Full Study Title: Remote Diet Intervention to REduce long COVID symptoms Trial (ReDIRECT)

ReDIRECT
Remote Diet Intervention to
REduce long COVID symptoms Trial

PROTOCOL VERSION NUMBER AND DATE:	Version 1.1 (19/11/2021)
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Sponsor:	NHS Greater Glasgow & Clyde
Sponsors Number:	GN21ME311
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Funders Number:	COV-LT2-0059

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

NHS
Greater Glasgow and Clyde

University of Glasgow

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Study Intervention Provider	**Counterweight Ltd** Contact: Laura Sloman (Chief Operation Officer) Tel: +447742 797522 Email: laura.sloman@counterweight.org

ROLE OF STUDY SPONSOR AND FUNDER/SUPPORTER

NHS Greater Glasgow & Clyde will be the sponsor of the trial. Sponsor will provide approvals, support regulatory submissions and ensure the requirements of the study are met as per the statement on the signature page of this protocol.

The study is funded through an award from the National Institute for Health Research (NIHR) to the University of Glasgow.

Counterweight Ltd, sub-contracted to the University of Glasgow, is the study intervention provider. Counterweight Ltd is represented by Laura Sloman, Chief Operation Officer.

ROLES & RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/ GROUPS & INDIVIDUALS

Trial Management Group (TMG)

The study will be coordinated by the Study Management Group (SMG). The SMG will consist of all co-applicants, plus an independent GP advisor, the project manager and representatives from both NHS GG&C and other organisations relevant to the study. The role of the group is to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet on a 2-monthly basis.

Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will meet every 4 months and will:

- review the trial protocol and agree substantial protocol amendments
- provide advice to the investigators on all aspects of the trial
- include an independent chairperson, at least 2 other independent members (including an independent statistician and Clinical Trials Specialist), the sponsor and a participant or carer representative.

Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the TSC who will advise the sponsor. The TSC will meet at the start of the study, and 6-monthly thereafter. The TSC will have its own charter outlining the role and responsibilities of its members. The TSC may invite other attendees from the trial team to present or participate in discussions on particular topics. These attendees will be non-voting members.

PROTOCOL CONTRIBUTORS

The protocol has been developed by a group with extensive clinical and research experience relevant to this study – our list of contributors can be found on Pages iv to vi of this protocol.

The study will be supported by the Robertson Centre for Biostatistics, University of Glasgow and Clinical Research & Innovation and the Project Management Unit, NHS GGC

PROTOCOL APPROVAL

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Good Clinical Practice (GCP) guidelines, the Sponsor's (Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor (NHS Greater Glasgow and Clyde):

Date: 15/11/2021

Signature: 

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Name (please print): DR MAUREEN TRAVERS

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Position: Research Coordinator

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Chief Investigators:

Date: 15/11/2021

Signature: 

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Name: (please print): DR DAVID BLANE

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Position: Clinical Research Fellow in General Practice & Primary Care.....

Date: 15/11/2021

Signature: 

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Name: (please print): PROFESSOR EMILIE COMBET

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Position: Professor of Human Nutrition

.....

Study Statistician:

Date: 15/11/2021

Signature: 

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Name: (please print): PROFESSOR ALEX MCCONNACHIE

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Position: Assistant Director of Biostatistics

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ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CEAC	Cost-Effectiveness Acceptability Curve
CFQ-11	Chalder Fatigue Scale
CHO	Carbohydrate
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Indemnity Scheme
CRF	Clinical Record Form
CTIMP	Clinical Trial of Investigational Medicinal Product
eCRF	Electronic Clinical Record Form
eGFR	Estimated Glomerular Filtration Rate
EQ-5D-5L	EuroQol 5 Dimension 5 Level Questionnaire
EU	European Union
GCP	Good Clinical Practice
GCTU	Glasgow Clinical Trials Unit
GP	General Practitioner
Gp1	Group 1
Gp2	Group 2
HADS	Hospital Anxiety and Depression Scale
HbA1c	Glycated Hemoglobin
HEAP	Health Economic Analysis Plan
ICF	Informed Consent Form
ICU	Intensive Care Unit
ISO	International Standards Organization
MR	Meal Replacement
MRC	Medical Research Council
MS SQL	Microsoft SQL Server
NHS	National Health Service
NHSGGC	NHS Greater Glasgow & Clyde
NIHR	National Institute for Health Research
NPT	Normalisation Process Theory
NRS PCN	NHS Research Scotland Primary Care Network
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
PSS	Personal Social Services
PV	Pharmacovigilance
QALYs	Quality Adjusted Life Years
QoL	Quality of LIfe
REC	Research Ethics Committee
RUSAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SES	Socioeconomic Status
SOP	Standard operating Procedure

