# Statistical Analysis Plan

## Impact of exercise training in combination with Dapagliflozin on physical function in adults with type 2 diabetes mellitus: Study protocol for the Dapagliflozin, Exercise Training and physicAl function (DETA) randomised controlled trial

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| Date | Version | Justification for SAP version |
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| 14/03/2025 | 0.1 | First Draft |
| 20/06/2025 | 0.2 | Refined based on further statistical review and feedback from the DMSC |
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### SAP responsibilities

| Role in SAP development | Name, affiliation | Role in trial |
|---|---|---|
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| SAP author | Aikaterina Tziannou, University of Leicester | Statistician |

### SAP signatures

| Role | Name, affiliation | Date | Signature |
|---|---|---|---|
| Trial PI | Prof. Melanie Davies, University of Leicester | 28/07/2025 | |
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# 1 Introduction

## 1.1 Trial background and rationale

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are associated with weight loss, diverse cardiorenal benefits and improved glycaemic control. However, the effects of SGLT2i on lean (muscle) mass, physical function and fitness are uncertain. The Dapagliflozin, Exercise Training and physicAl function (DETA) trial investigates whether an SGLT2i, dapagliflozin (DAPA), alone or in combination with structured exercise training, improves physical function, fitness and strength compared to diet-induced weight loss in adults with type 2 diabetes mellitus (T2DM), overweight/obesity, and impaired physical function. The full background and trial protocol can be found in Sargeant et al. 2024 as an open access publication.

## 1.2 Funder

The trial is funded by AstraZeneca through an investigator-initiated grant.

## 1.3 Primary hypotheses

- $H_0$: DAPA, alone and in combination with exercise training, will not improve physical function compared with matched diet-induced weight loss.
- $H_1$: DAPA, alone and in combination with exercise training, will improve physical function compared with matched diet-induced weight loss, with greater improvements in the combined therapy group.

# 2 Methods

## 2.1 Trial design

The trial is a single centre parallel group randomised controlled trial, in which participants are randomised (1:1:1) to either a diet control group (DIET-CON), DAPA (10mg once daily), or DAPA with exercise training (DAPA+EX). Participants are followed up for 24 weeks, with an intermediate assessment after 12 weeks.

## 2.2 Randomisation

Randomisation is stratified by, sex (men/women) and ethnicity (White European/ Other) and previous use of glucose lowering therapies (mono/combination therapy).

## 2.3 Sample size

To detect a clinically meaningful two-unit difference in the primary outcome (mPPT), with an SD of 2.4 units, 90% power and an alpha error rate of 0.025, 38 participants per group were required to complete the trial.

## 2.4 Framework

This is a superiority trial. Each of the 2 intervention groups (DAPA and DAPA+EX) will be compared separately to the control group.

## 2.5 Interim analyses and stopping guidance

No interim analyses are scheduled.

## 2.6 Timing of final analysis

Analyses described in this SAP will be performed following completion of the trial and database lock.

### 2.7 Timing of outcome assessments

Outcomes are assessed at 24 weeks, with an intermediate assessment at 12 weeks.

# 3 Statistical principles

## 3.1 Confidence intervals and p-values

Since there are 2 primary comparisons (each intervention group vs diet control), the estimates of effect for the primary outcome will be reported with 97.5% confidence intervals. Secondary outcomes will be reported with 95% confidence intervals.

## 3.2 Adherence and protocol deviations

Adherence to the intervention will be summarised as follows:

**DAPA+EX**: Those that have complied with their study medication prescription during the intervention period (at least 75% of the prescribed medication has been taken, with no evidence to the contrary) and that adhered to at least 75% of prescribed exercise sessions.

**DAPA**: Those that have complied with their study medication prescription during the intervention period (at least 75% of the prescribed medication has been taken, with no evidence to the contrary).

**DIET-CON**: Those that achieve at least 3% weight loss or more at 24 weeks and have not initiated SGLT2i therapy through primary care during the intervention period.

Initiation of GLP-1 receptor agonist or insulin therapies in any group will also be noted.

## 3.3 Analysis populations

The primary analyses will use a modified Intention-to-Treat (ITT) population, in which individuals are included in the group to which they were randomised; individuals with missing primary outcome data at follow-up will be excluded.

