Statistical Analysis Plan

Remission of type 2 diabetes and improved diastolic function by combining structured exercise with meal replacement and food reintroduction among young adults: RESET for REMISSION randomised controlled trial

Trial registration number: ISRCTN83465245

SAP revision history

Date	Version	Justification for SAP version
31 May 2024	0.1	First draft for investigator review
07 March 2025	0.2	Updates based on DMEC feedback
18 March 2025	1	Updated and revised based on further statistical review

SAP responsibilities

Role in SAP development	Name, affiliation	Role in trial
SAP author 1	Thomas Yates, University of Leicester	Study Co-Nominated Principal Investigator
SAP author 2	Elham Rahme, McGill University	Study Co-Investigator (Biostatistician)
SAP author 3	Kaberi Dasgupta, McGill University	Study Co-Nominated Principal Investigator
SAP reviewer 2	Stephen Sharp (to be sent for review), University of Cambridge	Data Monitoring Committee, Independent Statistician
SAP reviewer 3	Raman Agnihotram, Biostatistical Consulting Unit, CORE, Research Institute of the McGill University Health Centre	Analyst
SAP reviewer 4		
SAP reviewer 5		

SAP signatures

Role	Name, affiliation	Date	Signature
SAP author 3 and Trial Co-NPI	Kaberi Dasgupta, McGill University	18/07/2025	
SAP author 1 and trial Co-NPI	Thomas Yates, University of Leicester	18/07/2025	
SAP author 2	Elham Rahme, McGill University	7/18/25	

1 Introduction

1.1 Trial background and rationale

Type 2 diabetes mellitus (T2DM) onset before 45 years of age has a magnified lifetime risk of cardiovascular disease. Diastolic dysfunction is among its earliest cardiac manifestations. Low energy diets incorporating meal replacement products can induce diabetes remission, but do not lead to improved diastolic function measures, unlike supervised exercise interventions. The RESET for REMISSION trial investigates the impact of a combined low energy diet and supervised exercise intervention on T2DM remission, with peak early diastolic strain rate, a sensitive MRI-based measure, as a key secondary outcome.

1.2 Primary trial objectives

- To investigate whether a low energy diet combined with exercise training leads to diabetes remission after 24 weeks in younger (18-45 years) adults with T2DM

1.3 Key secondary trial objectives

To investigate whether a low energy diet combined with exercise training in this population results in the following outcomes, compared to usual care:

- Diabetes remission at 12 weeks
- Hypertension remission at 12 and 24 weeks
- Improved diastolic function at 24 weeks
- Improved markers of muscle strength, physical function, and cardiorespiratory fitness at 12 and 24 weeks
- Preserved lean mass whilst reducing fat mass at 12 and 24 weeks
- Improvements in other clinical markers of cardio-metabolic-renal health

We list the specific outcomes in Table 1, as published in our protocol, with additional indication as to whether the variables are categorical or continuous.

Table 1. Trial outcomes and variable types

	Week 12	Week 24	Categorical	Continous
PRIMARY OUTCOME				
Diabetes remission		X	X	
KEY SECONDARY OUTCOMES				
Other remission, glycemic, and insulin resistance measures				
Diabetes remission	X		X	

Hemoglobin A1c and fasting glucose and insulin, Homeostatic Model Assessment for Insulin Resistance	X	X		X
Main Cardiac Magnetic Resonance Imaging (CMR) measures				
Left ventricular peak early diastolic strain rate (circumferential and longitudinal, MRI)		X		X
Left ventricular end-diastolic mass, volume and mass to volume ratio		X		X
Main fitness measure				
VO_2 peak (absolute and relative to total lean mass and total body mass)	X	X		X
Main adiposity and lean mass measures				
Total tissue, fat, and lean mass (DXA)	X	X		X
Weight and BMI	X	X		X
Cardiometabolic indicators				
Systolic and diastolic blood pressure and heart rate	X	X		X
Hypertension remission	X	X	X	
Total cholesterol, HDL, LDL and triglycerides	X	X		X
OTHER SECONDARY OUTCOMES				
Renal function measures				
Creatinine and estimated glomerular filtration rate	X	X		X
Urine albumin to creatinine ratio	X	X		X
Hepatic function measures				
Aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase and bilirubin	X	X		X
Depression, anxiety, and distress				