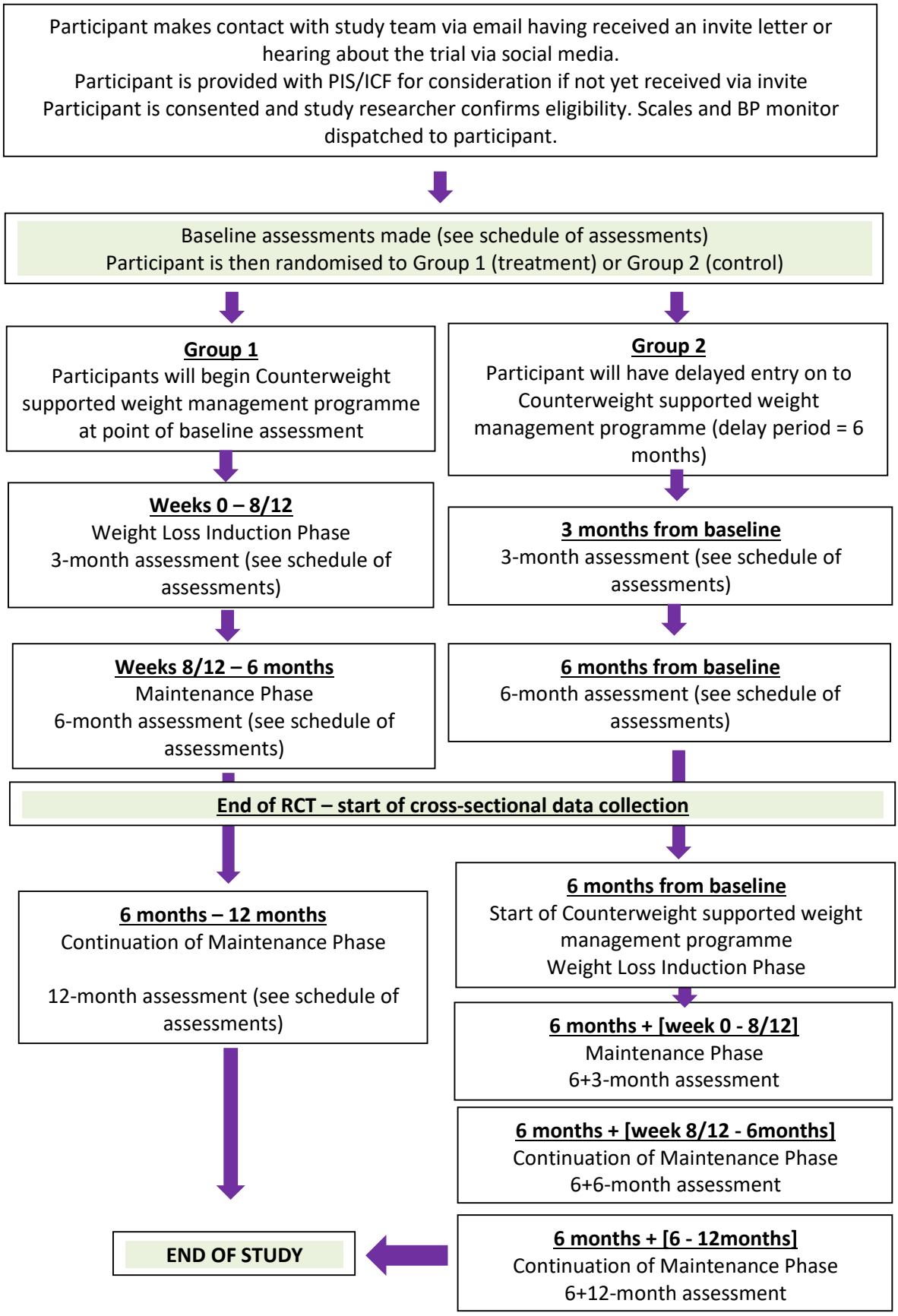
T2D	Type 2 Diabetes
TDR	Total Diet Replacement
TMG	Trial Management Group
TSC	Trial Steering Committee
WPAI	Work Productivity and Activity Impairment

STUDY SYNOPSIS

Title of Study:	Remote Diet Intervention to REduce long COVID symptoms Trial (ReDIRECT)
Study Centre:	University of Glasgow
Duration of Study:	18 months
Primary Objective:	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 • Other – for other symptoms with no pre-specified scale, we will use a Visual Analogue Scale (0 to 10).
Secondary Objective:	• All non-selected primary symptom outcomes (fatigue, breathlessness, pain, anxiety / depression, other) • Self-measured weight, blood pressure, medications and Quality of Life (EQ-5D 5L), Work Productivity and Activity Impairment (WPAI) at baseline, and all timepoints. • Healthcare utilisation at baseline, and all timepoints.
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.
Sample Size:	200 randomised participants (n=100 per randomised group)
Screening:	All participants aged ≥18 with symptoms of long COVID and living with obesity/overweight
Registration/Randomisation:	Following completion of baseline data, participants will be allocated to one of the two groups using a mixed minimisation/randomisation approach, designed to maintain balance with respect to main symptom (fatigue, breathlessness, pain, anxiety/depression, other), sex (male, female or other), age (<50, ≥50), ethnicity (South Asian, Other) and index of multiple deprivation (< median, ≥median). 80% of participants will be allocated according to a minimisation algorithm, or allocated at random if neither allocation achieves lower imbalance, and the remaining 20% will be allocated at random.
Main Inclusion Criteria:	• People with Long COVID symptoms persisting >3months before first recruitment contact, not currently hospitalised; • People who are aged 18 years or above; • People with body mass index (BMI) above 27kg/m2 (>25kg/m2 for South Asians).
Main Exclusion Criteria:	• People who have had lengthy hospitalisations (>10 days) or intensive care unit (ICU) admissions related to COVID-19; • People who are currently on insulin or anti-obesity drugs; • People who have had a proven myocardial infarction within the last 6 months; • People with severe mental illness (including severe depression and eating disorder);

	• Women who are pregnant or considering pregnancy; • People who have a history of substance abuse; • People with an active illness likely to cause a change in weight; • People who underwent bariatric surgery within the last 3 years or are planning bariatric surgery; • People with advanced kidney problems (eGFR <50), gallstones or pancreatitis; • People currently participating in another clinical research trial likely to affect diet or weight change. • People with learning disabilities • People who are unable to understand English (written or verbal)

