C5Research
Cleveland Clinic Coordinating Center for Clinical Research

Statistical Analysis Plan
IND Number: 154728

Supplements, Placebo, or RosuvastaTin Study

SPORT Study

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Approval of Statistical Analysis Plan

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Supplements, Placebo, or RosuvastaTin Study
SPORT Study

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The Statistical Analysis Plan for the SPORT study has been reviewed and approved by:

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1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with IND Number: 154728. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2. Objectives and Endpoints

2.1. Primary Objective

The primary objective of this study is to compare the low density lipoprotein cholesterol (LDL-C) lowering of rosuvastatin with the effect of six commonly-used nonprescription dietary supplements promoted for cholesterol health.

2.2. Secondary Objective

The secondary objective of this study is to assess the effect of each supplement on inflammatory markers compared with rosuvastatin 5 mg.

2.3. Primary Endpoint

The percent change in LDL-C for rosuvastatin 5 mg compared with each dietary supplement after 4 weeks of treatment

2.4. Secondary Endpoints

The secondary endpoints of this study are:

- The percent change in LDL-C for rosuvastatin 5 mg and each dietary supplement compared with placebo after 4 weeks.
- The percent change in high sensitivity C reactive protein (hsCRP) for rosuvastatin 5 mg and each dietary supplement compared with placebo after 4 weeks.
- The percent change in HDL-C, total cholesterol, and triglycerides for each supplement compared with rosuvastatin.
- The percent change in HDL-C, total cholesterol, and triglycerides for each supplement compared with placebo.

3. Study Design

SPORT is a randomized, single blind study design used to evaluate rosuvastatin 5 mg. vs. placebo and 6 commercially available over the counter supplements in a hierarchical testing order. Each participant will take study medication/supplement for a total of 4 weeks. Eight groups will be studied, rosuvastatin 5 mg compared with each of the following:

1. Placebo (visually similar to rosuvastatin 5mg)
2. Fish oil (Nature Made™ 2 soft gels / day)

3. Cinnamon (1200mg, 2 capsules / day)
4. Garlique™ (1 tablet / day)
5. Turmeric (Bio Schwartz Turmeric Curcumin, 1500mg, 3 capsules / day)
6. Plant sterol (Nature Made CholestOff™ Plus, 2 soft gels 2x / day)
7. Red yeast rice (Arazo Nutrition, Red Yeast Rice, 1200mg, 2 capsules / day)

3.1. Randomization

Randomization will occur using REDCap Cloud electronic database platform. Study medication/supplement will be dispensed by the investigational pharmacy in a blinded fashion for in person visits to study personnel or shipped to the subjects by the investigational pharmacy following randomization. Day 1 of the study is the first day that subjects start study medication/supplement. In the event that study medication/supplement is shipped to subjects, study personnel will verify the start of study medication/supplement (Day1) for medication/supplement accountability.

The study medication/supplement will be supplied from commercially available products and administered according to the package insert. The rosuvastatin 5mg and placebo will be provided by Astra Zeneca. The over the counter supplements will be purchased and due to documented history of supplement tainting, supplements may be tested for unlabeled enhancing impurities retrospectively if deemed necessary per data findings. If we observe > 15% lowering in LDL cholesterol, we will test for impurities.

3.2. Blinding

Subjects, investigator staff, persons performing the assessments, and the clinical trial team will be blinded to assigned study group. Baseline laboratory values will not be blinded to the subjects, investigator staff, and the clinical team. Additional lipid labs will be prohibited for the 4 week participation period. The Day 28 labs will not be blinded.

It is expected that the need for unblinding of a patient's study group will be extremely rare. Every effort should be made to preserve the blind unless there is a compelling reason that knowledge of the specific treatment would alter the medical care of the patient.

3.3. Sample Size and Power

Eligible subjects will be randomized 1:1:1:1:1:1:1:1 to the study groups in a blinded fashion. There will be 25 subjects per study group. The total sample size will be 200 patients. Assuming a common standard deviation of 15 and an alpha of 0.05, enrolling a total of 25 in each group will have 90% power to detect an

average difference in percent change in LDL-C of 15 between rosuvastatin and each supplement.

