## Title page

# Statistical Analysis Plan

**Protocol title**

Protocol for a Randomised, Double-Blinded, Placebo-Controlled Trial Investigating the Combined Effects of Statins and Exercise on Physiological Health Markers and Quality of Life in Patients With Dyslipidaemia

**Trial registration:** ClinicalTrials.gov Identifier: NCT06841536

**SAP version:** 1.0

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**Ethics approval:** Faroe Islands Ethical Committee (2024-10)

# Authors

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**Participating clinical site(s)**

National Hospital of the Faroe Islands (Tórshavn)

**Document status and purpose**

This statistical analysis plan (SAP) supplements the main study protocol and prespecifies analyses for all primary, secondary, and exploratory outcomes. It is finalized prior to unblinding and follows contemporary guidance for SAP content in clinical trials (Gamble *et al.*, 2017).

**Signature Page**

We, the undersigned, approve and will adhere to the Statistical Analysis Plan detailed herein:

**SAP authors**

| Name | Title | Role | Signature | Date |
|---|---|---|---|---|
| Tórur Sjúrðarson[1] | PhD | Sponsor-investigator; SAP co-author |  | 16.12.2025 |
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# Section 2: Introduction

**7. Background and Rationale (adapted from the published protocol)**

Detailed background and rationale are presented in the published protocol (Sjúrðarson *et al.*, 2025). In brief, statins are first-line therapy for dyslipidaemia a but have been hypothesized to attenuate exercise-induced improvements in skeletal-muscle mitochondrial content and function as well as cardiorespiratory fitness (Mikus *et al.*, 2013). This trial is designed to quantify the exercise × statin interaction on mitochondrial function and related physiological and clinical markers in middle-aged adults with dyslipidaemia, using citrate synthase (CS) maximal activity as a validated biomarker of mitochondrial content/oxidative capacity and peak oxygen uptake ($VO_{2peak}$) as a complementary integrated marker of whole-body fitness. The central scientific question is whether concomitant high-dose atorvastatin attenuates adaptations normally observed with supervised high-intensity interval training.

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**8. Objectives**

**Overall objective.** To estimate the individual and combined effects of 12 weeks of atorvastatin and supervised exercise training on physiological, biochemical, and patient-reported outcomes in adults with dyslipidaemia.

**Primary objective.**

To evaluate the effect of 12 weeks of atorvastatin, exercise training, and their combination on skeletal-muscle CS maximal activity across all four intervention groups.
The main mechanistic contrast of interest is Exercise + Placebo vs Exercise + Atorvastatin, testing whether atorvastatin blunts training-induced mitochondrial adaptations.
Additional pre-specified pairwise comparisons among the four groups will be analyzed to fully characterize exercise, drug, and combined effects (see Section 12).

**Key secondary objective.**

To evaluate changes in $VO_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) across the four groups, with the same principal contrast (Exercise + Placebo vs Exercise + Atorvastatin), testing whether atorvastatin blunts training-induced adaptations in $VO_{2peak}$.

For details on outcome selection and rationale, see the published protocol.

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# Section 3: Study Methods

**9. Trial design**

This investigator-initiated, randomized, double-blinded (medication) and placebo-controlled, 2 × 2 factorial trial evaluates the effects of high-dose atorvastatin and supervised high-intensity interval training (HIIT), alone or combined, over 12 weeks in adults with dyslipidaemia. Participants are allocated to one of four parallel arms:

1. Exercise + Placebo
2. Exercise + Atorvastatin
3. No Exercise + Atorvastatin
4. No Exercise + Placebo

Medication allocation is double-blinded (participants and investigators). Exercise allocation cannot be blinded to participants or trainers; however, outcome assessors and laboratory personnel will remain blinded to medication allocation, and data analysts will remain blinded to both medication and exercise allocation until database lock.
The factorial design allows estimation of the main effects of statin therapy and exercise, as well as their interaction, while also supporting predefined pairwise contrasts (see Section 12).