STUDY FLOW CHART



SCHEDULE OF ASSESSMENTS

Trial Activity	**Initial Consultation**	**Baseline**	**3 Month**	**6 Month**	***9-Month***	**12-Month**	***18 Month***
Visit Number (Conducted Remotely)	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	***Visit 5***	**Visit 6**	***Visit 7***
Group 1 – immediate entry visits (n=5)	**X**	**X**	**X**	**X**		**X**	
Group 2 – delayed entry visits (n=7)	**X**	**X**	**X**	**X**	***X***	**X**	***X***
Screening – Inclusion/Exclusion Criteria	ALL						
Written Informed Consent	ALL						
Dispatch of scales and blood pressure monitor to participant	ALL						
Medical History/review		ALL	ALL	ALL	*Gp2*	ALL	*Gp2*
Self-reported height		ALL					
Self-reported weight		ALL	ALL	ALL	*Gp2*	ALL	*Gp2*
Self- reported blood pressure		ALL	ALL	ALL	*Gp2*	ALL	*Gp2*
Completion of participant nominated symptom scores and selection of most prominent / troublesome (1 of below options): **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 scales (HADS) Questionnaire **Other**: Visual Analog Scale (0-10)		ALL	ALL	ALL	*Gp2*	ALL	*Gp2*
Within Trial Resource Use Questionnaire: Healthcare Resource Usage, Out-of-pocket		ALL	ALL	ALL	*Gp2*	ALL	*Gp2*
Randomisation		ALL					
Start of Counterweight supported weight management programme (Group 1)		Gp1					
Start of Counterweight supported weight management programme (Group 2)				Gp2			

1. Introduction

1.1 Rationale

The aim of this research is to test the effectiveness and cost-effectiveness of a remotely delivered supported weight management programme for people with Long COVID and overweight/obesity.

Around 10% of people infected with COVID-19 experience persistent symptoms for 12 weeks or longer ('Long COVID') (1). There are strong, likely causal links between overweight/obesity and severity of COVID-19 (2), exemplified by links to type 2 diabetes (T2D) or hypertension (3), and many people with Long COVID have overweight/obesity (4). An inflammatory mechanism has been proposed to mediate some aspects of Long COVID, aggravated by susceptible individuals having overweight/obesity (5). Some of the commonest symptoms (fatigue, pains, breathlessness (4, 6)) are also common with overweight/obesity, and helped by weight loss (7, 8). However, robust trial data are needed to establish the impact of intentional weight loss on Long COVID symptoms, and interventions must suit people whose symptoms impair mobility and ability to attend external appointments.

ReDIRECT is a randomised controlled trial to reduce the symptom-burden in people with Long COVID and overweight/obesity. We will use an existing dietary weight management programme, shown to be safe, effective and cost-effective in achieving and sustaining mean weight loss of >10kg and remission of T2D (9, 10), **delivered entirely remotely** with professional personal support to people at home. We will use an **innovative approach to personalisation**, with each participant selecting their dominant symptom as primary outcome.

1.2 Background information including literature review

There are approximately 1.1 million people in the UK experiencing self-reported Long COVID (1). Long COVID will be a major public health issue in the years ahead, with substantial impact on individuals and families affected, and associated economic costs (loss of work, care and support costs).

Results from a survey conducted by our PPI team found that people with Long COVID are interested in the role of nutrition in self-management and how diet and weight management might affect their symptoms. Without rigorous assessment of dietary interventions, non-evidence-based approaches will be promoted. A further risk is that people with Long COVID who have overweight/obesity might be put off weight management if they do not feel it is safe or feasible given their current symptoms.

Weight management can impact positively on several areas of health, including cardiometabolic health and inflammation, lung function, and quality of life (8, 11, 12). The weight management programme to be adapted in this research has proven health benefits in the general population and in world-leading research on remission of T2D. We now need to assess its impact on Long COVID symptoms. This is strongly aligned to the Long COVID Research priorities report (13), which highlighted the need for "non-pharmaceutical interventions" and "anti-inflammatory therapeutics" (weight loss being a proven anti-inflammatory intervention (14-17)).

There is limited existing literature on effective therapies to support non-hospitalised individuals with Long COVID (18). There is, however, excellent evidence to support: a) the link between obesity and COVID (>500 studies, 12 meta-analyses), and b) the use of the online/remote Counterweight-Plus/DiRECT weight management programme for individuals with obesity.

1.3 Obesity and COVID

There are several potential mechanisms linking obesity to COVID (5). First, obesity appears to reduce capacity to raise antibodies to COVID-19, and possibly to the COVID vaccines (19). Second, accumulation of ectopic fat (affecting ~40% of adults) and associated chronic low-grade inflammatory state may increase the risk of both COVID and Long COVID. The metabolic complications of obesity (T2D, hypertension, dyslipidaemia) have been shown to be rapidly reversible with weight loss and loss of ectopic fat (9, 11).

The dominant symptom of Long COVID is fatigue, which is often an obstacle to engagement with conventional dietary programmes for weight management. Strengths of the proposed intervention are that it:

- Focusses on diet with no requirement for exercise (seldom appropriate or acceptable with Long COVID);
- Is fully remote, with no burden associated with study visits out-of-home;
- Simplifies meal planning and decision-making, which is particularly helpful for those experiencing cognitive dysfunction or fatigue;
- Is effective and safe, nutritionally complete, delivered with a recognised NHS provider.

Acceptability and retention on the weight management programme for this new group of people needs to be evaluated and optimised.

1.4 Counterweight-Plus/DiRECT weight management programme

UoG has pioneered a new generation of community-based weight management to achieve and maintain much greater weight losses than previously possible without surgery. The core programme, Counterweight-Plus, has already been subjected to both feasibility and full-scale randomised controlled trials, and was successfully adopted for the Diabetes Remission Clinical Trial (DiRECT) (9, 10). In brief, the programme provides 8-12 weeks of an 850 kcal/day nutritionally complete formula diet (as per the original DiRECT trial), which will induce 10-20kg weight loss if followed correctly. Counterweight-Plus has developed a suite of pragmatic diet solutions delivering equivalent successful weight loss via partial meal replacement, or a food-based low carb/low fat diet. Phase 1 (weight loss) is followed by a structured food-based behavioural theory-informed diet weight loss maintenance programme, with low intensity professional support for 1 year. The Counterweight-Plus/DiRECT weight management programme is commercialised by Counterweight Ltd, accepting participants referred from primary care and self-referrals.