4. Study Analysis Sets

4.1. Full Analysis Set

The full analysis set (FAS) consists of all enrolled patients. Efficacy variables will be analyzed based on the FAS as the primary population.

4.2. Safety Analysis Set

The safety analysis set (SAS) consists of all patients who received at least one dose of study medication/supplement. The safety population will be used for the analyses of safety variables.

4.3. Per-protocol Analysis Set

The per-protocol analysis set (PPAS) consists of all patients who received at least 80% of the prescribed study medication/supplement. Patients will be categorized by they study medication/supplement taken.

5. General Data Considerations

Continuous variables will be summarized in terms of the number of observations (n), mean, standard deviation (SD), median, Q1 (25th percentile), Q3 (75th percentile), minimum and maximum. Other descriptive statistics (e.g. geometric mean) may be reported when appropriate.

Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will be identified with the analysis in the applicable SAP section.

SAS version 9.4 or higher will be used to perform all analyses and to generate output.

6. Data Handling

All data will be exported from the REDCap Cloud database. Randomization data will also be exported from the REDCap Cloud database. Assigned study medication will be blinded to study personnel. A general description of how the data will be handled is outlined below however, it may not encompass all that is found at the time of the analysis.

6.1. Missing data

Missing data will not be imputed unless otherwise specified. Only observed data will be used in the summaries and analyses.

6.2. Incomplete dates

If a day or month is recorded as missing, it will be replaced by the first day of the month or January, respectively, provided this does not contradict any other dates recorded.

6.3. Data Definitions

The following sections provide a general description of the derived variables for data analyses.

6.3.1. Study Day

6.3.1.1. Fasting lipid panel

The fasting lipid draw and complete metabolic panel (CMP) at Day 0 and Day 28 must be obtained from a Cleveland Clinic lab. Recently acquired lipid labs and complete metabolic panel may be used in place of a Day 0 lab draw if acquired within 4 weeks of screening at a Cleveland Clinic lab and performed in the fasting state.

6.3.1.2. Study Medication

Day 1 of the study is the first day that subjects start study medication/supplement.

6.3.1.3. Body Weight

Historical documented height and weight may be used. Weight to be within the last 3 months. Subject reported is acceptable.

6.3.2. Baseline laboratory values

Baseline is defined as the Day 0 lab draw. Recently acquired lipid labs and CMP may be used in place of a Day 0 lab draw if acquired within 4 weeks of screening at a Cleveland Clinic lab and performed in the fasting state

6.3.3. Change from baseline

Change from baseline will only be calculated for measures that have post-baseline records. Change from baseline is calculated as:

(Day 28 value) – Baseline value.

Percentage change from baseline is calculated as:

((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and percentage change from baseline is set to missing as well.

6.4. Study medication/supplement adherence

Study medication/supplement adherence will be determined by the pill count returned, the pill count dispensed, and the amount of pills that are expected to be taken:

(Number of pills dispensed – number of pills returned) /
(number of pills indicated per day per study medication/supplement*number of days of follow-up†)

The number of pills expected to be taken through day 28 days will vary for each medication/supplement (Appendix A). The expected amount per day will be multiplied by the number of days of follow-up to get the total number of pill expected by the end of the study period.

Study medication/supplement adherence is defined as patients consuming at least 80% of the expected amount.

†The range of follow-up is 24-32 days. Only patients with at least 24 days of follow-up will be included in the study medication/supplement adherence calculation.

7. Study Population

A limited amount of baseline patient and laboratory data will be collected from historical records. Patient reported data may be used as noted.

7.1. Subject Disposition

The number of patients screened will be presented by study group and overall for the screened set. In addition, the reasons of screen failures will be provided for screened set as well. The number and percentage of patients who completed the study, who discontinued the study and the reason for discontinuation will be presented for each study group and all patients. The frequency (%) of patients with major protocol deviations will be presented in separate tables.

