StatinWISE TRIAL STATISTICAL ANALYSIS PLAN

FULL TITLE OF STUDY	A series of randomized controlled N-of-1 trials in patients who have discontinued or are considering discontinuing statin use due to muscle-related symptoms to assess if atorvastatin treatment causes more muscle symptoms than placebo		
SHORT TITLE	**STATIN: WEB-BASED INVESTIGATION OF SIDE EFFECTS**		
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Version 0.7	11 March 2018	Modification to allow for "don't know" in secondary outcome definition, editorial changes
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1 INTRODUCTION

This statistical analysis plan (SAP) provides details of the data analysis for the StatinWISE trial. This SAP is subject to change as the trial progresses but will be finalised before the database is locked for final analysis.

1.1 TRIAL SUMMARY

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

AIM: The StatinWISE trial will determine whether the muscle symptoms attributed to statin use by patients are caused by statins.

PRIMARY OUTCOME: Patient reported muscle symptoms (pain, weakness, tenderness, stiffness or cramp to the body) as measured by a visual analogue scale.

SECONDARY OUTCOMES:

a) Whether or not the patient experiences muscle symptoms that they believe were caused by the study medication
b) Site of muscle symptoms (single or multiple; head and neck/upper limbs/lower limbs/trunk)
c) Visual analogue scale scores for the extent to which muscle symptoms affect:
    a. General activity
    b. Mood
    c. Walking ability
    d. Normal work (includes both work outside the home and housework)
    e. Relations with other people
    f. Sleep
    g. Enjoyment of life
d) Other symptoms that the patient believes can be attributed to the study medication (grouped: musculoskeletal, gastrointestinal, respiratory, neurological, psychological, other)
e) Adherence to study medication as assessed by (i) self-report, and (ii) counting pills remaining in returned packages and the relationship between adherence and muscle symptoms
f) Participant decision regarding future statin use and the relationship to their primary outcome
g) Whether patients found their own trial result helpful in making the decision about future statin use

TRIAL DESIGN: A pragmatic, randomised, double-blinded series of N of 1 trials recruiting 200 patients who have a clinical indication for statin treatment.

DIAGNOSIS AND INCLUSION / EXCLUSION CRITERIA:

Inclusion criteria:

- Adults (aged 16 and over)
- Registered in a participating GP practice
- Previously prescribed statin treatment in the last 3 years
- Stopped OR is considering stopping statin treatment due to muscle symptoms
- Provided fully informed consent.

Exclusion criteria:

- Any previously documented serum alanine aminotransferase (ALT) levels at or above three times the upper limit of normal
- Have persistent, generalised, unexplained muscle pain (whether associated or not with statin use) and have creatinine kinase (CK) levels greater than 5 times the upper limit of normal
- Any contraindications listed in the Summary of Product Characteristics for Atorvastatin 20 mg (Appendix 3)
- Should not participate in the trial in the opinion of the general practitioner.

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

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

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

CRITERIA FOR EVALUATION: Patients who enter data on muscle symptoms at least once during a treatment period with the IMP and at least once during a treatment period with placebo), irrespective of adherence to allocated treatment.

1.2 STUDY OVERVIEW

StatinWISE trial is a series of N of 1 double-blinded placebo controlled trials to determine whether the muscle symptoms attributed to statin use by patients are caused by statins. Two hundred adults who have either stopped, or are considering stopping, statin treatment due to muscle symptoms will be allocated a randomised sequence of 6 treatment periods, comprising 3 placebo and 3 atorvastatin periods. Each treatment period will last two months.

Randomisation and baseline data: Eligible and consenting patients should be randomised as soon as possible, and the study treatment started within 4 weeks of randomization. The Baseline Data form (Appendix 1), completed directly via the online trial database by the Research Nurse at the screening visit, will be used to assess eligibility and collect baseline patient information.

Follow-up: At the end of each two-month treatment period, patients will be asked to complete the Patient Questionnaire (Appendix 2). During the last week of each two-month treatment period, patients will also be asked to complete daily VAS Pain Scale forms. Outcome collection will be by a method chosen by the patient at the screening visit: via a bespoke mobile app, the website, paper or by telephone to trial staff.

