.5

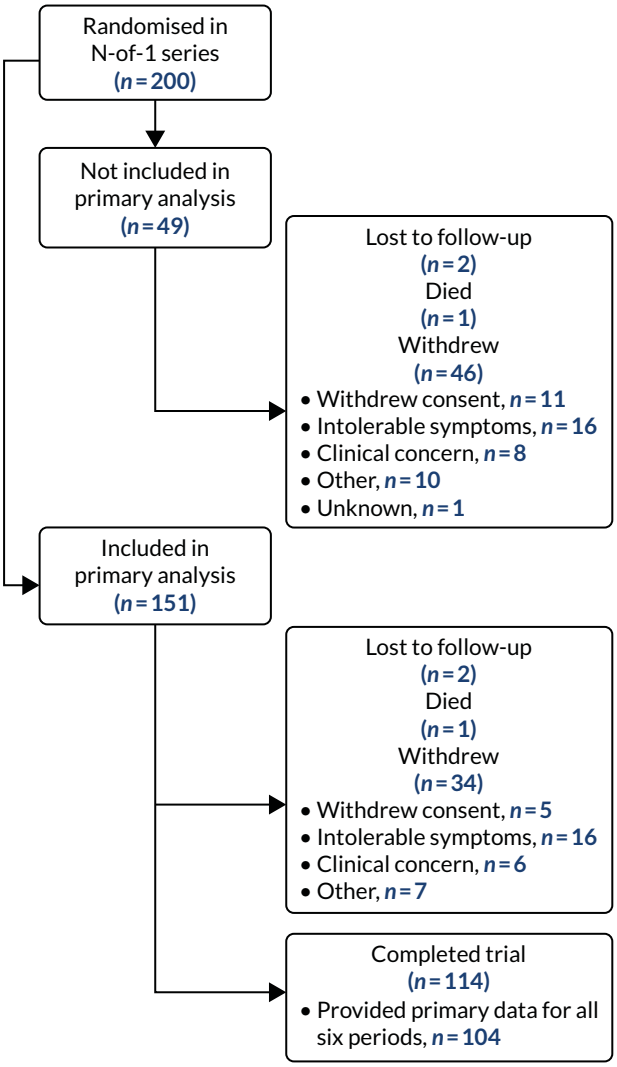

FIGURE 3 Recruitment and patient flow. This figure has been reproduced from Herrett *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

For the primary analysis of the daily muscle symptom scores, the linear mixed model was fitted on 151 participants, who contributed 5214 individual symptom score measurements (placebo, $n = 2576$; statin, $n = 2638$). The mean number of scores per participant was 34.5 (range 8–42). In period 1, 164 participants (82.0%) provided at least one daily report of muscle symptoms, which dropped to 149 participants in period 2 (74.5%) and 115 in period 6 (57.5%).

Outcomes

Primary outcome

Among the 151 patients who reported at least one primary outcome measure during a statin period and at least one primary outcome measure during a placebo period, there was no evidence of a difference in mean muscle symptom scores between statin and placebo periods (*Figure 4*; estimated mean difference statin minus placebo −0.11, 95% CI −0.36 to 0.14; $p = 0.398$). The observed mean muscle symptom score was lower during statin treatment periods (mean 1.68, SD 2.57) than during placebo periods (mean 1.85, SD 2.74).

The effect of statins on the primary outcome was not modified by the method of data collection (*Table 5*). *Figures 5* and *6* display summaries of the primary outcome measure (i.e. VAS scores) by period and randomisation sequence. *Figure 5* shows the trajectory of mean scores (daily patient VAS scores are averaged across the week and an overall mean is then calculated for each period in each sequence). *Figure 6* shows the trajectory of median scores (daily patient VAS scores are summarised for each period by the median and the overall median is then calculated for each period in each sequence). To indicate variability of the outcome measure, *Figure 6* also shows the IQR.

Table 6 provides descriptive summaries of the primary outcome by allocated sequence across the three paired treatment blocks.

Secondary outcome

Muscle symptoms without attribution to other causes

Among the 152 patients who contributed at least one secondary outcome measurement in a placebo period and one in a statin period (note that one additional participant provided secondary outcome data compared with primary outcome data), there was no evidence of an effect of statins on muscle symptoms overall [odds ratio (OR) 1.11, 99% CI 0.62 to 1.99], nor was there evidence of an effect of

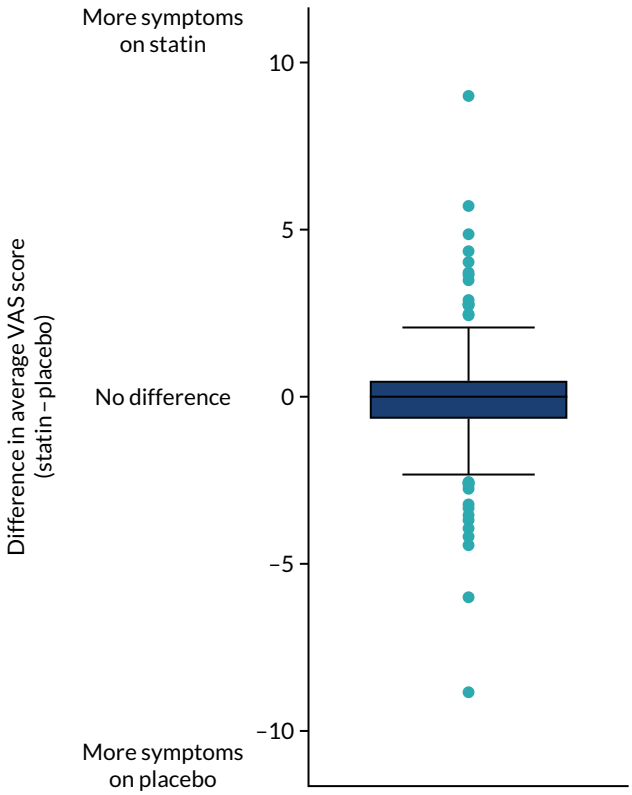

FIGURE 4 Box plot of mean difference in primary outcome (VAS daily symptom scores), comparing statin with placebo.