Recently, in part as a response to the COVID-19 restrictions, the entire Counterweight-Plus/DiRECT weight management programme has been adapted for entirely remote delivery (app, online portal, and personalised professional support via text chat, video or telephone. This extends reach and scalability and reduces costs. The results from an unselected ongoing audit of all clients/patients: at 12 weeks, n=101, -15.7kg (SD7.1); with similar results at 12 months. Retention is high, 93% for 12 weeks, and 77% for 12 months (personal communication). These results from the entirely remote service are better than were achieved using the original face-to face delivery.

The new online Counterweight-Plus/DiRECT programme offers potential advantages for use among people with Long COVID, who are commonly fatigued, through its ease of access, allowing individuals to make and attend online support sessions at their own convenience.

Theoretical perspective

To maximise adoption, implementation and maintenance of the intervention, we will draw on Normalisation Process Theory (NPT) (20), which Blane and O'Donnell have expertise in using (21,

22). Applying this theoretical framework will enable us to identify barriers and facilitators to implementation such as: shared understanding; who needs to participate; the work involved in implementation; and how it is monitored. This will be done through regular workshops with people with Long COVID and relevant stakeholders.

Using remote interventions can improve reach and engagement, compared to face-to-face methods, but could also introduce new inequalities through differential uptake, adherence or effectiveness. We will work with PPI and Stakeholder panels to co-design implementation strategies and materials to increase trial uptake and engagement, specifically in under-served groups (e.g. South Asian, Low SES). This may include reaching out through local media and community champions, creation of culturally-tailored materials to increase uptake, or consideration of the most acceptable communication methods for support (email, Whatsapp, Zoom, telephone).

Previous research has shown multiple clinical and personal benefits from weight loss, including increased energy levels, improved general wellbeing and better quality of sleep. It is not clear, however, whether supported weight loss can improve symptoms of Long COVID.

2. Prior experience of intervention

See above section on the Counterweight-Plus/DiRECT weight management programme.

3. Study Hypothesis

Previous research has shown multiple clinical and personal benefits from weight loss, including increased energy levels, improved general wellbeing and better quality of sleep. It is not clear, however, whether supported weight loss can improve symptoms of Long COVID.

The hypothesis being tested is that supported weight loss in adults with Long COVID and overweight/obesity can improve symptoms of Long COVID such as fatigue, breathlessness, pain and depression.

4. Aim/Primary and Secondary Objectives

Aims

The aim of this research is to implement a remotely delivered supported weight management programme for people with Long COVID, with personalized improvement goals; and to determine the effectiveness and cost-effectiveness of this intervention.

Primary Research objective

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.

Secondary Research objectives

1. Assess the implementation of the intervention in terms of dose, fidelity and reach, and explore differences by sociodemographic characteristics (age, sex, ethnicity, SES).
2. Explore how contextual factors influence variations in implementation and effectiveness, and identify barriers and facilitators to delivery.
3. Explore the experience of the intervention from the perspective of participants, including acceptability, patterns of use, and barriers and facilitators to use.
4. Evaluate within-trial cost-effectiveness of the intervention.

5. Study Design

This is a baseline randomised, remote-delivered, non-blinded, wait-list controlled trial (with entry after 6 months), with mixed methods process and economic evaluation.

5.1 Study Population

Adults with Long COVID and overweight/obesity.

5.2 Inclusion criteria

- People with Long COVID symptoms persisting >3months before first recruitment contact, not currently hospitalised;
- People who are aged 18 years or above;
- People with body mass index (BMI) above 27kg/m^2 (>25kg/m^2 for South Asians (23)).

PCR-diagnosis will be recorded (for subgroup analysis) but is not an inclusion criterion.

5.3 Exclusion criteria

- People who have had lengthy hospitalisations (>10 days) or intensive care unit (ICU) admissions related to COVID-19;
- People who are currently on insulin or anti-obesity drugs;
- People who have had a proven myocardial infarction within the last 6 months;
- People with severe mental illness (including severe depression and eating disorder)
- Women who are pregnant or considering pregnancy;
- People who have a history of substance abuse;
- People with an active illness likely to cause a change in weight;
- People who underwent bariatric surgery within the last 3 years or are planning bariatric surgery;
- People with advanced kidney problems (eGFR < 50), gallstones or pancreatitis;
- People currently participating in another clinical research trial likely to affect diet or weight change

- People with learning disabilities
- People who are unable to understand English (written or verbal)

5.4 Identification of participants and consent

We will conduct remote recruitment, consent, randomisation, and outcome assessment.

We conservatively estimate recruiting ~100 Participants from social media and existing networks (e.g. Long COVID Scotland groups) and ~100 Participants from primary care (2 patients/practice, from ~50 practices). Recruitment from GP practices will be facilitated by NRS Primary Care Network using: electronic records search; mail/text invitations; alerts for prospective/opportunistic identification.

5.5 Intervention & randomisation

Participants will be randomised at baseline in a 1:1 ratio to the intervention arm (Counterweight-Plus/DiRECT) or the wait-list control arm. After baseline data collection, participants will be allocated to one of the two groups using mixed minimisation/randomisation approach, designed to maintain balance with respect to main symptom (fatigue, breathlessness, pain, depression, other), sex (male, female or other), age (<50, ≥50), ethnicity (South Asian, Other) and Postcode based index of deprivation (<median, ≥median). Participants (80%) will be allocated according to a minimisation algorithm, or allocated at random if neither allocation achieves lower imbalance, the remaining 20% will be allocated at random. Randomisation will be achieved by accessing a web-based randomisation system incorporated into the study web portal developed by the Robertson Centre for Biostatistics. The randomisation list, the program that generated it and the random seed used will be stored in a secure network located within the RCB, accessible only to those responsible for provision of the randomisation system. The sequence will be unknown to all other personnel, including study coordinators, outcome assessors and investigators.