A sensitivity analysis of the primary outcome will be performed using two approaches: (1) Mixed Model for Repeated Measures (MMRM) incorporating both 12-week and 24-week data into the same model to account for missing data (see Section 5.2.3) and (2) a Per-Protocol (PP) population, comprising those that adhered to intervention as described above. Those that were prescribed GLP-1 receptor agonist or insulin therapies will be excluded from the PP analysis.

# 4 Trial population

## 4.1 Screening data

No screening data were collected.

## 4.2 Eligibility criteria

Eligibility criteria are described in Sargeant et al. 2024.

## 4.3 Recruitment

The numbers of individuals invited and recruited will be reported in the CONSORT diagram.

## 4.4 Withdrawal/loss to follow-up

The number (%) of individuals with complete data for the primary outcome (mPPT) and all specified secondary outcomes at baseline, 12 and 24 weeks will be reported by randomised group.

## 4.5 Baseline demographic characteristics

The following baseline characteristics will be summarised by randomised group, using mean and standard deviation (SD) for continuous variables with reasonably symmetric distributions, median and interquartile range (IQR) for continuous variables with skewed distributions, and number and percentage for binary or categorical variables.

- Age (yrs).
- Sex (men, women).
- Ethnicity (White European, South Asian, Other).
- Cardiovascular disease (myocardial infarction, angina, other).
- Hypertension (yes, no, unknown).
- Hypercholesterolemia (yes, no, unknown).
- Medication type (glucose lowering, antihypertensive, lipid lowering).
- Social deprivation (IMD score).
- Smoking status (current, past, never).
- Alcohol status (current drinker, ex-drinker, never) and alcohol consumption (units).
- Employment type (employed [full or part time], unemployed, retired, other).

Baseline values of all outcome variables will be summarised alongside the results at 12 and 24 weeks, as described in section 5.2.2.

# 5 Analysis

## 5.1 Outcomes

### 5.1.1 Primary outcome

The primary outcome is change in physical function at 24 weeks as measured by the modified physical performance test (mPPT); a continuous outcome ranging from 0 (completely impaired) to 36 (full functional capacity).

### 5.1.2 Secondary outcomes

***Deviation from the published protocol and trial registry***

The order of the secondary outcomes will be presented as listed here, which has been modified compared to trial registry and protocol. This order is presented to ensure presentation of data in the order of relevance to the primary outcome.

***Reported secondary outcomes***

Change in mPPT between baseline and 12 weeks will be a secondary outcome.

Change in the following variables between baseline and 12 weeks (where available), and between baseline and 24 weeks, will be considered secondary outcomes:

| | Week 12 | Week 24 | Categorical | Continous |
|---|---|---|---|---|
| **KEY SECONDARY OUTCOMES** | | | | |
| HbA1c (mmol/l, %) | X | X | | X |
| Weight (kg) | X | X | | X |
| BMI (kg/m$^2$) | X | X | | X |
| DXA assesed body composition - total fat mass (kg), fat mass percentage (%), lean mass (kg), lean mass percentage (%) | X | X | | X |
| MRI assessed absolute values will be reported for left ventricular end-diastolic volume (LVEDV) (mL), and LV mass (g). LV mass/LVEDV will be reported as a measure of concentricity. LVEDV and LV values indexed to body surface area will also be reported at baseline only. | | X | | X |
| $VO_2$ peak – as absolute value (ml), relative to body weight (ml/kg) and relative to lean mass (ml/kg) | X | X | | X |
| Strength - quadriceps strength (Nm at 60°[isokinetic], 90° [isometric and isokinetic]and 120º[isokinetic) - reported as absolute (Nm), relative to body weight (Nm/kg) and relative to lean mass (Nm/kg) values. Bicep strength (repetitions) will also be reported. | X | X | | X |
| PROM - WHO Disability Assessment Schedule 2.0 | X | X | | X |
| **OTHER SECONDARY OUTCOMES** | | | | |
| ***Other objective measures of function, fitness and strength*** | | | | |
| Short physical performance battery (SPPB) | X | X | X | X |
| Resting heart rate (beats/minute) | X | X | | X |
| Handgrip strength (kg) | X | X | | X |
| ***Body composition and muscle outcomes*** | | | | |
| DXA outcomes – appendicular (arms and legs) lean mass (kg), bone mineral density (T-score), total bone mineral density (g/m$^2$), total bone mass (kg) | X | X | | X |
| Waist circumference (cm), neck circumference (cm) | X | X | | X |
| Muscle ultrasonography - muscle cross-sectional area (cm$^2$), muscle and subcutaneous fat thickness (cm), fibre angle pennation and echo intensity | X | X | | X |
| Resting metabolical rate (kcal/day) | X | X | | X |
| ***Main CMR and Echo measures*** | | | | |
| MRI - LV ejection fraction (%) | | X | | X |
| Echo - Diastolic transmitral flow velocities, E/A ratio and early diastolic mitral annular velocities (e') to estimate LV filling pressures | | X | | X |
| ***Accelerometer-based physical activity measures and sleep*** | | | | |
| Ambulatory activity (steps/day), overall acceleration (mg), intensity gradient and most active continious 10 and 30 minutes (mg) | X | X | | X |
| Time spent sedentary (mins.day), and in light (mins/day), and moderate to vigorous physical activity (≥ 1 minute bouts) (mins/day) | X | X | | X |