**Interventions**

- **Wash-out:** 4-week discontinuation of lipid-lowering therapy before baseline (week 0).
- **Medication:** Atorvastatin 40 mg (Week 1-2), then 80 mg daily; matching placebo in placebo arms.
- **Exercise:** Supervised high-intensity interval training (HIIT) three times per week, performed at or above 90 % of maximal aerobic power (MAP), with intensity

monitored using power output (wattage), heart rate (HR), and ratings of perceived exertion (RPE).

- **Non-exercise arms:** Maintain habitual physical activity.

**Study visits:**

V0 = Screening, V1 = Baseline (all measurements completed before randomization), Week 6 = mid-intervention bloods, V2 = Post-intervention (12 weeks).

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**10. Randomization**

Randomization uses a computer-generated list prepared by an independent statistician. Allocation is performed by a non-involved colleague after completion of baseline assessments. Participants are randomized in a 60:40 exercise:non-exercise ratio to achieve approximately:

| Group | n |
|---|---|
| **Exercise + Placebo** | 36 |
| **Exercise + Atorvastatin** | 36 |
| **No Exercise + Atorvastatin** | 24 |
| **No Exercise + Placebo** | 24 |

Randomization is stratified by:

1. Sex (male/female)
2. Prior active statin treatment (yes/no)

Block sizes are concealed from investigators. Randomization codes are securely stored and revealed only after database lock.

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**11. Sample size calculations**

Sample-size calculations were prespecified for the primary mechanistic contrast (Exercise + Placebo vs Exercise + Atorvastatin) for the primary endpoint (ΔCS) and the key secondary endpoint ($\Delta VO_{2peak}$).

Power calculations (as prespecified in the published protocol) used prior training data (Sjúrðarson *et al.*, 2022*a*, 2022*b*): mean ΔCS ≈ 25 $\mu mol \cdot g^{-1} \cdot min^{-1}$, SD ≈ 18 $\mu mol \cdot g^{-1} \cdot min^{-1}$, and a target between-group difference of 17 $\mu mol \cdot g^{-1} \cdot min^{-1}$, consistent with attenuation magnitudes reported previously (Mikus *et al.*, 2013). For $VO_{2peak}$, we assumed Δ ≈ 3.6 ± 3.3 $mL \cdot kg^{-1} \cdot min^{-1}$ and targeted a 3.0 $mL \cdot kg^{-1} \cdot min^{-1}$ between-group difference.

**Final enrolled sample size.**

A total of N = 120 participants were randomized (36 per exercise arm; 24 per non-exercise arm). The primary mechanistic comparison—Exercise + Placebo vs Exercise + Atorvastatin—is effectively a two-group contrast, and power calculations were therefore based on the two exercise groups.

Using the effect-size assumptions prespecified in the published protocol, the achieved sample provides:

- **Citrate synthase (CS) activity:**
    - With full enrollment (n = 36 per group), power is approximately 97–98% to detect a 17 $\mu mol \cdot g^{-1} \cdot min^{-1}$ difference (SD ≈ 18).
    - With 10% attrition (≈33 per group), power remains high at ≈94–95%.
- **$VO_{2peak}$:**
    - With full enrollment (n = 36 per group), power is approximately 96–97% to detect a 3.0 $mL \cdot kg^{-1} \cdot min^{-1}$ difference (SD ≈ 3.3).
    - With 10% attrition (≈33 per group), power remains ≈93–95%.

Power calculations were performed in G*Power (version 3.1.9.7) using a two-sample, two-sided t-test with α = 0.05, assuming equal group sizes for the exercise arms. Power calculations are based on a two-sample t-test approximation for the primary exercise-arm contrast; the primary analysis will use a linear mixed-effects model, which is expected to provide similar or greater efficiency under the repeated-measures structure.

**Interpretation note (pre-specified).**

Because (i) a clinically meaningful CS difference is not firmly established and (ii) assay units/conditions vary across studies, true between-group differences smaller than 17 $\mu mol \cdot g^{-1} \cdot min^{-1}$ may still be clinically relevant.