TABLE 5 Estimated treatment effect from a linear mixed model allowing the statin effect to vary by data collection method chosen

Data collection method	Estimated mean difference	95% CI	*p*-value[a]
Statin (method: online)	0.008	−0.358 to 0.373	0.968
Statin interaction parameters			0.594
App	−0.065	−0.704 to 0.574	
Paper	−0.159	−0.676 to 0.358	
Telephone	−0.681	−1.680 to 0.318	
Collection method			
Online	Reference		
App	0.563	−0.223 to 1.349	0.161
Paper	0.604	−0.081 to 1.289	0.084
Telephone	1.949	0.352 to 3.545	0.017
Constant	1.441	1.053 to 1.829	< 0.001

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

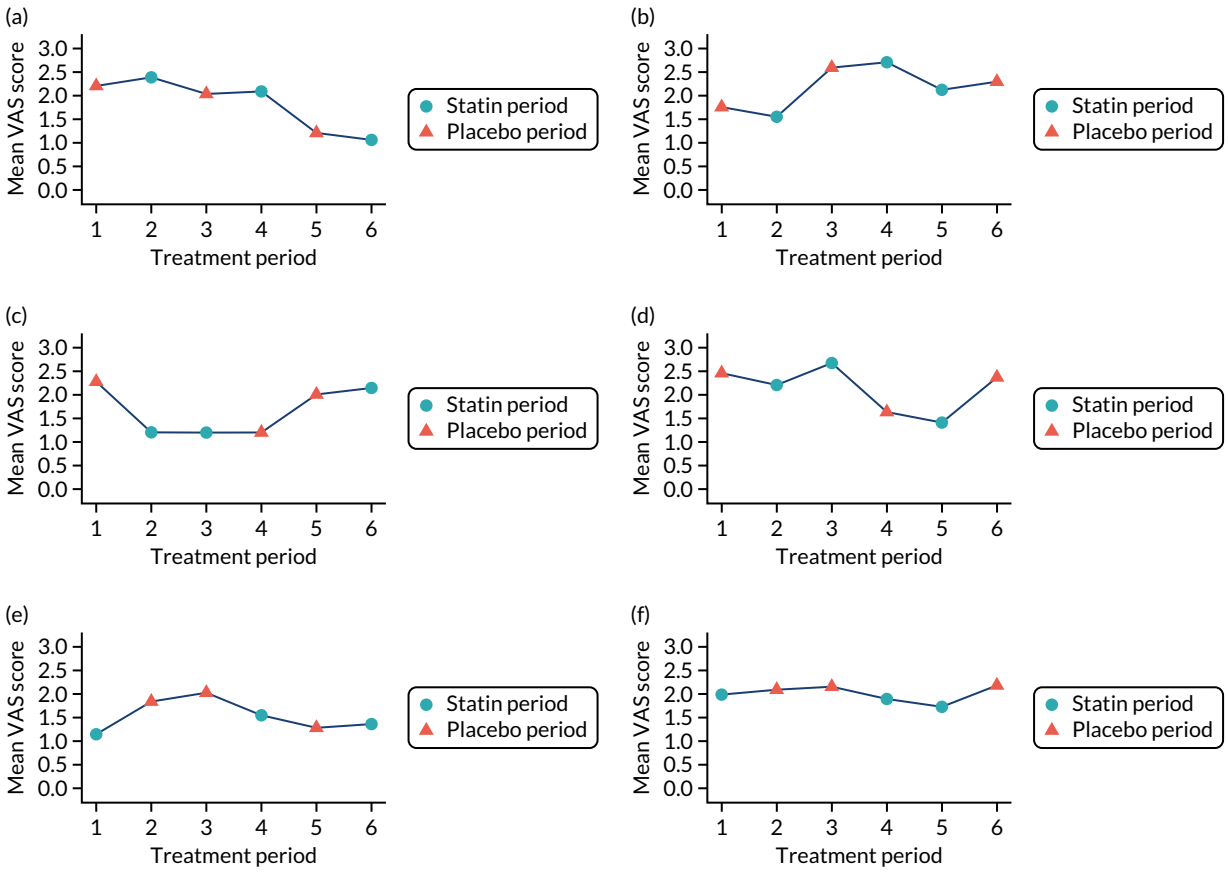

FIGURE 5 Trajectory plot of mean VAS scores by randomised sequence. (a) PSPSPS; (b) PSPSSP; (c) PSSPPS; (d) PSSPSP; (e) SPPSPS; (f) SPPSSP; (g) SPSPPS; and (h) SPSPSP. (*continued*)

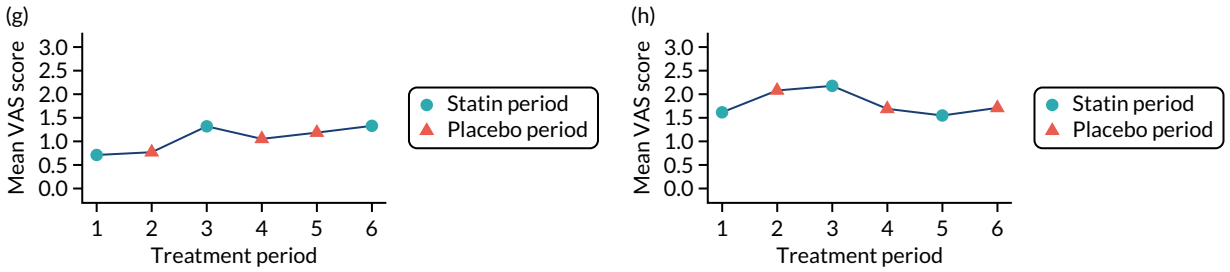

FIGURE 5 Trajectory plot of mean VAS scores by randomised sequence. (a) PSPSPS; (b) PSPSSP; (c) PSSPPS; (d) PSSPSP; (e) SPPSPS; (f) SPPSSP; (g) SPSPPS; and (h) SPSPSP.