Hospital Anxiety and Depression Scale and Diabetes Distress Scale	X	X		X
Indirect calorimetry				
Resting metabolic rate	X	X		X
Additional cardiac and aortic MRI-based measures				
Longitudinal and circumferential measures of systolic strain, left ventricular end systolic volume, ejection fraction, mean T1 time		X		X
Longitudinal and circumferential peak late diastolic strain rates and the ratio of peak early: peak late diastolic strain rate		X		X
MRI estimated pulmonary capillary wedge pressure		X		X
Cross-sectional areas and distensibility of ascending and descending aortae		X		X
Additional measures of lean mass and adiposity				
Neck, hip, and waist circumference	X	X		X
Visceral adipose tissue, pancreatic and liver fat percentages, subcutaneous adipose (MRI)		X		X
Appendicular lean mass (DXA)	X	X		X
Dietary variables				
Total energy and macronutrients (protein, carbohydrates, lipids)	X	X		X
Selected carbohydrate types (total sugars, starch, fibre), selected lipid types (saturated, monounsaturated, polyunsaturated, cholesterol), alcohol	X	X		X

Accelerometer-based physical activity measures and sleep (daily average)				
Steps, overall acceleration, and intensity gradient metric	X	X		X
Minutes for each of sedentary, light, and moderate to vigorous physical activity	X	X		X
Sleep time, duration of night, sleep efficiency (sleep time/duration of night)	X	X		X
Other exercise stress test measures				
VCO_2 peak, maximum gradient achieved	X	X		X
Tertiary outcomes				
Bone measures				
Total bone mineral density and bone mineral content (DXA)	X	X		X
Physical function				
Handgrip strength	X	X		X
Short Physical Performance Battery	X	X		X
Dyspnoea scale	X	X		X
Overall health state				
EQ-5D-5L score (EuroQuol group 5-dimensional 5-level questionnaire)	X	X		X
WHO Disability Assessment Schedule 2.0	X	X		X

2 Update and deviations from the published protocol

We provided a brief analysis plan in our published protocol [1]. We expand upon and update the analysis plan here. We have modified the criterion for adherence to the dietary intervention from 10% weight loss to 5% weight loss in line with widely considered minimum clinically important weight loss thresholds – see **section 4.2 .** Finally, because we enrolled a high number of participants from ethnic minorities, we have detailed an additional sub-group analysis by ethnicity (see **section 6.2.3**).

3 Methods

3.1 Trial design

The trial is a bi-country three-centre parallel group randomised controlled trial, in which participants are randomised to either a control group (usual care) or a low energy diet combined with exercise training. Participants are followed up for 24 weeks (concurrent with interventions), with an intermediate assessment after 12 weeks.

3.2 Randomisation

Individual randomisation (1:1) is stratified by country (Canada/England) and sex (women/men) in blocks of variable size.

3.3 Blinding

Group allocation is open to both the participant, treating physician and the rest of the intervention delivery teams. However, it is a blinded end-point trial, meaning the analysis of HbA1c, which informs the primary outcome, and the trial statistical analyst team will be blinded to allocation.

3.4 Sample size

In order to achieve the sample size calculation specified in the trial protocol [1], we estimated that 70 individuals would be required to complete the trial (28 UK, 42 Canada). This will enable detection of a remission rate of 35% or more at 24 weeks with 90% power and significance level of 0.05, assuming up to a 5% remission rate in the control group.

2.4 Framework

This is a superiority trial. We will compare the primary and secondary outcomes in the intervention group to the control group.

2.5 Interim analyses and stopping guidance

None planned.

