Remote Diet Intervention to REduce long COVID symptoms

ReDIRECT

STATISTICAL ANALYSIS PLAN (SAP)
6 month analysis

Study Title:	Remote Diet Intervention to REduce long COVID symptoms Trial
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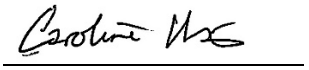
		Signature	Date
Prepared by:	Dr Caroline Haig Biostatistician, Robertson Centre for Biostatistics		28/04/2023
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1. INTRODUCTION

1.1. STUDY BACKGROUND

Around 10% of people infected with COVID-19 experience persistent symptoms for 12 weeks or longer ('Long COVID'). There are strong, likely causal links between overweight/obesity and severity of COVID-19, exemplified by links to type 2 diabetes or hypertension, and many people with Long COVID are overweight/obese. An inflammatory mechanism has been proposed to mediate some aspects of Long COVID, aggravated by susceptible individuals being overweight or obese.

Some of the most common symptoms (fatigue, pains, breathlessness) are also common with overweight/obesity, and helped by weight loss. However, robust trial data are needed to establish the impact of intentional weight loss on Long COVID symptoms.

The aim of ReDIRECT is to test the effectiveness of a well-established professional weight management programme in people with Long COVID.

1.2. STUDY OBJECTIVES

The primary research objective is to evaluate, at 6 months, whether:

i. Effective weight management improves self-selected personalised primary symptoms of Long COVID, vs standard care;
ii. The weight management intervention improves wider health and psychological outcomes, vs standard care;
iii. Symptom improvements persist to 12-months. The control group will be offered delayed entry treatment after 6-months, as an incentive. They will add observational data to 12-months but will not form part of the RCT analysis.

The secondary research objectives are to assess the implementation of the intervention in terms of dose, fidelity and reach, and to explore differences by sociodemographic characteristics (age, sex, ethnicity, SES). Explicitly, to:

iv. Explore how contextual factors influence variations in implementation and effectiveness, and identify barriers and facilitators to delivery.

v. Explore the experience of the intervention from the perspective of participants, including acceptability, patterns of use, and barriers and facilitators to use.

vi. Evaluate within-trial cost-effectiveness of the intervention.

1.3. STUDY OUTCOMES

1.3.1. PRIMARY OUTCOME

The primary outcome will be a continuous measure derived from the symptom score for the most important Long COVID symptom as reported by each participant at baseline, 3 and 6 months, with the 6-month measure the primary outcome.

Participants will complete symptom scores at baseline and will nominate the symptom they would most like to improve:

- Fatigue: validated Chalder Fatigue Scale (CFQ-11)
- Breathlessness: modified MRC Dyspnoea Scale

- Pain: P4 Numeric Pain Rating Scale
- Anxiety and depression: Hospital Anxiety and Depression Scale (HADS) questionnaire total score
- Other – for other symptoms with no pre-specified scale, using a Visual Analogue Scale (0 to 10).

Each measure will be standardised by subtracting the mean and dividing by the standard deviation, amongst those who select that particular symptom. Follow-up scores will be standardised according to the same mean and standard deviation.

1.3.2. Secondary Outcomes

Secondary outcomes are, at baseline and all timepoints:

- All non-selected primary symptom outcomes (fatigue, breathlessness, pain, HADS total score, other)
- Outcome subscales
    - Fatigue: physical, mental
    - HADS: anxiety, depression
- Self-measured weight, blood pressure, medications for symptoms of Long COVID, Quality of Life (EQ-5D 5L), Work Productivity and Activity Impairment (WPAI).

1.3.3. Exploratory outcomes / sub-studies

Longer-term follow-up after 12 months post weight management initiation for all treatment group participants and delayed entry participants, focusing on all primary and secondary outcomes listed above.

1.4. Study Design

Randomised, non-blinded, wait-list controlled trial.

1.5. Sample Size

Section 7.3 of the study prtocol states:

> *"Assuming the SD of the score at follow-up (derived from the symptom score at follow-up, standardised using the same mean and SD as used at baseline) is also 1, then to have 90% power to detect a between group difference of 0.5 at follow-up, at a 5% significance level, will require a sample size of 86 per group with follow-up data. To allow for attrition, we aim to randomise 200 people.*
>
> *If the intervention proves to be acceptable and safe, the 100 participants originally allocated to the control group will be offered the intervention as a delayed entry group. Their results (some may exceed the lifetime of the project) will be analysed as observational, and used to increase the study power for hypothesis generation, e.g. to explore relationships between extent of weight change and Long COVID symptoms."*

1.6. Statistical Analysis Plan (SAP)

1.6.1. SAP Objectives

The objective of this SAP is to describe the statistical analyses to be carried out for the REDIRECT Study at 6 months. This covers primary outcome data collected up to and including 6 months. A separate SAP will be produced for the 12 month analysis.