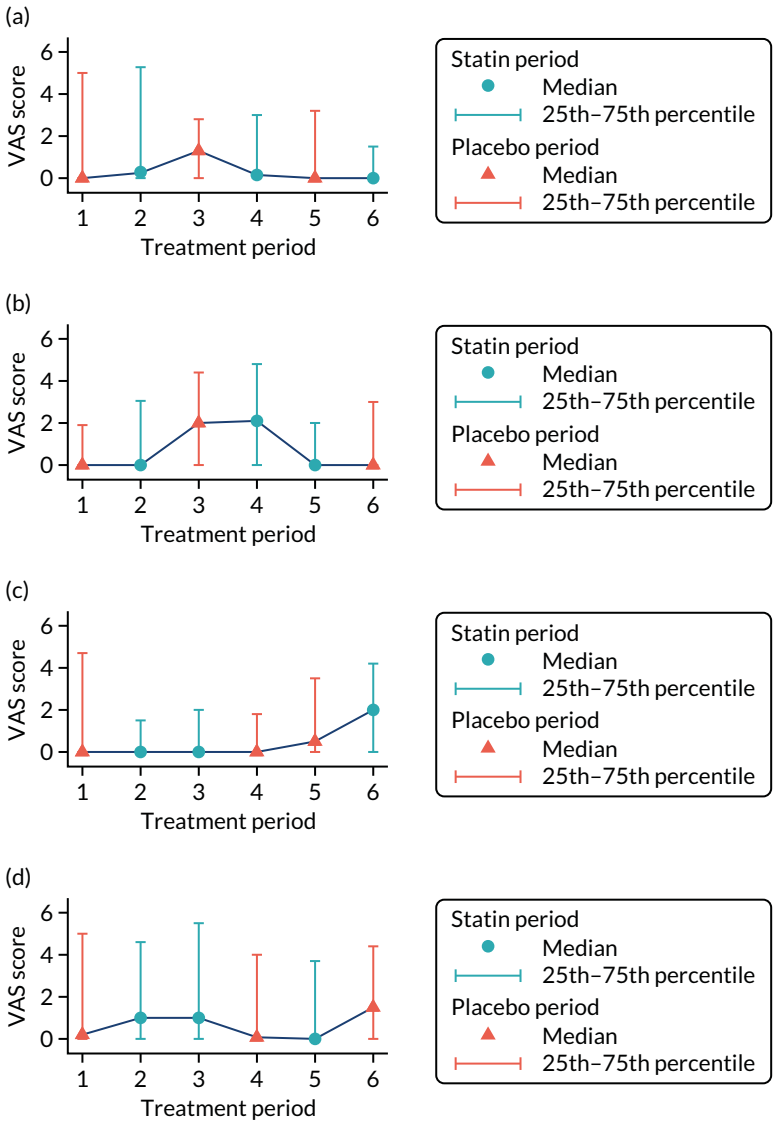

FIGURE 6 Trajectory plot of median VAS scores with IQRs by randomised sequence. (a) PSPSPS; (b) PSPSSP; (c) PSSPPS; (d) PSSPSP; (e) SPPSPS; (f) SPPSSP; (g) SPSPPS; and (h) SPSPSP. (*continued*)

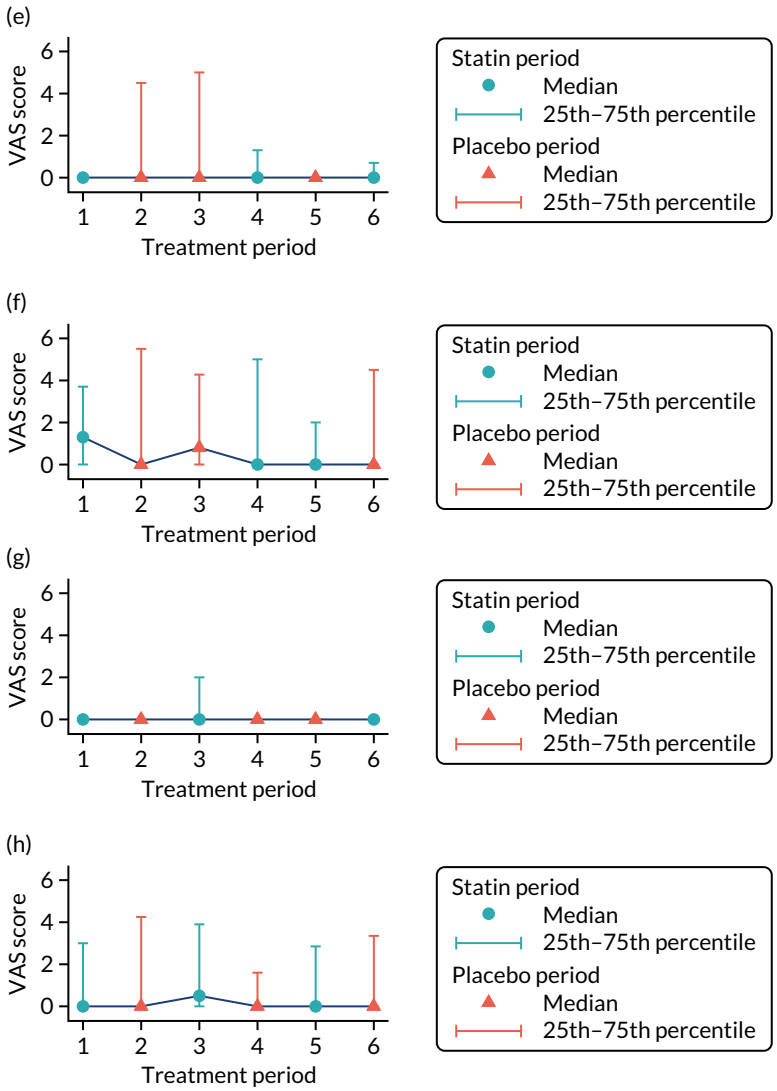

FIGURE 6 Trajectory plot of median VAS scores with IQRs by randomised sequence. (a) PSPSPS; (b) PSPSSP; (c) PSSPPS; (d) PSSPSP; (e) SPPSPS; (f) SPPSSP; (g) SPSPPS; and (h) SPSPSP.