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

In the two-monthly questionnaire, patients will be asked to self-report any event which resulted in unplanned hospital admissions. Where a patient indicates that there was an unplanned admission, the GP/Research Nurse will be asked to submit a brief report to the Trial Coordinating Team and where the event is believed to be unexpected and associated with statin use, an Adverse Event Report Form will be completed. Participating GPs will also report any event to the trial team which results in unplanned hospital admissions, patient death or where a patient has a baby with any congenital anomaly/birth defect within 24 hours of becoming aware of the event. To minimize the risk of unreported events, at two-monthly intervals, the Research Nurse/GP will conduct a search of their database for any StatinWISE patients who have been recorded as having died. The GP/Research Nurse will be asked to submit a brief report to the Trial Coordinating Team and where the event is believed to be unexpected and associated with statin use, an Adverse Event Report Form will be completed

1.3 PATIENT POPULATION

Two hundred adults with a clinical indication for statins who have either stopped, or are considering stopping, statin treatment due to muscle symptoms. There is no limit to the maximum number of patients to be recruited at each GP.

General Practitioner (GP) Practices will be recruited through the Clinical Research Network across England and Wales; practices will continue to be added until the sample size is achieved. Suitable collaborating practices and investigators will be assessed on their ability to conduct a trial. In advance of the trial starting at a practice, the Principal Investigator must agree to follow Good Clinical Practice Guidelines and all relevant regulations. All relevant regulatory and ethics approvals must be in place prior to practices recruiting their first patient.

1.4 ELIGIBILITY

Inclusion criteria:

- Adults (aged 16 and over)
- Registered in a participating GP practice
- Previously prescribed statin treatment in the last 3 years
- Stopped OR is considering stopping statin treatment due to muscle symptoms
- Provided fully informed consent

Exclusion criteria:

- Any previously documented serum creatine kinase (CK) levels at or above three times the upper limit of normal;
- Taken statins in the previous week and has an increase in serum alanine aminotransferase (ALT) at or above three times the upper limit of normal;
- Any contraindications listed in the Summary of Product Characteristics for Atorvastatin 20 mg (Appendix 3)

- Should not participate in the trial in the opinion of the general practitioner.

1.5 BLINDING AND UNBLINDING

Blinding will be achieved through the use of matching placebo.

Access to the interim data and results will be limited to members of the Data Monitoring Committee (DMC) and their externally based, independent DMC statistician who will be in charge of quality assuring the interim analyses and writing the reports.

In general, there should be no need to unblind the allocated treatment during the treatment phase. If some contraindication to statins develops after randomisation, the trial treatment can be stopped and all usual standard care given. Unblinding should be done only in those rare cases where the clinician believes that clinical management depends importantly upon knowledge of whether the patient is receiving statin or placebo. In those few cases when urgent unblinding is considered necessary, a 24-hour telephone service will be provided by the CTU and details provided in the Investigator's Study File and the Patient Alert Card. The caller will be told whether the patient is receiving statin or placebo. An unblinding report form will be completed by the person requesting the unblinding. Participation will not restart once unblinding has occurred.

1.6 OBJECTIVES

The StatinWISE trial will provide reliable evidence as to whether the muscle symptoms attributed to statin use by patients are caused by statins.

1.7 DEFINITION OF PRIMARY OUTCOME

The primary outcome is patient reported muscle symptoms (pain, weakness, tenderness, stiffness or cramp to the body), on a Visual Analogue Scale (VAS), with possibly responses ranging from 0 to 10. This will be collected daily via the VAS Pain Scale data form (Appendix 1) during the last 7 days of each of the 6 treatment periods via the patient's nominated collection method (app, website, phone call, or paper form).

1.8 DEFINITION OF SECONDARY OUTCOMES

The following secondary outcomes will be collected once at the end of each of the 6 treatment periods, via the patient questionnaire form (Appendix 2).