| | | | | |
|---|---|---|---|---|
| Sleep window (mins/night), sleep duration (mins/night), sleep efficiency (%), sleep midpoint variability | X | X | | X |
| ***Cardio-metabolic-renal indicators*** | | | | |
| Systolic and diastolic blood pressure (mmHg) and heart rate (beats/min) | X | X | | X |
| Cinical cardiometabolic biomarkers - fasting glucose (mmol/l), fasting insulin (mU/L), HOMA-IR, total cholesterol (mml/l), HDL (mmol/l), LDL (mmol/l) and triglycerides (mmol/l), C-reactive protein (mmol/l) NTproBNP (pg/ml) | X | X | | X |
| Renal function - estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio | X | X | | X |
| ***Dietary variables*** | | | | |
| Total energy (kcal/day) and macronutrients (g/day) (protein, carbohydrates, lipids) | X | X | | X |
| Food cravings – Control of Eating Questionnaire (CoEQ, VAS), Appetite Visual Analogue Scale (VAS) | X | X | | X |
| ***Patient reported outcomes (PROMS)*** | | | | |
| Hospital Anxiety and Depression Scale Questionnaire (HADS), Diabetes Distress Scale, mMRC Dyspnoea Scale, the European QoL-5 Dimensions (EQ-5D)(including VAS), General Practice Physical Activity Questionnaire (GP-PAQ) | X | X | X | X |

## 5.2 Analysis methods

### 5.2.1 Deviations from the published protocol

A brief analysis plan was reported in the published protocol (Sargeant et al. 2024). The analysis plan described below is intended to supersede the published protocol. In particular, greater detail is provided on the sub-group analysis and missing data. The order of outcomes has been rearranged (as described in section 5.1.2). Select outcomes (MRI- derived intra- and inter-organ adiposity, cardiac strain parameters and aortic distensibility) that were described in the study protocol and/or trial registries but are omitted from this SAP. This is to avoid multiplicity in secondary outcomes and retain a focus on clinical parameters linked to the primary outcome. Additional exploratory outcomes will be saved for sub-analyses. We have also revised the stratification criteria for age (from 65 years to 70 years) to reflect older than anticipated population at recruitment with functional status also added as a stratification factor for the sensitivity analysis, reflecting the focus of the trial and primary outcome.

### 5.2.2 Analysis of the primary and secondary outcomes

*Primary outcome*

The mean and SD of mPPT will be calculated at baseline, by randomised group. Mean and SD of the change values will be reported between baseline and 12 weeks and between baseline and 24 weeks. The outcome at 24 weeks is primary.

For the primary outcome, the 97.5% confidence intervals and p-values for the comparison of each intervention group with the control group will be derived from a linear regression model with change in

mPPT as the dependant variable and randomisation group included as a fixed factor. Baseline mPPT value, randomisation stratification variables (sex, ethnicity, background medications) and age will be included as covariates. It is anticipated the primary outcome will be normally distributed. This will be inspected and alternative distributions will be considered where appropriate. $P < 0.025$ will be considered significant. The adjusted intervention effect (intervention vs control) will be used to interpret results.