TABLE 6 Summary of the primary outcome (daily VAS symptom scores)

Period	Placebo		Statin		Difference (statin – placebo)	
	Number of participants	Median[a] (25th, 75th percentiles)	Number of participants	Median[a] (25th, 75th percentiles)	Number of participants	Median[a] (25th, 75th percentiles)
All patients with reported scores						
1 and 2	158	0.4 (0, 3.9)	155	0.2 (0, 2.4)	145	0 (–1, 0.6)
3 and 4	121	0.6 (0, 3.2)	128	0.8 (0, 3.4)	118	0 (–0.4, 0.6)
5 and 6	115	0.3 (0, 3.4)	116	0.1 (0, 2.8)	115	0 (–0.5, 0.1)
Patients with at least one report in a statin period and at least one in a placebo period (i.e. included in the primary analysis)						
1 and 2	147	0.4 (0, 3.8)	148	0.4 (0, 2.4)	145	0 (–1, 0.6)
3 and 4	121	0.6 (0, 3.2)	128	0.8 (0, 3.4)	118	0 (–0.4, 0.6)
5 and 6	115	0.3 (0, 3.4)	116	0.1 (0, 2.8)	115	0 (–0.5, 0.1)

a Median of mean daily VAS scores across each period.

statins when restricting to muscle symptoms that could not be attributed to another cause (OR 1.22, 99% CI 0.77 to 1.94) (*Table 7*). In the case of the other secondary outcomes (e.g. general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life), there was no evidence of a difference in symptom scores between the statin and placebo periods.

Location of symptoms and other details

In total, there were 493 reports of muscle symptoms during a treatment period arising from 140 participants. Of these 493 reports, 481 (97.6%) included the location of the muscle symptoms. *Table 8* shows that the majority of reports (65%) were in the lower limbs, with comparatively fewer reports in the head and neck (3.7%).

Among the 481 reports of location of muscle symptoms, 312 had a report of multiple sites attached. *Table 9* shows a summary of these reports.

TABLE 7 Estimated OR/mean differences in secondary outcomes (from patient questionnaire) comparing statin periods with placebo periods

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

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

TABLE 8 Location of muscle symptoms reported

Location	Frequency ($n = 481$)	% of reports
Head and neck	18	3.7
Lower limbs	312	64.9
Trunk	73	15.2
Upper limbs	78	16.2

TABLE 9 Location of multiple sites of muscle symptoms reported

	Multiple sites reported				
	Yes		No		
Location	*n*	%	*n*	%	Total (*n*)
Head and neck	15	83.3	3	16.7	18
Lower limbs	190	60.9	122	39.1	312
Trunk	60	82.2	13	17.8	73
Upper limbs	47	60.3	31	38.7	78

Table 10 shows that, of the 493 reports, 71 also reported other symptoms that may be due to the study medication. Those reporting no other symptoms or 'don't know' have no further details recorded. *Table 11* shows descriptive summaries of the secondary outcome by allocated sequence, across the three paired treatment blocks. *Appendix 3* shows the other symptoms listed in the 71 reports mentioning other symptoms. No attempt has been made to analyse these data.

Withdrawals

Overall, 80 patients (40%) withdrew from the trial before the end of the 12-month treatment period. A total of 16 of these 80 patients (20%) withdrew informed consent, 32 (40%) reported intolerable muscle symptoms, 14 (17.5%) withdrew because of clinical concerns raised by their GP and 18 (22.6%) withdrew for other or unknown reasons. Of the 80 withdrawals, 34 (42.5%) were during a statin period, 39 (49.75%) during a placebo period and seven (8.75%) after randomisation but prior to any study medication being taken.

TABLE 10 Other symptoms reported due to study medications

Other symptoms reported?	Frequency (*n* = 493)	% of reports
No	248	50.3
Yes	71	14.4
Don't know	174	35.3

TABLE 11 Summary of the secondary outcome: binary measure of symptoms experienced in each period (patient questionnaire)

		Placebo		Statin	
Symptoms	Periods	Number of participants	Frequency (%)	Number of participants	Frequency (%)
Any muscle symptoms experienced?					
Muscle symptoms	1 and 2	156	95 (60.9)	157	97 (61.8)
	3 and 4	125	78 (62.4)	129	89 (69)
	5 and 6	115	69 (60)	117	65 (55.6)
Any muscle symptoms experienced, not attributed to other causes?					
Muscle symptoms due to study drug	1 and 2	156	76 (48.7)	157	83 (52.9)
	3 and 4	125	65 (52)	129	78 (60.5)
	5 and 6	115	61 (53)	117	58 (49.6)

More participants withdrew because of intolerable symptoms during a statin period ($n = 18$) than because of intolerable symptoms during a placebo period ($n = 13$). Conversely, the number of participants withdrawing because of clinical concern was greater during a placebo period ($n = 9$) than during a statin period ($n = 4$).

Figure 7 shows the withdrawal of patients broken down by treatment period and randomised sequence.

Adherence

Participant-reported adherence was confirmed through verification of the number of pills remaining in returned medication packs. Adherence to the study medication was high, with the proportion of participants reporting taking their study medication 'every day' or 'most days' being at least 80% during each period among participants who had not yet withdrawn (*Figure 8*).

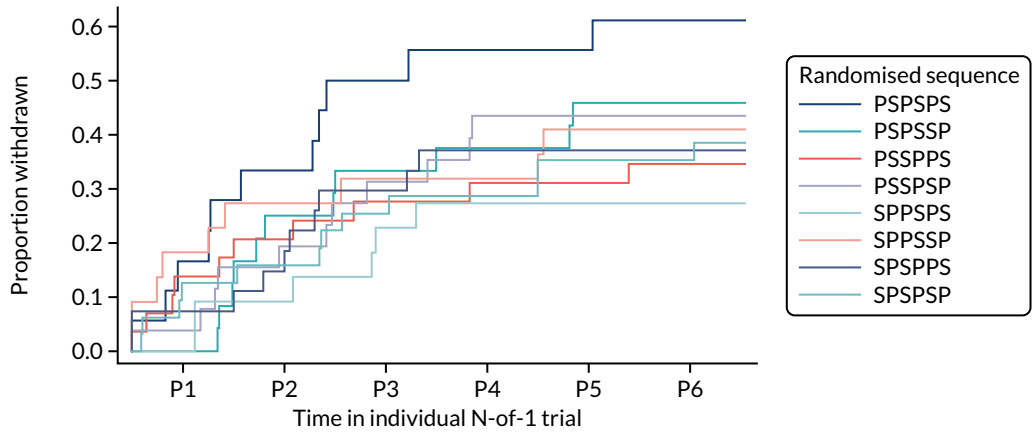

FIGURE 7 Withdrawals for each treatment period by randomised sequence. P, placebo; P1, period 1; P2, period 2; P3, period 3; P4, period 4; P5, period 5; P6, period 6; S, statin.