1.6.2. General Principles

Analyses will be carried out according to the intention to treat principle, that is, in relation to randomised treatment allocation, rather than treatment received.

Data will be summarised overall and by treatment group. Continuous variables will be summarised as the number of observations, number of missing values, mean, standard deviation, median, quartiles, and range. Categorical variables will be summarised as the number of observations, number of missing values, frequencies, and percentages.

Missing data will not be imputed in main analyses. Multiple imputation, and weighting by the inverse probability of being followed up will be used as sensitivity analyses. No adjustments will be made for multiple comparisons.

1.6.3. Current Protocol

The current study protocol at the time of writing is version 1.2 dated 27/07/2022. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. If no changes are required to this SAP following future amendments to the study protocol, this will be documented as part of the Robertson Centre Change Impact Assessment processes.

1.6.4. Deviations from Protocol

No deviation from the analyses specified in the Protocol are planned.

1.6.5. Additional Analyses

No analyses additional to those specified in the Protocol are planned.

1.6.6. Software

All statistical analyses will be carried out with SAS v9.3 or R 4.0 [R Development Core Team 2021] or higher versions of these programs.

2. Analysis

2.1. Study Populations

The Full Analysis Set (FAS) will consist of all patients who were randomised. Analyses within the FAS will compare treatment groups as randomised, regardless of whether any treatment was received.

2.2. Efficacy Outcomes

Efficacy outcomes will be analysed using the FAS. Missing data will not be imputed initially. No adjustments will be made for multiple comparisons.

A general linear model, adjusted for the baseline value of the primary outcome and stratification variables (age, IMD, sex, ethnicity and chosen symptom) will be used. The treatment effect estimate, 95% confidence interval (CI), and p-value will be reported.

Secondary analyses will use linear or logistic regression, as appropriate, to estimate between-group differences or odds ratios for secondary outcomes.

2.2.1. ADHERENCE

Number of Counterweight appointments attended will be summarised. In addition, the proportion who chose each program, the number who switched programs and the reasons for switching will be summarised.

2.2.2. SENSITIVITY ANALYSES

The analysis of each primary and secondary outcome will be repeated using multiple imputation. Multiple imputation using chained equations will be used, implemented using the mice package in R. All variables in the model will be used in the MICE procedure, plus education, EQ5D, BMI, baseline physical activity, and change in employment as auxiliary variables.

The analysis of each primary and secondary outcome will be repeated, with weighting by the probability of being followed up. This probability will be obtained from a logistic regression model with baseline data as predictors. This model will be developed blind to randomised group, prior to unblinding, and will be specified in full as part of the final statistical outputs.

2.2.3. SUBGROUP ANALYSES

For each primary and secondary outcome, subgroup effects will be explored by extending the main analysis regression models to include interaction terms. Within-subgroup intervention effect estimates and 95% CIs will be presented, including interaction p-values. The prespecified subgroups of interest are sex, age (in thirds of the baseline distribution), main symptom, socioecenomic deprivation (Deciles 1-5 vs. 6-10), and baseline BMI (<30 kg/m^2, ≥ 30 kg/m^2).

2.2.4. EXPLORATORY ANALYSES

The following analyses are exploratory, and will not form part of the main statistical outputs. They will be carried out after the main analyses specified above have been completed. The precise analyses will depend on the result of the main analyses, and the following are an indication of the types of analyses that may be performed.

Associations between baseline characteristics and the primary outcome will be explored by extending the main analysis regression models. Similar exploratory analyses may be applied to secondary outcomes.

Additional exploratory analyses will investigate if short-term differences between randomised groups (particularly early weight loss) are predictive of 6-month intervention effects.

2.3. SERIOUS ADVERSE EVENTS

The characteristics of serious adverse events (SAEs) that occur on or before the date of the 6 month assessment will be summarised as a whole and by treatment group. For subjects who withdraw, SAEs up to the point of withdrawal will be included. For subjects who did not have a 6 month assessment, but remained in the study, SAEs up to 182 days (26 weeks) from randomisation will be included.

Characteristics of SAEs to be reported are:

- days since randomisation;
- duration (in days);
- severity;
- relationship to study procedures/intervention;
- whether classified as a RUSAE;
- outcome;

The number and percentage of patients with at least one SAE on or before the date of the 6 month assessment will be reported for the study sample as a whole and by treatment group, for any SAE and by MedDRA system organ class and preferred term. These summaries will be repeated for fatal SAEs and RUSAEs.

3. DOCUMENT HISTORY

This is v1_0 of the Statistical Analysis Plan for REDIRECT 6 Month Analysis, dated 28/04/2023. This is the original version of this document.

4. TABLES

All statistical tables within the final statistical report will be produced using dummy treatment codes and the content and layout approved prior to database lock.

5. FIGURES

All figures within the final statistical report will be produced using dummy treatment codes and the content and layout approved prior to database lock.