- Whether or not the patient experienced muscle symptoms that they believe were caused by the study medication (yes/no/don't know).
- Site of muscle symptoms:
    - Single/multiple
    - head and neck/upper limbs/lower limbs/trunk
- Visual Analogue Scale scores (range 0-10) for how the participant's muscle symptoms impact on the following:
    - General activity
    - Mood
    - Walking ability
    - Normal work (includes both work outside the home and housework)
    - Relations with other people
    - Sleep
    - Enjoyment of life

  These are collected only if the participant reports muscle symptoms during that period. For comparisons between randomized treatments these VAS scores will be set to zero for participants who report no muscle symptoms in that period.
- Other symptoms that the patient believes can be attributed to the study medication. These will be entered as free text and grouped into: musculoskeletal/gastrointestinal/respiratory/ neurological/psychological/other (not mutually exclusive categories).
- Adherence to study medication:
    - not at all/some days/most days/every day

Adherence will also be assessed in the following ways:

- number of pills remaining in returned packages (0-56; collected each treatment period)
- self-report ("took pill yesterday" - yes/no; collected daily during the last 7 days of each of the 6 treatment periods)

The final secondary outcomes will be collected in the end of trial interview with the participant:

- Participant decision regarding future statin use and the relationship to their primary outcome (patient has been given a statin prescription in 4 weeks following trial - yes/no).
- Whether patients found their own trial result helpful in making the decision about future statin use (yes/no).

1.9 DEFINITION OF THE SAFETY VARIABLES

- Occurrence of adverse event
- Occurrence of serious adverse event

1.10 ANALYSIS PRINCIPLES FOR FINAL ANALYSIS

- All analyses will be conducted on an 'intention-to-treat' basis, defined as follows:
    - All patients who enter at least one VAS score for muscle symptoms during a statin period and at least one VAS score for muscle symptoms during a placebo period will be included in the final primary analysis.
    - For analyses of secondary outcomes from the patient questionnaire (single monthly measurement), analyses will include all patients who complete at least one measure during a statin period and at least one measure during a placebo period.
    - Periods of allocation to statin will be compared to periods of allocation to placebo, irrespective of adherence to the allocated treatment.
- All statistical tests will be two-sided, and the nominal level of α will be 5%. Confidence intervals for the primary outcome will be set at the 95% level.
- P values will not be adjusted for multiplicity. However, the outcomes are clearly categorised by degree of importance (primary and secondary). Confidence intervals for secondary outcomes will be set at the 99% level.
- The primary analysis will not impute missing values. Where the number of missing observations is substantial, we will report the number of observations used in the analysis. Robustness of conclusions to missing data will be explored via sensitivity analysis.
- Analyses exploring the effect of adherence on primary and secondary outcomes will be undertaken as secondary analyses.
- All adverse events will be coded using MedDRA Version 19.1.

1.11 INTERIM ANALYSES

Statins are widely used already. The primary outcome is itself a side effect. Despite this relatively low-risk setting, an independent DMC has been appointed for this trial to oversee the safety monitoring. The DMC will review on a regular basis accumulating data from the ongoing trial and advise the Trial Steering Committee regarding the continuing safety of current participants and those yet to be recruited, as well as reviewing the validity and scientific merit of the trial.

The DMC composition, name, title and address of the chairman and of each member, are in the DMC Charter. Membership includes expertise in the relevant field of study, statistics and research study design. The DMC Charter includes, but is not limited to, defining:

(a) the schedule and format of the DMC meetings
(b) the format for presentation of data
(c) the method and timing of providing interim reports
(d) stopping rules

Standard Operating Procedures: The Data Monitoring Committee (DMC) has the responsibility for deciding whether, while randomisation is in progress, the unblinded results (or the unblinded results for a particular subgroup), should be revealed to the TSC. The DMC Charter states that they will do this if, and only if, two conditions are satisfied:

(1) The results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of, participants in terms of the major outcome;

(2) The results, if revealed, would be expected to substantially change the prescribing patterns of clinicians who are already familiar with any other trial results that exist. Exact criteria for "proof beyond reasonable doubt" are not, and cannot be, specified by a purely mathematical stopping rule, but they are strongly influenced by such rules. The DMC Charter is in agreement with the Peto-Haybittle stopping rule whereby an interim analysis of major endpoint would generally need to involve a difference between treatment and control of at least three standard errors to justify premature disclosure. An interim subgroup analysis would, of course, have to be even more extreme to justify disclosure. This rule has the advantage that the exact number and timing of interim analyses need not be pre-specified. In summary, the stopping rules require extreme differences to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgment.

1.12 CONSENT-RELATED ISSUES

A patient is free to change their minds about participation at any time. If consent for use of data is withheld, data collected to the point of withdrawal of consent will be used as part of the intention to treat analysis. All relevant adverse events identified will be reported as required to all relevant authorities and included in the safety analysis.