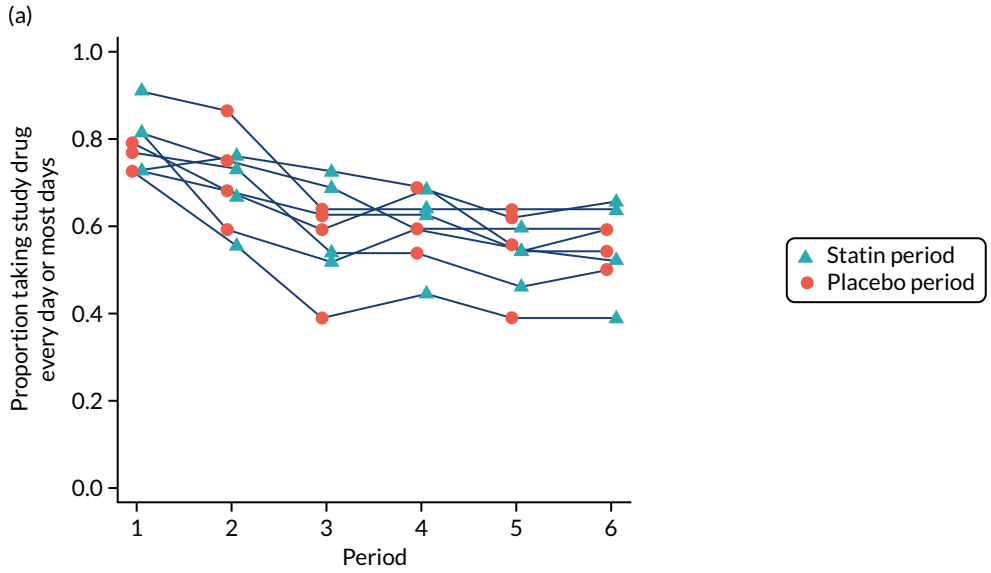

FIGURE 8 Adherence to study medication by period and sequence for (a) all recruited participants; and (b) those who had not yet withdrawn. This figure has been reproduced from Herrett *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure. (*continued*)

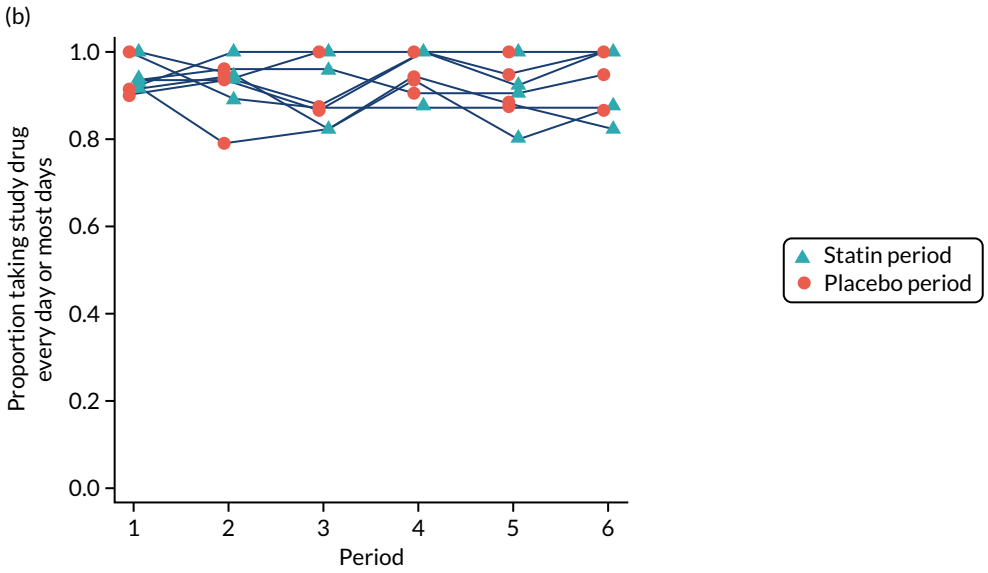

FIGURE 8 Adherence to study medication by period and sequence for (a) all recruited participants; and (b) those who had not yet withdrawn. This figure has been reproduced from Herrett *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Of the 114 patients who completed the full six treatment periods, 113 received their results during an end-of-trial discussion (56.5% of randomised participants) (one participant did not attend). At 15 months, 58 (51.3%) of these 113 participants had a prescription for statins, 74 (65.5%) said that they intended to resume statins and 99 (87.6%) said that their trial had been helpful (*Table 12*).

Adverse effects

During the trials there were 13 serious adverse events but none was considered attributable to the study medication. There were two fatal events (one during statin treatment and one after the end of treatment) and 11 non-fatal events (five during statin treatment and six during placebo).

No emergency treatment unblinding was needed.

TABLE 12 Experience of the trial for participants who completed their own N-of-1 trial and received results

Experience	Frequency (%) ($n = 113$)
Participant had a subsequent prescription for statin (by 15 months' follow-up)	58 (51.33)
Does participant intend to resume statins following trial?[a]	
No	25 (22.1)
Yes	74 (65.5)
Don't know	14 (12.4)
Patient found their trial helpful?	
No	13 (11.5)
Yes	99 (87.6)
Missing	1 (0.9)

a Or has had a statin prescription following the trial.

Chapter 4 Discussion

This series of N-of-1 trials recruited participants who either were considering discontinuation of their statin due to muscle symptoms or had stopped taking a statin due to muscle symptoms. We showed that, for the majority of participants, there were no differences in the frequency or severity of muscle symptoms between periods using statins and periods using placebo, among those who received at least one treatment period of each. In addition, there were no differences between statin and placebo periods for a range of secondary outcomes related to the effect of the muscle symptoms on aspects of participants' daily life. Although 25% of participants did not complete sufficient treatment periods to contribute to the primary analysis, 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. In addition, the study remained powered for the primary outcome. The majority of participants (87.6%) said that their N-of-1 trial had been helpful, with nearly two-thirds of participants reporting that they intended to resume statins or already had after the trial.