For $VO_{2peak}$, relatively small differences may also be clinically meaningful. While meta-analytic evidence indicates that each 1-MET (≈3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) higher cardiorespiratory fitness is associated with substantially lower all-cause and cardiovascular mortality risk (Myers *et al.*, 2002; Kodama *et al.*, 2009), $VO_{2peak}$ is also associated with prognosis on a continuous per–$mL \cdot kg^{-1} \cdot min^{-1}$ scale in clinical and older adult cohorts (Keteyian *et al.*, 2008; Tari *et al.*, 2024). Accordingly, a between-group difference of ~2.0 $mL \cdot kg^{-1} \cdot min^{-1}$ (≈0.6 MET) represents a potentially meaningful difference in cardiorespiratory fitness.

With 120 randomized participants, the study has approximately 80% power to detect between-group differences of ~12 $\mu mol \cdot g^{-1} \cdot min^{-1}$ in CS activity and ~2.1 $mL \cdot kg^{-1} \cdot min^{-1}$ in $VO_{2peak}$.

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**12. Framework**

Analyses will follow a superiority framework. The 2×2 factorial design allows estimation of main effects of exercise and statin therapy and their interaction; these analyses are pre-specified and interpreted in a mechanistic framework but are not part of the confirmatory testing family.

Confirmatory inference is prespecified to focus exclusively on the primary mechanistic endpoint and the pairwise group contrasts that directly address this question. Accordingly, confirmatory testing is restricted to the six pre-specified pairwise contrasts for the primary endpoint (change in CS activity), specified a priori to characterize exercise, statin, and combined effects.

Multiplicity across this confirmatory family of six ΔCS contrasts will be controlled using the Holm–Šidák procedure, maintaining a familywise two-sided $\alpha = 0.05$. Superiority will be claimed only for contrasts meeting this adjusted criterion.

All secondary and exploratory outcomes, including $VO_{2peak}$, will be analyzed using the same general model framework, with emphasis on effect estimates and 95% confidence intervals; p-values will be reported without multiplicity adjustment and interpreted descriptively rather than as confirmatory evidence.

### 12.1 Statistical Hypotheses

The primary mechanistic hypothesis is that supervised exercise training increases skeletal-muscle CS activity and that concomitant high-dose atorvastatin attenuates this response.

The key secondary hypothesis is that concomitant atorvastatin treatment attenuates training-induced improvements in cardiorespiratory fitness, assessed as the between-group difference in change in $VO_{2peak}$ between Exercise + Placebo and Exercise + Atorvastatin. This hypothesis is evaluated descriptively and is not part of the confirmatory testing family.

For the primary endpoint (ΔCS), six pre-specified pairwise contrasts will be evaluated to characterize exercise, statin, and combined effects:

| No. | Comparison | Scientific question |
|---|---|---|
| **1** | Exercise + Placebo > Exercise + Atorvastatin | Does atorvastatin blunt exercise-induced mitochondrial gains? *(Primary contrast)* |
| **2** | Exercise + Placebo > No Exercise + Atorvastatin | Benefit of exercise alone vs. drug alone |
| **3** | Exercise + Placebo > No Exercise + Placebo | Absolute effect of exercise training |
| **4** | Exercise + Atorvastatin > No Exercise + Atorvastatin | Can exercise mitigate potential statin-related attenuation? |
| **5** | Exercise + Atorvastatin > No Exercise + Placebo | Combined treatment vs. no intervention |
| **6** | No Exercise + Placebo > No Exercise + Atorvastatin | Do statins alone affect mitochondrial function? |

Contrasts are listed in the hypothesized direction for interpretation; all tests will be two-sided. Confirmatory inference is limited to the six ΔCS contrasts defined above; all other hypothesis tests are interpreted supportively.

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## 13. Statistical interim analyses and stopping guidance

No interim analyses for efficacy are planned, given the relatively short duration and the aim of this exploratory, mechanistic trial. No early stopping guidelines were specified.

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**14. Timing of final analysis**

Data collection is considered complete after the last participant's last visit. Analyses will begin only after:

1. all data have been entered and cleaned,
2. all queries have been resolved, and
3. The randomization code has been formally unblinded following database lock.

No unblinded interim looks are permitted before database lock.

**15. Timing of outcome assessments**

Primary and secondary outcomes are measured at V1 (baseline) and V2 (12 weeks). Mid-intervention blood sampling and questionnaires at week 6 provide exploratory trajectory information but are not part of confirmatory analyses. All analyses of change are defined as V2 – V1 unless otherwise stated.