2 STATISTICAL ANALYSIS

2.1 TRIAL PROFILE

Flow of patients through the study will be displayed in a CENT (CONSORT extension for reporting N-of-1 trials) flow diagram. We will report the number of screened patients who met study inclusion criteria and the number included and reasons for exclusion of non-included patients. Numbers allocated to each randomized sequence will be summarised by frequencies and percentages.

Additionally, for interim analyses only, recruitment will be summarised by graphs of patient and GP recruitment over time, and frequencies of patients recruited by GP practice.

2.2 BASELINE CHARACTERISTICS OF PATIENTS

Baseline characteristics of participants will be described overall. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which is less than the number of patients assigned to the treatment group) will be stated in either the body or footnote of the corresponding summary table. Continuous variables will be summarised using standard measures of central tendency and dispersion, i.e. mean and SD, or median and 25^{th}, 75^{th} percentiles.

Study procedures, including participation in the voluntary genetic sub-study and choice of method for primary outcome data collection, will be described overall as for baseline participant characteristics.

2.3 DESCRIPTION OF ANALYSES

2.3.1 PRIMARY OUTCOME

Medians and 25^{th}, 75^{th} percentiles, or mean and SD, as appropriate, of the average VAS daily muscle symptom scores will be reported separately for the six placebo and statin periods, along with summaries of the paired differences (statin-placebo within paired treatment blocks). Trajectory plots will be made for individual patients, and for all patients together grouped by allocated sequence. Numbers of missing measurements will be tabulated by period and allocated treatment.

The overall effect of statin on muscle symptoms, as measured by self-report VAS pain scores, will be estimated by a mean difference (statin – placebo) with a 95% confidence interval (CI). This will be obtained from a linear mixed model with a random participant effect, and allowing the treatment effect to vary by participant (i.e. the model will include both a fixed and random treatment effect, with an unstructured covariance matrix between the two random effects). Residual errors will be modelled using a first-order auto-regressive error structure across all trial days for each personto account for correlation between the 7 daily measurements (i.e. an order auto-regressive error structure with “days under treatment in the trial” as the timescale; noting that each period is exactly 56 days), with robust standard errors to account for non-normality of the VAS scores. In the event of model convergence problems (which may occur if patients report few of the 7 daily VAS scores), the auto-regressive structure will be omitted and robust standard errors used.

The mixed model will be fitted via maximum likelihood. A likelihood ratio test will be used as the test of statistical significance of statin allocation versus placebo on VAS muscle symptom scores.

2.3.2 SECONDARY OUTCOMES

Descriptive analyses of muscle symptoms

Details of symptoms experienced (whether the patient believes they were caused by the study medication, the site, the extent to which the pain impacts on other aspect of life, other symptoms experienced) will be reported for all periods in which the patient reports experiencing muscle symptoms. For these descriptions, the denominator will be the number of periods in which symptoms are experienced; no attempt will be made to account for the clustering by patient. These descriptive statistics will be repeated splitting by treatment actually received.

Descriptions of symptoms experienced will also be made using the patient as the unit of analysis. For these descriptions, patient-level variables for patients who report one or more period where they experienced muscle symptoms will be defined as follows: (i) a new location variable: always multiple sites/sometimes multiple sometimes single/always single site, (ii) four new site variables indicating symptoms ever experienced in head/neck versus not, etc., and (iii) mean VAS score for impacts on other aspects of life across periods in which symptoms were experienced by that patient.

Because these descriptive statistics do not respect the randomised allocation of treatment, no comparisons between treatment groups will be made; no formal statistical inference will be undertaken.

Randomised comparisons of muscle symptoms experienced

The patient questionnaire collects a binary measure of whether the patient experienced muscle symptom or not during that treatment period. This binary measure will be compared between randomized treatment groups (statin – placebo) with an odds ratio and confidence interval, obtained using a logistic mixed model with random participant and random treatment effects with an unstructured covariance matrix between random effects.

As a more specific measure, a single binary outcome of whether the participant reports having muscle symptoms that they believe to be caused by the study medication will be derived (taking the values one if the participant reports symptoms and that they believe these are – or they don't know whether they are – related to the study medication, and zero if either the participant has no symptoms or the participant has symptoms but does not believe these are related to the study medication). This binary measure will be analysed as described in the previous paragraph.