*Secondary outcomes*

Secondary outcomes that are changes in continuous variables between baseline and either 12 or 24 weeks will be analysed using the same method as the primary outcome. However, secondary outcomes will be reported with 95% confidence intervals. P values will not be reported for secondary outcomes; results for the intervention effect that do not cross the null will interpreted as significant. Binary variables will be analysed using logistic regression.

### 5.2.3 Missing data

*All continuous outcomes: missing follow-up data*

For all outcomes, participants with missing data will be excluded from the relevant analysis. This "complete-case analysis" is valid under the assumption that the outcome is missing at random (MAR), conditional on randomised group, baseline value and other covariates in the model.

Demographic characteristics of participants at baseline will be summarised in those with and without data for the primary outcome at 24 weeks.

*Primary outcome: sensitivity analyses*

A sensitivity analysis will be conducted using a mixed model for repeated measures (MMRM) to account for missing data. Under a MMRM approach, all data (e.g. at both 12 and 24 weeks) contributes to the model and missing values are implicitly handled under the assumption of MAR. For the MMRM analysis, the fixed variables of the analysis model will include randomisation group, timepoint (12 or 24 weeks), group by timepoint interaction, baseline value of the outcome, randomisation stratification variables (sex, ethnicity, background medications) and age as covariates. An unstructured covariance matrix for measurements within the same participant will be used. Post-hoc comparisons at 24 weeks will be extracted and compared to the primary analysis.

A per protocol (PP) analysis will additionally be performed, including participants who have adhered to the intervention as described in section 3.2.

### 5.2.6 Subgroup analyses for primary outcome

For the primary outcome only, interactions between randomised group and (1) sex (men/women), (2) age (<70 years/≥70 years), and (3) functional status (SPPB ≥ 10 vs SPPB < 10) will be tested by including the relevant interaction parameters in the analysis model and performing an F-test of the null hypothesis that these parameters are 0 (i.e. no significant interaction).

If the p-value for any of the interactions tested above is <0.05, then estimates and 97.5% confidence intervals of the 2 intervention effects (DAPA vs DIET-CONT, DAPA+EX vs DIET-CONT) on the primary outcome will be reported within the relevant subgroups, based on fitting the linear regression model described in section 5.2.2 within each subgroup. For example, if the p-value for the randomised group x sex interaction is <0.05, then the primary outcome results will be presented separately within men and women.

### 5.2.7 Other analyses

For the primary outcome only, if the p-value for either of the 2 intervention effects is <0.025, the effect of DAPA vs DAPA+EX and 97.5% confidence interval will also be estimated for the primary outcome using the same linear regression model described in section 5.2.2. For this scenario, if there is a difference in the intervention effect for primary outcome between DAPA and DAPA+EX, then the secondary outcomes will also be analysed for the same comparison using the approach described in section 5.2.2. This will be considered an exploratory analysis.

### 5.2.8 Multiplicity

Since there are 2 primary comparisons, 97.5% (rather than 95%) confidence intervals will be reported for the primary outcome. All other secondary outcomes will be reported with 95% confidence intervals.

No formal corrections will be made to account for the large number of secondary outcomes and comparisons that will be presented. However, p-values for secondary outcomes will not be reported, and interpretation of the effects and confidence intervals will be made with caution, recognising the potential for chance findings among the multiplicity of outcomes and comparisons.

## 5.3 Safety data

The number (%) of individuals experiencing a serious adverse event and any adverse event of interest (**Dapagliflozin**: hypoglycaemia, diabetic ketoacidosis – DKA, Infections (genital and urinary only), dehydration/volume depletion; **Exercise**: musculoskeletal injury) by randomised group.

## 5.4 Statistical software

Analyses will be performed using R version 4.5.1

# 6 References

Sargeant JA, Ahmad E, James E, et al. Impact of exercise training in combination with dapagliflozin on physical function in adults with type 2 diabetes mellitus: study protocol for the Dapagliflozin, Exercise Training and physicAl function (DETA) randomised controlled trial. BMJ open. 2024 Nov 1;14(11):e084482.