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# Section 4: Statistical principles

**16–18. Confidence Intervals, P-values, and Multiplicity**

For all outcomes, we will report within-group estimated mean changes (V2–V1) and between-group differences in change (contrasts of V2–V1), each with 95% confidence intervals (CIs); formal hypothesis testing will be restricted to pre-specified between-group contrasts, while within-group changes will be presented descriptively to aid interpretation.

Confirmatory testing comprises exclusively the six pre-specified contrasts for the primary endpoint (ΔCS activity). Multiplicity across this confirmatory family will be controlled using the Holm–Šidák procedure, maintaining a familywise two-sided $\alpha = 0.05$.

For all other secondary and exploratory outcomes, effect estimates and 95% CIs will be emphasized. Unadjusted p-values for other pre-specified between-group contrasts will be reported but interpreted descriptively/supportively, rather than as confirmatory evidence.

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**19–20. Adherence, Protocol Deviations, and Analysis Populations**

**Analysis Populations**

**Modified Intention-to-Treat (mITT):**
mITT (primary analysis set): All randomized participants who initiated any allocated intervention (≥1 supervised exercise session for exercise arms and/or ≥1 dose of study medication for medication arms). Participants randomized but with no intervention exposure will be retained in CONSORT/randomization summaries but excluded from mITT. A supportive analysis of the primary endpoint will also be conducted in the full ITT set (all randomized participants analyzed as allocated) to assess sensitivity to the mITT definition.

**Per-Protocol (efficacy under adherence):**
Participants without major protocol deviations who (i) complete V1 and V2 assessments and (ii) meet adherence criteria for their assigned intervention(s):

- Medication arms: ≥75% of planned doses at assigned dose (80 mg; 40 mg if medically indicated).
- Exercise arms: ≥75% session attendance and ≥75% of prescribed high-intensity interval time performed at ≥90% maximal aerobic power (MAP).

**Adherence definitions and quantification**

**Medication adherence (%):** (doses taken / doses planned) × 100; sources: medication logs + pill count.

**Exercise adherence:**

- **Session attendance (%):** (sessions attended / sessions prescribed) × 100 (3 sessions/week planned).
- **Intensity adherence (%):** (completed high-intensity interval time at ≥90% MAP / prescribed high-intensity interval time) × 100. MAP is defined as the lowest cycling

power output eliciting $VO_{2peak}$ during the incremental test. Primary source: power output; HR as backup. If session-level data are missing, within-participant imputation from temporally adjacent sessions in the same phase may be used.

**Protocol Deviations**

Major deviations include prohibited medications, <75% adherence to allocated medication/exercise criteria, withdrawal of consent, or non-attendance of V2 testing. All deviations will be listed and summarized by intervention group.

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# Section 5: Trial Population

**21. Screening data**

Screening and enrolment figures will be summarized in the CONSORT flow diagram. Individual-level screening data will not be reported.

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**22. Eligibility criteria**

Inclusion criteria:

- Age: 40–65 years.
- LDL-C >4.0 mmol/L, calculated via the Friedewald equation (LDLC=Total Cholesterol-(HDL-C+0.45×Triglycerides)).
- Written informed consent provided prior to any study procedures.

Exclusion criteria:

- Diagnosed with serious chronic disease including type 1 or 2 diabetes.
- Cancer.
- A history of atherosclerotic cardiovascular disease.
- A history of major depression or other severe psychiatric disorders.
- Severe renal dysfunction (creatinine clearance <30 mL/min).
- Severe hepatic impairment, defined as alanine-aminotransferase ≥3×the upper limit of normal.

- Active pregnancy or breastfeeding.
- Active cigarette or e-cigarette smoker.
- Regular (>2 hours per week) aerobic high-intensity exercise training

*Rationale:* These criteria ensure a metabolically homogeneous dyslipidaemic cohort without overt cardiovascular disease, while minimizing safety concerns for high-intensity exercise and statin exposure.

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**23. Recruitment**

CONSORT flow will report numbers assessed, randomized, allocated, treated, completed, and analyzed per arm.