A continuous measure of muscle symptoms will be derived by setting the primary outcome – daily VAS muscle symptom score – to zero if the patient reports that they believe their symptoms are – or they don't know whether they are – related to the study medication. This secondary outcome will be analysed in exactly the same way as the primary outcome.

Impact of muscle symptoms on other aspects of life (general activity, mood, walking, normal work, relations with other people, sleep, and enjoyment of life) will be set to zero for participants in periods where no muscle

symptoms are experienced, and compared between randomized treatment (statin – placebo) using mean differences and confidence intervals. These will be obtained from linear mixed models for each VAS measurement including a random participant effect, and a random treatment effect. Robust standard errors will be used to account for non-normality of the VAS scores.

Participant response to individual N-of-1 trial

We will relate 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.

2.3.3 SAFETY OUTCOMES

Adverse events listed by MedDRA terms will be tabulated by allocated treatment. Serious adverse events will be tabulated by allocated treatment. Suspected unexpected serious adverse reaction listed by MedDRA terms will be tabulated by allocated treatment.

2.3.4 SENSITIVITY ANALYSES

The sensitivity analyses planned were chosen in line with the view that sensitivity analyses should address exactly the same question as the main analyses but be valid under different (potentially verifiable) assumptions, and that if the results are qualitatively different to those in the main analysis, there would be genuine doubt as to which are the correct results. If this does occur, both the main analyses and the results of the sensitivity analyses will be reported in a transparent manner.

Correlation structure

We will explore the robustness of conclusions to different assumptions about the correlation structure of residual errors between the primary outcome measures from the same participant within the same week.

Fixed treatment effect

We will compare the main analyses with random treatment effects to models with a fixed treatment effect only.

Period and carry-over effects

We will add fixed period effects to the primary and secondary outcome models. Because participants will start their individual N-of-1 trials at different times of the year, there is no reason to expect there to be a period effect. We will not explore carry-over effects; the trial was designed to avoid such effects.

Missing data

The mixed model described above is valid under outcome data being missing at random given the observed outcome data. We will use multiple imputation to perform an analysis valid under missing at random given both the observed outcome data and the measured baseline characteristics. We will then consider a number of simple scenario analyses to assess the robustness of our findings to outcome data being missing not at random.

2.3.5 SUBGROUP ANALYSES

There are no a priori subgroup analyses planned. If an overall population-level effect is detected, we may investigate whether the effect varies within subgroups defined by measured baseline characteristics. These analyses will be regarded and interpreted as being exploratory.

2.3.6 ADJUSTED ANALYSES

Comparisons are made within the same participant, comparing placebo with statin periods. Thus, baseline imbalance of patient characteristics will not occur. No adjusted analyses will be performed.

2.3.7 SECONDARY ANALYSES

Withdrawal, Loss to follow-up and Adherence – Descriptive analyses
Loss to follow up and withdrawal, with reasons for withdrawal, will be summarized by overall frequencies and percentages. Protocol violations will be tabulated. Descriptive statistics, including graphical summaries, will be used to summarise the measures of adherence to randomized treatment and withdrawal, and their relationship to the statin and placebo periods.

Withdrawal – Comparison between statin and placebo periods
We will explore whether the period in which a patient was first known to have withdrawn was more likely to have been a placebo or a statin period. If this date is after the end of a treatment period but the patient chooses not to begin the next period, the period in which the withdrawal happens will be set to the period just ended.

Adherence – Randomised comparison
We will explore whether adherence was lower on statin periods compared with placebo periods using mixed models similar to those described above.

Adherence – Efficacy analyses
We will use the measures of adherence to randomised treatment to perform an efficacy analysis based around an instrumental variables approach. Because these analyses require much stronger assumptions than the intention-to-treat analysis above, the results of the efficacy analysis will be presented and interpreted as a secondary analysis.

2.3.8 CHANGES FROM TRIAL PROTOCOL

In the original protocol, the primary analysis model was exactly as above, but with fixed period effects in addition. These fixed effects have been removed, due to a strong belief that the clinical situation makes it unlikely for period effects to occur. The primary analysis model specified in the original protocol will be undertaken as a sensitivity analysis, as detailed in Section 2.3.4.

The original protocol did not mention one of the secondary analyses, which sets the primary outcome measure to zero if the patient attributes the symptoms to another cause (Section 2.3.2). This analysis was added after the protocol was finalised, but was included in the published protocol paper.