3.5 Timing of final analysis

The Biostatistical Consulting Unit at the Research Institute of the McGill University Health Centre (Raman Agnihotram) will perform analyses described in this SAP following completion of the trial and database lock.

3.6 Timing of outcome assessments

We assess outcomes at 24 weeks, with an intermediate (secondary) assessment at 12 weeks – see **Table 1**.

4 Statistical principles

4.1 Confidence intervals

We will report estimates of effect with 95% confidence intervals.

4.2 Intervention adherence

Adherence to the dietary component of the intervention will be summarised as follows:
The number (%) achieving a weight loss threshold of at least 5% at 24 weeks will be considered as adherent.

Adherence to the exercise component of the intervention will be summarised as follows:
The number (%) of prescribed and supervised exercise sessions completed will be reported. Attendance of at least two thirds of supervised sessions (e.g. at least 12 sessions) and maintenance review sessions (e.g. at least 3 sessions) will be considered as adherent.

4.3 Analysis population

The primary outcome (diabetes remission at 24 weeks) and the secondary outcome of remission at 12 weeks will use an Intention-to-Treat (ITT) population, in which individuals are included in the group to which they were randomised. For those with missing follow-up data, information from clinical records will be extracted where available, or by assuming no remission where clinical records are unavailable (see **section 6.2** for details).

All secondary outcomes will use a modified ITT population whereby individuals are included in the group to which they were randomised using a complete case sample (i.e. those with missing follow-up data will be removed from the analysis). Missing values will be handled implicitly through a Mixed Model for Repeated Measures (MMRM).

A secondary analysis of the primary outcome will be undertaken using a Per-Protocol (PP) population, comprising the following:

Control – all individuals

Intervention – those judged to have adhered to both the diet and exercise components of the intervention (see **section 4.2** for definitions)

5 Trial population

5.1 Eligibility criteria

Eligibility criteria are described in published protocol [1]

5.2 Recruitment and screening

We will present a CONSORT diagram outlining participant flow throughout the study. This will include the number of individuals invited to participate; categorized by source (e.g., primary care, secondary care, existing databases, publicity or press releases, and participant referrals), as well as the number reached, screened for eligibility, and deemed eligible. We will also report the number of individuals who expressed interest or declined participation (including reasons for non-participation when available), those who completed the run-in period, screening calls, or baseline visits, and those who were randomized. Finally, the diagram will capture the number of participants who were withdrawn or lost to follow-up, who completed trial evaluations, and who adhered to trial procedures.

5.3 Baseline characteristics

The following baseline characteristics will be summarised by randomised group in Table 1, using mean (SD) or median (IQR) as appropriate for continuous variables, and number and percentage for binary or categorical variables.

- Age (yrs).
- Sex at birth (female/male)

- Ethnicity (European/South Asian/Other)
- Family history of diabetes in first-degree relatives (yes/no).
- Diabetes Duration
- Medication (glucose lowering, antihypertensive, lipid lowering).
- Smoking status (current, past, never)
- Employment type (full time, part time, unemployed, retired, other)

Baseline values (as mean [SD] for continuous variables or number [%] for categorical variables) of all reported secondary outcome variables will be incorporated into the Table of Results.

6 Analysis

6.1 Outcomes

6.1.1 Primary outcome

We define diabetes remission as HbA1c <6.5% (48mmol/mol) at 24 weeks, without prescribed glucose lowering medications between 12 and 24 weeks of the study period. We will report the number (%) of remission at 24 weeks.
The number (%) of remission at 12 weeks, without glucose lowering medications between 0 and 12 weeks, will be reported as a secondary outcome.

6.1.2 Secondary outcomes

We report secondary outcomes and follow-up time points in **Table 1,** with the corresponding methods reported in the protocol paper [1].