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**24. Withdrawal/Follow-up**

Participants who discontinue the intervention will be encouraged to attend the post-intervention (V2) assessments whenever feasible to minimize missing data. Reasons for withdrawal or loss to follow-up will be summarized descriptively by randomization group. Participants withdrawing before receiving any intervention will be excluded from the mITT population but included in CONSORT summaries.

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**25. Baseline Participant Characteristics**

Baseline characteristics will be summarized descriptively for all randomized participants and stratified by randomization group:

1.Exercise + Atorvastatin; 2. Exercise + Placebo; 3. No Exercise + Atorvastatin; 4. No Exercise + Placebo. Unless otherwise specified, summaries will be based on the mITT population.

The distribution of each variable will be inspected visually using Q–Q plots and histograms. Variables with approximately normal distributions will be summarized as mean ± SD; non-normally distributed variables will be reported as median [25th–75th percentiles]. Categorical variables will be reported as counts and percentages.

**Table 1** will summarize key demographic, anthropometric, cardiorespiratory, metabolic, biochemical, and patient-reported variables. The final variable list may include but is not limited to the following:

| Variable | Total (n = ) | Exercise + Atorvastatin | Exercise + Placebo | No Exercise + Atorvastatin | No Exercise + Placebo |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Sex (M/F) (n (%)) | | | | | |
| Age (years) | | | | | |
| **Anthropometry** | | | | | |
| Height cm | | | | | |
| Weight kg | | | | | |
| BMI $kg \cdot m^{-2}$ | | | | | |
| Waist circumference (cm) | | | | | |
| Hip circumference (cm) | | | | | |
| Body fat (%) | | | | | |
| Lean mass (kg) | | | | | |
| **Cardiorespiratory** | | | | | |
| $VO_{2peak}$ $(mL \cdot min^{-1})$ | | | | | |
| $VO_{2peak}$ $(mL \cdot kg^{-1} \cdot min^{-1})$ | | | | | |
| Resting heart rate (BPM) | | | | | |
| Systolic BP (mmHg) | | | | | |
| Diastolic BP (mmHg) | | | | | |
| **Metabolic profile** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Fasting glucose (mmol/L) | | | | | |
| $HbA_1c$ (mmol/mol) | | | | | |
| Fasting insulin (pmol/L) | | | | | |
| Fasting c-peptide (pmol/L) | | | | | |
| HOMA-IR | | | | | |
| Lipids (total, LDL, HDL, TG) mmol/L | | | | | |
| Apolipoproteins (A-I, A-II, B etc.) | | | | | |
| **Muscle biochemistry** | | | | | |
| Citrate synthase activity ($\mu mol \cdot g^{-1} \cdot min^{-1}$) | | | | | |
| 3-HAD activity ($\mu mol \cdot g^{-1} \cdot min^{-1}$) | | | | | |
| PFK activity ($\mu mol \cdot g^{-1} \cdot min^{-1}$) | | | | | |
| **Clinical and patient-reported** | | | | | |
| SF-36 (total and subdomains) | | | | | |
| SAMS scores (0–10) | | | | | |

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**Section 6: Analysis**

**26. Outcome definitions**

**Primary outcome**

- *Citrate-synthase maximal activity* (µmol·g$^{-1}$·min$^{-1}$), measured in skeletal-muscle homogenates by fluorometry.
  The primary endpoint is the change from baseline (V1) to 12-week follow-up (V2).

**Key secondary outcome**

- *Maximal oxygen uptake ($VO_{2peak}$)* (mL·kg$^{-1}$·min$^{-1}$), assessed during an incremental cycling test to exhaustion.
  The key secondary endpoint is the change from V1 to V2.