Thirty-two participants withdrew from the trial because of intolerable symptoms, and two further participants withdrew consent with support of their GP because of perceived muscle side effects. This was more common during statin periods and, therefore, we cannot exclude the possibility that a minority of patients may experience muscle symptoms caused by their statin. Crucially, among this highly selected population of participants who identified themselves as experiencing symptoms on statins that were severe enough to discontinue, withdrawal because of intolerable symptoms was uncommon and the excess comparing statins and placebo was only 2%.

Comparison with other literature

StatinWISE, along with the concurrent SAMSON trial,[35] are the first large-scale N-of-1 trials to investigate the effect of statins on muscle symptoms. Our findings largely support evidence from large systematic reviews and meta-analyses of randomised controlled trials, which have shown no effect of statins on muscle symptoms in the absence of myopathy,[3,4,22] despite being powered to have detected extremely rare and serious side effects of statins (e.g. rhabdomyolysis, myopathy, haemorrhagic stroke and diabetes[4]). An ongoing meta-analysis[36] is investigating adverse event data from statin trials, aiming to provide a complete understanding of any other statin side effects. Although our trial cannot exclude the possibility of side effects among a minority of participants, it clearly indicates that the majority of patients taking statins do not experience symptoms because of their statin, and highlights the importance of blinding when assessing side effects.

Observational studies have frequently reported muscle side effects,[37] and patients' experience of muscle symptoms during statin use frequently causes them to discontinue use. Various explanations have been offered for the high frequency of symptoms found in observational studies and clinical practice. First is the nocebo effect, in which expectations of adverse effects may have led patients to attribute muscle symptoms occurring during statin use to the statins themselves.[12] Second, muscle aches and pains are common among the age group taking statins, and so occur by chance during statin use, causing patients to misattribute their pain to statins.[38] Lack of randomisation and blinding in observational studies means that spurious effects of statins are more likely. Given the proportion of patients who intended to resume statin use after their trial, our result is also in agreement with observational data showing that statin re-challenge can be tolerated.[39,40]

Strengths

We collected data on muscle symptom side effects of statins as a primary outcome, in the setting of a blinded, placebo-controlled series of trials with randomised order of treatments to minimise bias and confounding. The within-patient design created superior power that was boosted in our study by repeated measurements in each treatment period, thus allowing us to investigate differences between statin and placebo with more precision.

Owing to the within-participant trial design, we were able to feed back to individual participants about whether their muscle symptoms occurred more frequently with statins or placebo and allowing them to decide for themselves whether or not to continue on statin treatment.

In delivering this series of trials, we have created a diagnostic tool allowing patients to empirically evaluate whether or not their symptoms are caused by statins. The N-of-1 trial is a complex design, but was made easy for patients as trial medications were delivered directly to patients through the post. This pathway of care could be adopted by clinicians who are looking to establish the best course of treatment for patients who present with statin intolerance.

Limitations

Although the overencapsulated statin and placebo were identical in appearance, we cannot exclude the possibility that a determined participant may have opened the capsules and unblinded themselves based on taste.

Of the 200 randomised participants, 86 did not complete the 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 sized to account for this level of dropout. Although overall withdrawals were not related to statin or placebo periods, withdrawal due to intolerable symptoms was more common during statin periods, and although it is recommended that GPs measure creatine kinase among patients experiencing such symptoms, this was not part of our trial protocol.

For simplicity and pragmatism, the trial assessed the effect of statins on muscle symptoms using 20 mg of atorvastatin only, so we are unable to extrapolate our results to other types of statins, to other dosages or to other outcomes that have been suggested to be statin related.[41]

Although we intended to collect outcomes using web-based methodology, over half of the participants preferred to report their symptoms on paper or by telephone.

Generalisability

Our results are generalisable to patients who are considering discontinuing statins or have already discontinued statins due to muscle symptoms, and who are willing to re-challenge or participate in an N-of-1 trial. The N-of-1 methodology is applicable to other clinical situations in which the causal effect of a drug on a transient symptom is questioned.

Chapter 5 Conclusions

The evidence from StatinWISE suggests that, on re-challenge among patients who have previously experienced muscle symptoms that they attribute to statins, 20 mg of atorvastatin has no effect on muscle symptoms at the population level. Among a group of patients selected as having reported muscle symptoms when previously taking a statin, a proportion did have more muscle symptoms while taking a statin rather than the placebo and decided not to continue with a statin in the long term.

Among individual patients, a majority of those completing the trial decided to restart statins. Therefore, the N-of-1 trial design could be a useful method of encouraging patients to find out whether or not statins are causing their pain and guide individual therapy.

Implications for practice

The evidence from our series of N-of-1 trials suggests that this methodology could be a useful tool to aid decision-making about future statin use and encourage patients to find out whether or not statins are causing their symptoms.

General practitioners who are managing patients who believe that they are experiencing muscle symptoms as a result of the statin that they are taking should be aware that the majority of StatinWISE participants did not experience a difference in symptoms between statin and placebo, although a small proportion did have more muscle symptoms during statin treatment.

Recommendations for future research

1. We would recommend that series of N-of-1 trials be undertaken for other types of statins, higher dosages and non-muscle symptoms that are frequently attributed to statins. In particular, we would recommend this methodology among patients with existing CVD who require higher statin doses than tested in our series of N-of-1 trials.
2. We would recommend that N-of-1 trials be used in the context of transient symptoms that occur during the use of other medications.

Acknowledgements

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Haleema Shakur-Still (https://orcid.org/0000-0002-6511-109X) (Professor of Global Health Clinical Trials) was involved in the design, conduct, analysis and reporting phases.

Ian Roberts (https://orcid.org/0000-0003-1596-6054) (Professor of Epidemiology and Public Heath) was involved in the design, conduct, analysis and reporting phases.

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Danielle Beaumont (https://orcid.org/0000-0002-2530-9608) (Senior Trial Manager/Research Fellow) was involved in the design and conduct phases.

Zahra Jamal (https://orcid.org/0000-0002-3817-6795) (Trial Assistant) was involved in the reporting phase.

Ben Goldacre (https://orcid.org/0000-0002-5127-4728) (Senior Clinical Research Fellow) was involved in the design and reporting phases.