7.2. Demographic Characteristics

All demographic summaries will be based on the FAS. The following summaries of patient demographic characteristics will be provided by treatment group:

- Age
- Gender
- Race
- Ethnicity

7.3. Baseline Characteristics and Vital Signs

All baseline characteristics summaries will be based on the FAS. They will be presented in summary tables by study group. Continuous data will be summarized by descriptive statistics.

Baseline characteristics and vital signs will be summarized as follows overall:

- Weight (kg), BMI (kg/m2) will be summarized as appropriate to continuous variables
- Systolic and diastolic blood pressure - may be patient reported if no historical records are found

7.4. Medical History

The following medical history will be summarized by treatment group to describe the patient population enrolled in the study:

- Diabetes, if yes, insulin use
- Hypertension
- Hyperlipidemia
- Arrhythmia
    - Atrial fibrillation
    - Other
- Congestive Heart Failure
- Smoking - current use, previous, never

7.5. Study medications/supplements

Because each medication/supplement is dispensed at different amounts, adherence to study medication/supplement will summarized categorically:

- < 30%
- 30-50%
- 50-70%
- 70-90%
- ≥90%

Patients taking at least 80% of their randomized medication/supplement will be considered adherent.

7.6. Prior and Concomitant Medications

A predetermined list of medications will be summarized at baseline, day 28 and any unscheduled visit. Prior or concomitant medication/supplements will be summarized for the safety set in separate tabulations based on a predetermined list of medication/supplements. Prior medication/supplement are defined as any medication/supplement a subject was taking prior to randomization in the study. Concomitant medication/supplements will include any medication/supplements taken during the study period. They include the following:

- ACE-Inhibitors
- Anticoagulants
- Angiotensin II Receptor Blockers (ARBs)
- Aspirin
- Beta Blockers
- Calcium Channel Blockers
- Diuretics
- Nitrates
- Thyroid medications
- Vitamin D
- Diabetic medications (insulin, oral meds)

7.7. Laboratory Parameters

The following laboratory parameters will be summarized by treatment group:

- HDL-C (mg/dL)
- LDL-C (mg/dL)
- Total cholesterol (mg/dL)
- Triglycerides (mg/dL)
- High sensitivity C-reactive protein (mg/dL)

8. Analysis of Endpoints

8.1. Primary Endpoint

The primary endpoint is defined as percent change in LDL-C for rosuvastatin 5 mg compared with dietary supplement after 4 weeks.

To control the overall alpha of the study, the primary endpoint will be evaluated hierarchically. Each comparison to rosuvastatin will use an alpha of 0.05. Once a comparison is not met (2-sided p-value ≥ 0.05) all subsequent comparisons will be considered exploratory with nominal p-values. The change in LDL-C for rosuvastatin will be compared with the other 7 study groups using ANCOVA in a hierarchical fashion in the following order:

Rosuvastatin 5 mg compared with the following:

1. Placebo (visually similar to rosuvastatin 5mg)
2. Fish oil (Nature Made™ 2 soft gels / day)
3. Cinnamon (1200mg, 2 capsules / day)
4. Garlique™ (1 tablet / day)
5. Turmeric (Bio Schwartz Turmeric Curcumin, 1500mg, 3 capsules / day)
6. Plant sterol (Nature Made CholestOff™ Plus, 2 soft gels 2x / day)
7. Red yeast rice (Arazo Nutrition, Red Yeast Rice, 1200mg, 2 capsules / day)

A generalized linear model will be used to compare the percent change in LDL-C between rosuvastatin and each of the other study groups. Least-square means and standard error will be used to summarize the adjusted percent changes in LDL-C. The differences in the percent changes between rosuvastatin and each study medication/supplement will be calculated by subtracting the LS-means of each comparison. At a minimum, adjustments for baseline LDL-C and age will be used in each model. Other adjustments may be warranted if differences in factors across study groups are statistically significant.