- **Control**: Participants allocated to the control arm will be given access to the Counterweight-Plus/DiRECT programme after 6-months.
- **Treatment:** The Counterweight-Plus/DiRECT diet programmes are delivered by Counterweight Ltd via an online platform with text chat, video or telephone support contact. Individuals will be allocated a named 'Counterweight Coach' for personal support, for regular appointments and to moderate an online 'chat' facility to enable peer support between participants. Counterweight Coaches include many specialist dietitians, and professionals experienced in behaviour change (e.g. psychology graduates). Coaches receive formal competency-based training from Counterweight specialists, then ongoing supervision and mentoring, to maintain programme fidelity.

The format and support provided by the Counterweight-Plus/DiRECT programme comprises:

- *Weight loss induction phase (from week 0 to week 8-12)*

  Low energy diet, with Total Diet Replacement (TDR) formula diet (850kcal/day) will be offered to all initially in the treatment arm. Those unable to follow the TDR formula diet (10% in the published DiRECT study, with TDR formula diet) will be offered a 'switch' to a different approach, e.g. either:

- A food based 1200kcal “low carb” or “low fat” diet.
- A 1200kcal Meal Replacement (MR) diet (maximum 2 meal replacements/day)

Coaches/dietitians will allow intervention ‘switching’ between weeks 0 - 4 if the participant fulfills one of the following criteria:

- Unable to tolerate, or dislikes the meal replacements
- Unable to adhere to the dietary approach, e.g. less than 3% weight loss achieved by week 4

Coaches/dietitians will record the following information:

- date participants switched diets
- diet switched to
- why they switched

Digital delivery with monthly dietitian/coach support, text chat (individual and group), in-app weekly monitoring, nudges, and personalised messaging. The dietitian/coach support is flexible and can be tailored to individual participants.

- *Maintenance phase (week 8-12 to month 6)*
  - Stepped food reintroduction (TDR) or transition period (e.g. carbohydrate and fat reintroduction for the low carb and low fat diet options), individualised to participants;
  - Standard evidence-based behaviour change techniques including self-monitoring (of behaviours and behavioural outcomes), goal-setting and self-rewards, action-planning, problem-solving;
  - Relapse treatments for >2kg regain. Reinforcing behaviour change techniques and options to return to TDR or 1200kcal MR or 1200kcal low carb diet or low fat diet for 2 weeks. Alternative evidence-based dietary strategies (meal replacements, intermittent or alternate-day fasting (24), time-restricted eating.

Digital delivery with monthly dietitian/coach support, text chat (individual and group), in-app weekly monitoring, nudges, and personalised messaging. The dietitian/coach support is flexible and can be tailored to individual participants.

The weight loss maintenance phase continues from 6 to 12 months. Impact on dominant symptoms needs to be evidenced by the 6-month mark for the intervention to be deemed successful. A key challenge of weight management is longer-term maintenance of weight loss, so outcome data will also be collected after 12-months and analysed cross-sectionally.

Some participants may find adherence to TDR challenging, so intensive support will be provided by the coaches/dietitians. The TDR will be offered for 12 weeks but flexibility will be permitted to support individual participants. In our research to date, participants report that the TDR regime is easier to follow than they expected, that they experienced no tiredness but rather that their energy levels increased with increased general well-being.

Relapse management will be discussed pre-emptively with strategies to avoid withdrawal from the study, e.g. adding in 1 meal/day or “days off”, with encouragement to resume the full TDR at subsequent visits, and to maintain whatever weight has already been lost, moving onto the maintenance phase early if necessary to avoid dropping out altogether. These strategies were found to be useful in previous research.

5.6 Medication review

Each participant will be asked to describe any medications they are currently taking in the eCRF. Dosage and medication regime will be recorded where available. This information will then be passed to the Counterweight Team for the dietitians to determine the most suitable approach to TDR on the weight loss management programme.
Based on the experience of the Counterweight team and the results from the DiRECT study there may be cases where a participant is required to modify their prescribed medications in order to facilitate their participation in the trial. In these cases, the Counterweight dietitians will liaise directly with the participant's GP, as per their standard practice to make the modifications and ensure that the participant is monitored for any effects of modifying medication, locally. Appendix 2 and 3 of this protocol provides an overview of the diabetes and hypertension medication management system adopted by Counterweight as their standard practice – this protocol shall be utilised on the ReDIRECT study also. Study clinicians will be on hand to provide supplementary advice and guidance regarding participant medication where required.

5.7 Withdrawal of subjects

Participants will be reminded that they may withdraw from the study at any point. If a participant wishes to withdraw from the study, data collected up until that point will be retained, in accordance with the PIS and consent form. Participants who withdraw from the intervention protocol, or who fail to return for follow-up assessments, will continue to have data collected from their routine diabetic clinic/GP visits, unless they specifically withdraw consent for this. Data analysis will use best available follow-up weights (closest within a window of ±3 months from routine attendances) and end of study Long COVID status for participants who discontinue the formal weight management programme. Drug intolerance, diet intolerance or poor-compliance will be recorded: these patients will be included in ITT analysis.

6. Study Outcome Measures

Outcomes measured at baseline, 3 and 6 months (with follow-up at 12-months in the treatment group and 9, 12, 18-months for the delayed entry group, for cross-sectional analysis).

6.1 Primary Outcome Measure

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. 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) (25).
- Breathlessness: MRC Dyspnoea Scale (26).
- Pain: P4 Numeric Pain Rating Scale (27).
- Anxiety and depression: Hospital Anxiety and Depression scale (HADS) questionnaire (28).
- Other – for other symptoms with no pre-specified scale, we will use a Visual Analogue Scale (0 to 10) (29).

6.2 Secondary Outcome Measure

- All non-selected primary symptom outcomes (fatigue, breathlessness, pain, anxiety / depression, other)

- Self-measured weight, blood pressure, medications and Quality of Life (EQ-5D 5L), Work Productivity and Activity Impairment (WPAI) (30) at all timepoints.
- Healthcare utilisation at all timepoints.