**Additional secondary outcomes**

Unless otherwise specified, outcomes refer to the within-participant change (V2 – V1). They include (but are not limited to) variables in the following domains:

1. **Cardiorespiratory and hemodynamic:** $VO_{2peak}$ (absolute & relative), steady-state $VO_2$, resting HR, systolic and diastolic BP.
2. **Body composition and anthropometry:** body weight, fat %, lean mass (BIA), waist/hip circumference.
3. **Lipid and lipoprotein profile:** total, LDL, HDL, triglycerides, lipoprotein(a), apolipoproteins (A-I, B-100 etc.), CETP, LCAT, albumin, transthyretin.
4. **Glucose metabolism and insulin sensitivity:** fasting glucose, insulin, $HbA_1c$, HOMA-IR, Matsuda index, ISR, oral disposition index.
5. **Muscle biochemistry and mitochondrial function:** 3-HAD, PFK, CoQ10, intramuscular atorvastatin (CoQ10 and intramuscular atorvastatin will be quantified only where sufficient muscle tissue is available after primary analyses).
6. **Patient-reported outcomes:** SF-36 (total + subdomains), SAMS (severity & type).
7. **Exploratory outcomes:** anaerobic capacity (Wingate), systemic biomarkers (CoQ10, CRP, cytokines), white-blood-cell count, telomere length, PFAS, hemoglobin mass (CO-rebreathing), targeted / untargeted muscle proteomics, RPE (training/testing).

*Note:* Detailed laboratory and assay procedures (e.g., DIA-PASEF, UHPLC-MS) are specified in the main protocol. Outcome definitions may be refined based on data quality and scientific relevance before database lock.

## 27. Analysis method

Analyses will primarily follow the modified intention-to-treat (mITT) principle (see Section 20), with complementary per-protocol (PP) analyses assessing efficacy under adherence conditions.

### Primary Analysis

All continuous outcomes will be analyzed using linear mixed-effects models (LMMs) with restricted maximum likelihood (REML), unless otherwise stated. Model specification (for most outcomes):

- Fixed effects: group (four arms), time (V1/V2; categorical), and group × time interaction.
- Random effects: participant-specific intercept.
- Covariates: sex and prior active statin treatment (randomization stratification factors).
- Estimation: REML with Kenward–Roger degrees-of-freedom correction.
- Diagnostics: residuals and fitted values will be inspected; right-skewed outcomes may be log-transformed.

Rationale: Baseline is not included as a separate covariate because it is explicitly modeled as part of the repeated outcome; treatment effects are estimated from the group × time interaction, consistent with a constrained longitudinal data analysis framework. The primary estimand is the between-group difference in mean change from baseline (V2–V1) for each pre-specified contrast.

### Reporting

For each outcome the following will be reported:

- Between-group differences in change (V2–V1) for pre-specified contrasts with 95% CIs and p-values (Holm–Šidák-adjusted for the six confirmatory ΔCS contrasts; unadjusted and descriptive for all other outcomes).

- Group-specific estimated means/changes with 95% CIs, reported descriptively (no within-group hypothesis tests).
- Effect sizes will primarily be reported in raw units (mean differences in change); standardized effect sizes (e.g., Cohen's d/Hedges' g) may be reported for selected outcomes where they aid interpretation or comparability. For log-scaled outcomes, effects will be reported as ratios of geometric means (back-transformed).

Categorical outcomes (e.g., presence/absence of SAMS) will be analyzed by logistic regression including the same covariates. If convergence fails or assumptions are grossly violated and not resolved by transformation, supportive analyses using GEE or non-parametric methods may be used.

All analyses will be performed with investigators blinded to treatment codes until programming and verification are complete. Statistical significance will be claimed only for contrasts in the pre-specified confirmatory family using Holm–Šidák-adjusted inference (familywise two-sided $\alpha = 0.05$); all other outcomes will emphasize estimation (effect sizes and 95% CIs) and will be interpreted supportively.

**Additional and robustness analyses**

- **Per-protocol analysis:** conducted in the predefined PP population (see Section 20) to estimate efficacy under adherence conditions.
- **Model-robustness checks:** Alternative random-effects and/or residual covariance structures will be considered only if they materially improve fit (e.g., lower AIC/BIC) without changing the estimand; conclusions for confirmatory contrasts will be checked for robustness to such choices.

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**28. Handling Missing Data**

Missingness may occur due to withdrawal, assay failure, or QC exclusion.
Analyses assume outcome data are missing at random (MAR) conditional on observed data included in the analysis model. This assumption will be evaluated by comparing baseline characteristics of completers vs non-completers. Missing data will be handled implicitly in

the LMM using maximum likelihood estimation. The extent and reasons for missingness will be summarized by group.