If the percent change in LDL-C has a non-normal distribution (graphically assessed), median values will be used to summarize the endpoints and compared with a non-parametric test. The primary endpoint will be analyzed in the FAS. A sensitivity analysis will be performed using the PPAS, to determine the differences in the percent change in LDL-C in patients using the prescribed about of study medication/supplement.

8.2. Secondary Endpoints

The following secondary endpoints will be analyzed in the FAS:

- Percent change in high sensitivity C reactive protein (hsCRP) for each dietary supplement compared with rosuvastatin 5 mg after 4 weeks treatment
- The percent changes in HDL-C, total cholesterol, and triglycerides for each dietary supplement compared with rosuvastatin 5 mg after 4 weeks treatment
- The percent changes in HDL-C, total cholesterol, and triglycerides for each dietary supplement compared with placebo after 4 weeks treatment

A generalized linear model will be used to analyze the percent changes for secondary endpoints. Percent change from baseline for each laboratory measurement will first be calculated. Least-square means and standard error will be used to summarize the adjusted percent changes in LDL-C. The differences in the percent changes for each secondary endpoint will be calculated by subtracting the LS-means of the percent change of each study medication/supplement to its comparator. The mean and 95% confidence intervals will be used to summarize the effect of each study group. At a minimum, adjustments for baseline laboratory measurement and age will be used in each model. Other adjustments may be warranted if differences in factors across study groups are statistically significant.

No hierarchical testing of the secondary endpoints will be conducted. Since the study was not powered to test secondary endpoints, all testing and p-values will be considered exploratory. No adjustments will be made for multiplicity. A sensitivity analysis will be performed using the PPAS, to determine the differences in the

percent change in each laboratory measurement in patients using the prescribed about of study medication/supplement.

9. Analysis of Safety Data

9.1. Adverse Events

Adverse events will be summarized by study group. A subject with multiple adverse events of the same type is only counted once towards the total of that event, however the total number of adverse events experiences will also be calculated. Adverse events will be collected through the end of the study period. No formal statistical tests will be conducted. All summaries and analyses of the safety data will be conducted on the SAS.

Adverse events will be summarized in patient listings with the following characteristics:

- Seriousness (mild, moderate, severe potentially life threatening)
- Relatedness (possibly, unknown, not related)
- Status (expected, unexpected)
- Action taken (drug withdrawn, drug interrupted, not applicable, unknown)
- Resolution (unresolved, resolved, resolved with sequelae, unknown)
- Considered a serious adverse event

Adverse events occurring at least 5% of the time in the overall population will be summarized in a separate table.

9.2. Serious Adverse Events

Adverse events classified as serious adverse events (SAEs) will separately be summarized by treatment group. SAEs will also be summarized in a listing with the following characteristics:

- Death
- Life threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Other important medical event

9.3. All-Cause Mortality

All-cause mortality through the end of the study period will be summarized by treatment group. Listings may be produced with any available information that is collected.

10. Safety Monitoring Review

Medical monitoring review will begin 3 months after enrollment of the first patient and then every 3 months thereafter during the enrollment phase of the study through completion of the final visit by the last patient. The Medical Monitor will escalate any findings regarding death, serious adverse events, adverse events, and safety data to the Principal Investigator.

Elements of the report may include but are not limited to:

- Cumulative number of subjects enrolled
- Patient demographics
- Protocol deviations
- Study drug discontinuations due to adverse events
- Adverse event tables and listings (as described in section 9.1)
- Serious adverse event tables and listing (as described in 9.2)
- Any MEDWATCH form related to rosuvastatin or the supplements
- Any Suspected Unexpected Serious Adverse Reaction (SUSAR)

All safety monitoring reports and listings will be unblinded to study treatment.

11. Appendix A

Study medication/supplement expected pill count:

Study medication/supplement	Expected 28-day pill count (total)
Rosuvastatin	28
Placebo	28
Fish Oil	56
Cinnamon	56
Garlique™	28
Tumeric	84
Plant Sterol	112
Red yeast rice	56