6.3 Process Measures

We will conduct a mixed-methods process evaluation, embedded within the main trial, following MRC Guidance. We will use quantitative data to describe factors such as fidelity to the intervention, dose (based on interactions with the programme) and reach. We will use qualitative methods to understand how the intervention was implemented and experienced, and to explore any unanticipated impacts of the intervention.

Quantitative data related to intervention dose and fidelity will be collected by the Counterweight dietitians and shared in anonymised Excel file with the research team.

Qualitative data will be collected through longitudinal semi-structured telephone or video interviews at baseline, 6-month, and 12-month. The 12-month interviews are beyond the RCT framework, but capture the experience of people with Long COVID following weight maintenance. At the point of initial consent, all participants will be asked if they are happy to be contacted to take part in individual interviews. A purposive sample (N~30) of those who agree to further contact will be invited to take part in semi-structured interviews. At 6-month, we will subsample (N~15) to account for dropouts and conduct 12-month interviews with this group. Interviews will focus on patient expectations, motivations, experience of the intervention, impact on Long COVID symptoms, and contextual factors that affect (and may be affected by) implementation, intervention mechanisms and outcomes.

6.4 Measurements

Trial outcomes will be measured remotely to minimise participant burden and cost and maximise retention. At baseline, participants will receive digital scales and automated blood pressure monitors. Web-based questionnaires will collect self-measurements, healthcare usage and alternative treatments, Quality of Life (QoL) and psychological outcomes. All data will be entered directly in the eCRF by the participants themselves, with the data checked by the research staff, or by the research staff themselves, following telephone interview with the participant. Data linkage to CHI numbers will be used to validate (& calibrate) self-report hospitalisation data.

Key measurements, to be captured in the eCRF include:

- Personal and contact details [baseline]
- Socio-demographic and household details [baseline]
- Self-reported measurements (weight, blood pressure) [All timepoints]
- Self-reported height [baseline]
- People with type 2 diabetes/ prediabetes: most recent HbA1c obtained by GP or clinic [All timepoints]
- COVID-19 history [baseline] and reinfection [All post-baseline timepoints]
- Medical history [baseline]
- Medications [All timepoints]
- COVID-19 vaccination [All timepoints]
- Long COVID history and management [All timepoints]
- Physical activity and weight management status [All timepoints]
- Long COVID symptoms (primary and secondary outcomes) [All timepoints]
- Quality of Life [All timepoints]
- Work before COVID [baseline]

- Work productivity and activity impairment [pre-COVID 19 history (retrospective), and all timepoints]
- Healthcare usage questionnaire [All timepoints]
- Personal food and drink costs [All timepoints]

7. Statistics and Data Analysis

7.1 Statistical analysis plan

This study will have a comprehensive Statistical Analysis Plan, which will govern all statistical aspects of the study, and will be authored by the Trial Statistician before unblinded data are seen.

General considerations

The Statistical Analysis Plan (SAP) will be based on intention to treat principles in line with CONSORT guidelines. The analysis will focus on estimation of treatment effect differences with 95% CIs and p-values. All pre-specified secondary outcome analyses will be reported in study publications.

Primary outcome

The primary outcome will be personalised: a continuous measure derived from the score for the most important symptom as determined by each participant. Symptom scores will be standardised, e.g. according to the symptom-specific mean and standard deviation (SD) of baseline scores, so that the mean and SD of the baseline composite score are zero and one. The precise method of standardisation will be developed during the trial, based on blinded analysis of baseline data.

7.2 Statistical analysis

The primary outcome at 6 months will be compared between randomised groups using a linear regression model, adjusting for the baseline value of the primary outcome, and factors used to balance the randomisation/minimisation procedure. The intervention effect will be reported as the adjusted mean difference between groups, with a 95% confidence interval, and p-value.

Secondary analyses will use linear or logistic regression, as appropriate, to estimate between-group differences or odds ratios for secondary outcomes. Missing data will not be imputed initially, but the sensitivity of main analyses will be explored using multiple imputation, and analyses weighted by the inverse probability of follow-up, based on a non-parsimonious model of the probability of being followed up, as a function of baseline characteristics.

Associations between baseline characteristics, primary and secondary outcomes will be explored by extending the main analysis regression models. Subgroup analyses will be carried-out by including the subgroup variable and its interaction with treatment group in these models. Prespecified subgroups of interest will include sex, age, main symptom, and baseline BMI. Additional exploratory analyses will investigate if short-term differences between randomised groups (particularly early weight loss) are predictive of 6m intervention effects.

Additional observational analyses will explore within-group changes in outcomes between 6 and 12 months on both randomised groups, and predictors of long-term outcomes in the intervention arm of the trial.

7.3 Sample size

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.

7.4 Economic analysis

Building directly on the methods employed in the published within-trial economic evaluation of the Counterweight-Plus intervention in DiRECT (31) the economic analysis will be carried out according to a detailed Health Economic Analysis Plan (HEAP). The HEAP will detail the methods to be employed for the within trial economic evaluation (& subsequent model). Intervention costs will be re-estimated from the original DIRECT trial (given online delivery) and all resource use and Quality Adjusted Life Years (QALYs) across arms will be measured and valued within an incremental cost-utility analysis.

Work-related productivity, healthcare resource utilisation and other relevant personal costs (including weekly food, drink and lifestyle expenditure and over the counter medications) will form the basis of a bespoke resource use questionnaire. This will be adapted to the Participant population, tested with the PPI group, and administered at baseline, 3, 6 and 12 months. The EQ5D-5L preference-based quality of life instrument will be combined with trial duration to estimate Quality Adjusted Life Years (QALYs).