Tjeerd van Staa (https://orcid.org/0000-0001-9363-742X) (Professor in Health e-Research) was involved in the design and reporting phases.

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Publications

Herrett E, Williamson E, Beaumont D, Prowse D, Youssouf N, Brack K, *et al.* Study protocol for statin web-based investigation of side effects (StatinWISE): a series of randomised controlled N-of-1 trials comparing atorvastatin and placebo in UK primary care. *BMJ Open* 2017;**7**:e016604.

Herrett E, Williamson E, Brack K, Beaumont D, Perkins A, Thayne A, *et al.* Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. *BMJ* 2021;**372**:n135.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 StatinWISE trial organisation

Trial Steering Committee

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Data Monitoring Committee

John Norrie (a member of the NIHR HTA and Efficacy and Mechanism Evaluation Editorial Board), Nicholas Mills and Hannah Castro.

Protocol Committee

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Trial Co-ordinating Team

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Trial Collaborators

Please see *Appendix 4* for a list of GP practices involved in the research.

The following staff were involved in the trial at the GP practices:

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Appendix 2 Summary of product characteristics for 20-mg atorvastatin 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.

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

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

Method of administration

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

4.3 Contraindications

Atorvastatin is contraindicated in patients:

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

4.4 Special warnings and precautions for use

Liver effects

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

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

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

Skeletal muscle effects

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

Before the treatment

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

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

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

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

Creatine kinase measurement

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

Whilst on treatment

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

Concomitant treatment with other medicinal products

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

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

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

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung 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>30kg/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 derivates 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

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

Ezetimibe

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

Colestipol

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

Fusidic acid

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

Effect of atorvastatin on co-administered medicinal products

Digoxin

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steadystate digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.

Oral contraceptives

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

Warfarin

In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and

frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Paediatric population

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings in section 4.4 should be taken into account for the paediatric population.

Table 1 Effect of co-administered medicinal product on the pharmocokintetics 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 pharamacokinetics 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 (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (≤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: Very rare:	allergic reactions anaphylaxis
Metabolism and nutrition disorders	
Common: Uncommon:	hyperglycaemia 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>30kg/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.

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

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

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

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

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

Acute coronary syndrome

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

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

Prevention of cardiovascular disease

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

Patients were treated with antihypertensive therapy (either amlodipine or atenololbased regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

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

Event	*Relative risk reduction (%)*	*No. of events (atorvastatin vs placebo)*	*Absolute risk reduction1(%)*	*P value*
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.

Table 3 Absolute and relative risk reduction effect of Atorvastatin in the ASCOT-LLA study

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:

Event	*Relative risk reduction (%)*	*No. of events (atorvastatin vs placebo)*	*Absolute risk reduction1 (%)*	*P value*
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.

Table 4 Absolute and relative risk reduction effect of Atorvastatin in the CARDS study

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 $\geq$ 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 $\geq$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 ≥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 AUC0-24h 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.

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

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1290

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/08/2010

10 DATE OF REVISION OF THE TEXT

02/09/2015

Appendix 3 List of other symptoms reported

The other symptoms reported were as follows:

- *Aches in fingers.*
- *Annoying itching under shoulder blades.*
- *Blood sugar levels is quite high I never had diabetic problems but since I have taken these tablet my blood sugar level is high.*
- *Calves on both legs have been very swollen, hard and very tender.*
- *Cough.*
- *Cramp – very slight for 2 or 3 days. Not bad.*
- *Cramp, nose bleeds.*
- *Cramps in leg. Muzzy head.*
- *Dry mouth sometimes.*
- *Experiencing a lot of cramps. Pains shooting through body. But seem to have a bit more energy and motivation.*
- *Feet losing sensation. This is why I gave up Atorvastatin in the first place. My feet appear to have stabilised since abandoning the medication but not gone back to their original state. But I am really not sure whether there is any effect so far on this regime.*
- *Forgetfulness.*
- *From Day 4 to Day 24 I had a headache, joint, muscle pain, burning. Pins and needles in my hand. After Day 24 it eased off, but still had pins and needles but not so bad. In the past 7 days the pins and needles have almost gone, my energy levels are up, as at past few weeks were low.*
- *Further difficulty rising from chair.*
- *Giddiness.*
- *Giddiness. Caused to have a couple of falls.*
- *Have pain in knees at times also.*
- *Have to think about going shopping etc as legs stiff when I get up after sitting and just don't walk far as I my legs just don't feel right.*
- *Headache. Tingling in fingers and toes and also a very warm feeling in fingers and toes. Lumber area just above the hips. Very dry throat. Calves on both legs. Diarrhoea. Dry throat. Very little sleep. Aching in all leg joints. Very unwell feeling.*
- *I also have problems with my discs in my neck, and the pain in that area has been a lot worse.*
- *I am becoming very sleepy and lethargic. Could this be caused by your medication?*
- *I am characteristically very active. The symptoms I suffer from is tiredness and lethargy.*
- *I am irritable, muzzy head ache and lack of energy.*
- *I have a pre-existing condition, Discitis, resultant of a Microdiscectomy L5/S1 in October 2016, Discitis diagnosed 20th December 2017. Throughout 2017 recovery has been slow with constant pain (scale 1 to 2) developing to higher levels following manipoulation*[sic]*/exercise (Scale 3 to 5). In October 2017 I had a bout of Sciatica which resolved itself by mid December 2017. I have experienced 'tingling' in calf muscles and minor cramps in same areas but only occassionally* [sic]*. Thus I am unsure as to whether this is due to pre-existing or Statinwise medication.*
- *I have had an increase in weight caused by medication. Hungry all the time.*
- *I have had pains in the back of my calves for some time.*
- *I have suffered restless leg syndrome on quite a few occasions. This occurred only when returning to bed for the night. Some nights were worse than others, which I needed to take medication to ease the discomfort (co-codamol). I spoke to the study nurse and she advised that I stop taking my statin tablet for 2 days while an appointment could be made for me to see the doctor. After seeing the doctor he stated that I should carry on taking the statin and if I had any discomfort with the restless legs I should just carry on taking the co-codamol to which he has now prescribed for me. Please note that there are two tablets left in the pack and also I had to use one of spares as when I took the tablet out of the foil it was broken.*