**Sensitivity analyses**

Sensitivity analyses for the primary outcome (CS activity) and the pre-specified secondary outcome ($VO_{2peak}$) may be conducted if dropout exceeds 10% in any randomization group to assess robustness to missing-data assumptions. In such cases, simple plausibility-bound scenarios may be applied (e.g., no-change (baseline value) assumption for missing V2; and within-arm mean change substitution). These analyses are intended as plausibility bounds rather than definitive MNAR analyses; confirmatory inference for ΔCS will remain based on the prespecified LMM under the MAR assumption; $VO_{2peak}$ sensitivity results will be interpreted descriptively.

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**29. Additional analyses (supportive/exploratory)**

Analyses in this section are hypothesis-generating and will be interpreted in the context of effect sizes and 95% confidence intervals rather than confirmatory significance claims. Where p-values are presented, they will be considered descriptive unless explicitly stated otherwise.

**29.1 Pre-specified mechanistic endpoints (supportive)**

Exploratory mechanistic outcomes (e.g., anaerobic capacity, systemic biomarkers including inflammatory markers and per- and polyfluoroalkyl substances) will generally be analyzed using the same model framework as in Section 27 (e.g., LMMs with group, time, and group × time, plus relevant covariates), with emphasis on between-group differences in change and their 95% CIs. Multiplicity adjustment will not be applied unless extensive testing within a tightly related set makes control advisable for interpretability.

**29.2 High-dimensional discovery analyses (omics)**

Untargeted proteomic and metabolomic data will be processed using current best-practice pipelines (e.g., DIA-NN, Spectronaut, and/or established R-based workflows). Statistical methods (e.g., moderated t-tests/linear models [LIMMA], empirical Bayes approaches, or

mixed models where repeated measures are available) will be selected based on data dimensionality, variance structure, and diagnostics. Multiplicity in omics analyses will be addressed using false discovery rate (FDR) control (e.g., Benjamini–Hochberg), and findings will be reported as hypothesis-generating.

**29.3 Genetic and effect-modification analyses (exploratory)**

Pre-specified candidate polymorphisms will be evaluated as potential effect modifiers of statin and/or exercise responses. Models may include genotype (e.g., allele dosage) and its interaction with group × time terms; subgroup summaries (e.g., carriers vs non-carriers) may be presented where allele frequency permits. Results will be interpreted cautiously as exploratory, with multiplicity control (e.g., FDR) applied where appropriate.

**29.4 Sex-dependent analysis (exploratory)**

Potential sex differences will be explored by extending the primary model to include a group × time × sex interaction. These analyses are intended to describe potential heterogeneity of response and will be interpreted as hypothesis-generating.

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**30. Harms**

Adverse events (AEs), including statin-associated muscle symptoms (SAMS), will be monitored prospectively from intervention initiation (first dose and/or first supervised training session) until the post-intervention visit (V2).

All reported events will be summarized descriptively by intervention group according to:

- **Frequency** (number and percentage of participants reporting ≥1 AE),
- **Severity** (mild, moderate, severe)
- **Assessed relationship to study intervention** (related, possibly related, unrelated).

Pre-specified questionnaires (e.g., a structured SAMS symptom inventory) will supplement spontaneous reports to ensure standardized data collection. Serious adverse events (SAEs) and withdrawals due to AEs will be listed individually and summarized by category.

Safety summaries will be based on the Safety population (participants with ≥1 exposure to the allocated intervention; consistent with the mITT definition). If sample size permits,

exploratory subgroup summaries (e.g., by sex or adherence status) may be presented to describe patterns in AE reporting; no formal hypothesis testing is planned for safety endpoints.

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**31. Statistical software**

Primary and confirmatory analyses will be conducted in R (version ≥4.0). SAS (version ≥9.4) and/or Python (version ≥3.10) may be used for supportive analyses, data processing, and independent verification where appropriate. Exact software and package versions used for the final locked analysis will be documented in the analysis log and/or supplementary materials.

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