In line with NICE guidance the primary within-trial and lifetime cost-utility analyses will adopt an NHS and personal social services (PSS) perspective. Secondary analyses, with specific PPI input, will consider a broader societal perspective (personal out-of-pocket expenses, productivity and food & drink expenditure). Total costs and QALYs will be estimated using seemingly unrelated regressions with robust standard errors to control for clustering by household. Differences in cost and QALYs between the intervention and control groups will be estimated using generalised linear models (32).

Costs and QALYs will be adjusted for baseline covariates. A probabilistic sensitivity analysis will be conducted using non-parametric bootstrapping with replacement. The results of the bootstrapping will be presented on a cost-effectiveness plane, and a cost-effectiveness acceptability curve (CEAC) will be constructed. A discount rate of 3.5% will be used and if cost/outcome differences transpire, a longer-term cost-utility model will be developed building on the existing DIRECT model.

8. Data Handling

8.1 Case Report Forms / Electronic Data Record

Data collection

An electronic case report form (eCRF), developed by the Robertson Centre for Biostatistics, will capture all data required to meet this protocol's requirements. Access to the eCRF will be restricted, via a trial-specific web portal, and only authorised personnel will be able to make entries or amendments to the participants' data via the web portal. It is the investigator's responsibility to ensure completion and confirm that the data is accurate, complete and verifiable. Data will be stored in a MS SQL Server database.

Direct access to the web portal will be granted, on request, to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

8.2 Data sharing with study intervention provider

Counterweight Ltd. Will have a viewer-only access to the eCRF in order to ascertain participant's contact details and clinical / medical history for safe delivery of the study intervention. Access will be granted by the Robertson Center and secure passwords will be issued to relevant intervention providers within Counterweight Ltd. A data sharing agreement will be established between Counterweight and sponsor to guarantee safe handling of patient data.

8.3 Data validation

Where it is practical, data will be validated at the point of entry into the eCRF. Any additional data discrepancies will be flagged to the investigator and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

8.4 Data security

The Robertson Centre for Biostatistics systems are fully validated in accordance with industry and regulatory standards, and incorporate controlled access security. High volume servers are firewall protected and preventative system maintenance policies are in place to ensure no loss of service or data. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. Data are backed up on-site nightly and off-site to a commercial data vault weekly. The Robertson Centre for Biostatistics has an ISO 9001:2008 quality management system and ISO 27001:2013 for Information Security, and is regularly inspected against the standards by the British Standards Institution.

8.5 Data Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with EU GCP guidance, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

9. Monitoring, Audit and Inspection

NHSGGC conducts monitoring and/or audit of studies on a risk basis and in accordance with local Standard Operating Procedures. The level, frequency and priorities of monitoring and/or audit will be agreed with the NHS Governance Manager.

10. Safety Reporting

10.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a trial specific procedure has been administered, including occurrences which are not necessarily caused by or related to that trial specific procedure.

Serious Adverse Event (SAE)

Any adverse event or adverse reaction that:

a. Results in death
b. Is life threatening
c. Requires hospitalisation or prolongation of existing hospitalisation
d. Results in persistent or significant disability or incapacity
e. Consists of a congenital anomaly or birth defect
f. Is otherwise considered medically significant by the investigator
g. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above

Related Unexpected Serious Adverse Event (RUSAE)

Any SAE thought to be related to a trial specific procedure performed on that subject that is thought to be unexpected; that is the event is not listed within the protocol or would not be expected to occur when carrying out the trial specific procedure in normal clinical practice.

10.2 Recording and reporting of adverse events

AEs will not be collected during the course of the trial. Counterweight dietitians will be asked to collate and report only SAEs to the study researchers, who will log them into the eCRF and escalate to sponsor pharmacovigilance where related and unexpected.

10.3 Recording and reporting of serious adverse events

Where an SAE requires recording; full details including the nature of the event, start and stop dates, severity, relationship to research product and/or trial procedures, and the outcome of the event will be recorded in the participant's medical notes and eCRFs. These events will be monitored and followed up until satisfactory resolution and stabilisation.

Each SAE should be assessed to determine if related to the research specific procedures and assessed for expectedness. Where an event meets the criteria of an SAE and is both:

- **Related:** that is, it resulted from administration of study medicines or any of the research procedures, **AND**
- **Unexpected**: that is against the procedure events listed below as an expected occurrence.

The SAE is considered a Related and Unexpected Serious Adverse Event (RUSAE) and is reportable to the Sponsor.

10.4 Expected Events Related to Total Diet Replacement

There is little risk to participants taking part in this study; however there may be side effects from rapid weight loss, relating to the induction period using the total diet replacement sachets (shakes and soups) such as:

- Constipation, increased sensitivity to cold, headache, and dizziness were commonly reported side effects in DiRECT, and all dissipated over time.
- Other side effects that are less commonly reported are: fatigue, mood changes, nausea, diarrhoea, indigestion, hair loss. All participants are provided with information on all possible side effects and management strategies should they be problematic.

These events would be considered expected within this study.

10.5 Reporting to the Sponsor

The Sponsor will be made aware of any RUSAEs entered onto the eCRF as soon as an event is assessed as related and unexpected.

Should the eCRF be unavailable a copy of the non CTIMP SAE form can be downloaded from http://www.glasgoctu.org/Home/media/2304/sae_non-ctipv-1-1.pdf . The SAE form should be completed and signed by appropriately delegated staff. The form should be faxed or e-mailed to the PV Office (pharmacovig@glasgowctu.org) and a copy placed in the Study Site File.

If necessary a verbal report can be given by contacting the PV Office on 0141 330 4744. This must be followed up as soon as possible with a signed written (or electronic) report.

If all of the required information is not available at the time of initial reporting, the CI (or designee) must ensure that any missing information is forwarded to the PV Office as soon as this becomes available. The report should indicate that this information is follow-up information for a previously reported event.