- *I was feeling very slow. Lazy. My back was stiff. Rather painful. I had difficulty in general movement. I am suffering from sciatica pain in my back and left leg. I have contacted my GP and he has sent me for blood tests. I am waiting for blood results.*
- *I've been struggling during exercise with general lack of energy. Not sure if this was the drugs or not and it was worse at the start of June I'd say. Was cycling regularly and always struggling and not showing any sign of improvements whatsoever which I felt was unusual. Some arm aches too . . . upper arms that is. My legs also felt weak during exercise. I did have a virus of sorts back in May and I wouldn't like to say whether I'd fully shaken that off (or not).*
- *Irritable and lack of energy.*
- *Leg ache (both legs) occasionally at night.*
- *Leg cramp – a new thing to have.*
- *Loose bowels – going 3 times a night. Have to get up. Need to think about being near a toilet from the morning – impacts on all aspects of life. Varicose veins – discussed with GP.*
- *More tingling and numbness in my fingers, hands and toes.*
- *Muscle pain in upper arms, shoulder and sometimes neck.*
- *Muscle weakness. Cramps in right leg. Also in arms. Unsteadiness on feet (as if drunk).*
- *NO PAIN, ONLY STIFFNESS.*
- *Nightmares, cramps, blurred vision, fatigue.*
- *Nose bleeds.*
- *Nose bleeds.*
- *Nose bleeds.*
- *Occasionally pain in upper arms. Tingling in left hand.*
- *Pain in all joints, but particularly knees.*
- *Pain in back under shoulder blade and some pain in left thigh the back pain has been constant for about two weeks leading me to believe that the first month I want taking statics but this month I am. Although the first month I have to say going to the toilet which is normally regular was changed dramatically. I also often get pin and needles and numbness when I sit in the same position for a while or even sleeping.*
- *Pain in joints.*
- *Pain in my legs. Tight chest. Out of breath.*
- *Patient felt a worsening of muscle symptoms and pain, but also general pain. Patient generally did not feel good this period.*
- *Periodic cramp-like symptoms in the left calf muscle might be attributed to a pre existing condition (L5/S1 nerve root/nerve damage, However, the cramp was specific to the area as opposed to elsewhere on the siatic* [sic] *nerve path in the leg. Therefore it is possible the cramps were cause by statins assuming my intake wasn't placebos.*
- *Possibly?? Burning sensation in my legs – between my ankles and knee – for 7/10 days during January.*
- *Possibly sever cramp [i]n left leg from foot to hip.*
- *Sensation of burning in my legs knee to ankle area over a period of –10 days in early December. Possibly treatment related???*
- *Severe ache to left neck/shoulder.*
- *Sex drive has plummeted.*
- *Sleep disturbance and nightmares.*
- *Some pain in lower back area and right shoulder.*
- *Sometimes felt lack of energy, but like flu-like symptoms. Which didn't like but, glad to say didn't last all day/have everyday. Also breathless at times.*
- *Stopped taking statin 15th day second box. Lethargic difficulty concentrating always tired and moody no enjoyment of life no enthusiasm just wanted to sleep.*
- *Strange feeling under my feet.*
- *Strangely excellent bowel movements. Pain down right-hand side of right leg infrequent and only occurs in bed.*

- *Swollen and painful hands. painful wrists (could lift bedding or a glass), elbows, shoulders (front and back) and neck. Also before taking the break, I was experiencing pain in my right knee which started to also let me down. Then I felt very distressed by it all. I am awaiting X-ray and blood tests results but we can't be sure at this stage what could cause it all.*
- *Swollen hands. Had to take ibuprofen day and night for all the pain.*
- *The bone joints in my right hand lock when trying to hold small items.*
- *The period 16th june [sic] to 22nd june [sic] I suffered from nightmares. I don't know if this was related to the medication or not.*
- *The pills have a laxative effect. Need to go to the toilet 2 to 3 times a day. Stools rather loose.*
- *The pins and needles I had in my hands slowly went in the first month but seemed worse when I had beer to drink.*
- *There is no pain, everything refers to stiffness. Neck and bending.*
- *Tiredness.*
- *Upset stomach.*
- *Very occasional pain in back of upper arms and lower back of leg.*
- *Weight loss from 11.5 stone to 10.5 stone.*
- *Feelin[g] depressed.*

Appendix 4 Randomisations by site

TABLE 13 Randomisations by site

Site	Number of patients randomised
Albion Street Practice	4
Bay Medical Group	20
Beechtree Surgery	2
Bentley Surgery	3
Bicester Health Centre	2
Brigstock & South Norwood Partnership	8
Brownlow Health	1
Clarence Medical Centre	6
Cleveleys Group Practice	11
Conisbrough Group Practice	1
Creffield Medical Centre	7
The Exchange Surgery	1
Falkland Surgery	6
Freshney Green Primary Care Centre	3
Great Sutton Medical Centre	2
Hampstead Group Practice	2
Hope Family Medical Centre	n/a
Hornsey Rise	n/a
Hoveton & Wroxham Medical Centre	8
Hurley Clinic	1
Jorvik Gillygate Practice	4
Keats Medical Practice	3
King's Road Surgery, Swansea	n/a
Long Stratton Medical Partnership	1
Mathukia's Surgery	3
Mattishall & Lenwade Surgeries	2
North House Surgery	10
Oak Lodge Medical Centre	3
Oak Tree Surgery	3
Paxton Green Group Practice	2
Pendle View Medical Centre	2
Queen Square Medical Practice	12

continued

TABLE 13 Randomisations by site (*continued*)

Site	Number of patients randomised
Regent House Surgery	3
Riverside Medical Practice	2
Rosedale Surgery	8
School Lane Surgery	n/a
Scott Practice	3
Snaith & Rawcliffe Medical Group	3
Station House Surgery	6
Strawberry Place Surgery	8
Streatham Common Practice	3
The Village Practice	8
Tottenham Health Centre	2
Vanbrugh Group Practice	2
Wallington Family Practice	4
Watling Medical Centre	6
West Hampstead Medical Centre	1
William Harvey Heart Centre	1
Windermere & Bowness Surgery	6
Woodlands Practice	1

n/a, not applicable.

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