6.2 Analysis methods

6.2.1 Analysis of the primary outcome

Given that remission counts in the control arm are likely to be less than 2, we will compare remission counts between intervention and control arms using Fisher's exact test statistics (i.e., stratification by country and by sex). If the number of remission cases in the control group are higher than expected, we will consider a Pearson chi-square test. Further, in this scenario, we will also consider logistic odds ratios (ORs) with 95% CIs (exact method) to further quantify the efficacy of intervention over the control group, after adjusting for factors used to stratify the randomisation (country and sex); we will not have missing values for these covariates.

The primary outcome will be analysed using a full ITT approach; therefore, if trial evaluation data for diabetes status outcomes are missing, we will use clinical records-based on the most recent information on HbA1c (recorded +/- 6 weeks from scheduled 24-week follow-up) and glucose lowering medication use to determine if remission occurred. Where data is also missing from clinical records, we will assume no remission.

We will repeat these analyses for the per-protocol population (see **section 4.2**)

6.2.2 Analysis of secondary and tertiary outcomes

We will analyse continuous secondary/ tertiary outcomes at 12 and 24 weeks using a Mixed Model for Repeated Measures (MMRM), adjusted for the fixed effects of group allocation, time (12 and 24 weeks), group allocation x time interaction, baseline value and randomisation factors (sex and country). Under a

MMRM approach, missing values are handled implicitly under the assumption of missing at random. An unstructured covariance matrix to account for measurements within the same participant will be selected as default, but may be updated based on model fit. The group allocation x time interaction will allow for post-hoc contrasts to be extracted for the 12- and 24-week intervention effects (intervention group minus control group with 95% CI), along with the corresponding within group change values (mean 95% CI).

We will analyse the categorical secondary outcomes (diabetes remission at 12 weeks, hypertension remission at 12 and 24 weeks) as described for the primary outcome (Fisher's exact test statistics). We define hypertension remission as a systolic/diastolic blood pressure of ≤ 130/80 mm Hg without use of antihypertensive agents during prior 12 weeks.

6.2.3 Subgroup analyses for primary outcome

The primary outcome model will be repeated within (stratified)by the following subgroups: (1) country (UK, Canada), (2) sex (men/women), (3) ethnicity (White European/South Asian/Other) and degree of weight loss (<5%, 5% to <10%, 10% to <15%, ≥15%).

6.2.4 Missing data

Primary outcome and categorical secondary outcomes at 12 and 24 weeks
Missing data will be replaced with data from clinical records where available (recorded +/- 6 weeks from scheduled 12-week and 24-week follow-up) or by assuming no remission where there are no relevant clinical records.

All continuous secondary/ tertiary outcomes: missing baseline values
For continuous outcomes, participants with a missing baseline value of the variable, but with a value at the relevant follow-up time (12 or 24 weeks) will be included in the analysis using the missing indicator method, which is a valid method for pre-randomisation measures in trials [2], or by carrying the 12-week (if available) or 24-week value backwards depending on the level of missingness.

All continuous secondary/ tertiary outcomes: missing follow-up data
For continuous secondary outcomes, we will exclude participants with missing data at the relevant follow-up time (12 or 24 weeks). 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.

6.2.5 Multiplicity

We will not make any formal corrections to account for the number of secondary outcomes. However, all secondary outcomes listed as ‘other secondary outcomes’ or ‘tertiary outcomes’ in Table 1 will not be interpreted in isolation but in relation to the overall pattern of results.

6.3 Safety data

We will summarize the number (%) of individuals experiencing either an adverse event or a serious adverse event, by adverse event category and by randomised group.

6.4 5.4 Statistical software

To be added

7 References

1. Dasgupta K, Boulé N, Henson J, Chevalier S, Redman E, Chan D, McCarthy M, Champagne J, Arsenyadis F, Rees J, Da Costa D. Remission of type 2 diabetes and improved diastolic function by combining structured exercise with meal replacement and food reintroduction among young adults: the RESET for REMISSION randomised controlled trial protocol. BMJ open. 2022 Sep 1;12(9):e063888.
2. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. Statist. Med. 2005;24:993-1007.