10.6 Reporting to the Sponsor

All RUSAEs must be reported to the Pharmacovigilance Office immediately (within 24 hours) using the generic non-CTIMP SAE form which is available from The SAE form should be completed and signed by appropriately delegated staff. The form should be faxed or e-mailed to the PV Office (pharmacovig@glasgowctu.org) and a copy placed in the Study Site File. If necessary a verbal report can be given by contacting the PV Office on 0141 330 4744. This must be followed up as soon as possible with a signed written (or electronic) report.

If all of the required information is not available at the time of initial reporting, the CI (or designee) must ensure that any missing information is forwarded to the PV Office as soon as this becomes available. The report should indicate that this information is follow-up information for a previously reported event.

10.7 Reporting of RUSAEs to the Ethics Committee

The PV office will report all RUSAEs to the ethics committee within 15 days of the PV office becoming aware of the event, via the 'report of serious adverse event form' for non-CTIMPs published on the Health Research Authority web site https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safty-reporting/ . The form should be completed in typescript and signed by the Chief Investigator.

11. Ethical and Regulatory Considerations

11.1 Assessment and management of risk

Research staff trained in Good Clinical Practice (GCP) will obtain consent. Participants who are fully oriented and able to provide informed consent will be approached for recruitment into the study. Due to the remote nature of this study, research staff will exercise their judgement as to a participant's suitability for being consented on to the study, and ensure that each participant's specific health circumstances are considered when recruiting them to the study.

Potential risks

This research study is testing a well-established weight loss intervention in a population with a relatively new condition - post-COVID-19 syndrome or 'Long COVID'.

The potential risks from intensive weight loss associated with a Total Diet Replacement (TDR) approach are:

- Constipation. Participants will be advised to consume ample fluids and a soluble fibre supplement (Fybogel 2x3.5mg/day) will be encouraged if required.
- Dizziness is possible when standing up suddenly. This is due the body adjusting to a healthier lower blood pressure and happens mainly in those who were taking medication to control their blood pressure. Blood pressure and postural symptoms will be monitored at all follow-up appointments. We will follow established protocols used in the DiRECT study for management of blood pressure and inadequate glucose control (see Appendices 2 and 3). After discussion with participants (and their GP if requested), we will withdraw antihypertensive and diuretic drugs on commencing TDR, ahead of the expected fall in blood pressure with rapid weight loss. These will be reintroduced if necessary, according to clinical guidelines. If dizziness occurs, participants will be advised to take more time when standing up and to drink plenty of water. These protocols have been established as CWT dietitian standard practice and used in a clinical trial where no safety signals were raised..
- Gallstones may become symptomatic. This is relatively uncommon and will be minimised by dietary provision which includes some fat consumption.

The time consideration for participation in the study is significant, and this will be fully discussed prior to enrolment in the study. It is fully described in the participant information sheet.

11.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from a REC for the study protocol, informed consent forms and other relevant study documents.

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.

All correspondence with the REC will be retained and stored within the relevant CI/PI site files.

The Chief Investigator will notify the REC of the end of the study.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

11.3 Regulatory Review & Compliance

Before the site can enroll Participants into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with the study sponsor so they can put the necessary arrangements in place to implement the amendment

Given the short turnaround for this study, we do not anticipate any requirements for amendments while the study is recruiting at this time. However, should there be a need for an amendment, this will be completed as per sponsor's standard operating procedures. The CI and project manager will be responsible for submitting any amended documents to the sponsor for review prior to submission to the REC. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

The project manager will also be responsible for notifying both the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating local research team. This will be done electronically via email.

Appendix 1 of this protocol will be used to track the amendment history of the study protocol.

11.4 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enroll a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator, Sponsor and GCTU immediately. Deviations from the protocol that are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

11.5 Data protection and Participant confidentiality

All investigators and trial site staff must comply with the requirements of applicable data protection legislation with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of such legislation.

Personal information will be collected via the eCRF to enable participant completion of questionnaires and to facilitate intervention delivery and record linkage. These data items will be encrypted and only those individuals who require to see these data, i.e. research staff, Counterweight Ltd. dieticians or the person performing record linkage, will be able to view them. All electronic data will be held securely in accordance with ISO 27001:2013 at the Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit. All Centre staff are required to sign confidentiality agreements and to follow Standard Operating Procedures in accordance with Good Clinical Practice and ISO certification.

The trial data managers, statisticians, health economists or any other staff who will perform data related tasks will only be able to access depersonalised data where the participant's identifying information is replaced by a unique study identifier. Only those that have been trained and approved will be able to enter or view any data via the web portal.

Participant consent forms will be stored in a secure password-protected folder on the University of Glasgow servers.

Study data will be held for up to 20 years and archived/destroyed in accordance with sponsor's standard operating procedures.

11.6 Indemnity

The NHS Indemnity Scheme will apply to this study to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research.

The University of Glasgow Clinical Trials Insurance will apply to this study to meet the potential legal liability of the sponsor or employers for harm to participants arising from the design of the research.

The NHS Indemnity Scheme will apply to this study to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research.

The sponsor has not made any arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises.

11.7 Access to the final study dataset

Study investigators based at the University of Glasgow and NHS Greater Glasgow & Clyde will have access to the final dataset. This will be restricted to the relevant staff involved in drafting and reviewing the final study report. The final dataset will be backed-up on a secure university folder, with password protection.

The data generated from this study may underpin a future study proposal for additional research work in this clinical area. All future studies will be subject to obtaining sponsor and regulatory approvals.

12. Dissemination Policy

NHS Greater Glasgow and Clyde, and University of Glasgow are joint controllers of the data arising from this study.

Once the study has been completed, a final report will be prepared for publishing purposes, and to feedback research results to both sponsor and REC. This will be provided to sponsor/REC via email, and will be made accessible to the wider research community on international study registry websites such as clinicaltrials.gov or EudraCT. The CI will have the right to publish the study data. There are no sponsor review requirements on publications.

There are no plans to notify participants of the outcome of the study. The results will instead be used to provide evidence for future research proposals that will be subject to sponsor and the appropriate regulatory approvals. Participants will be provided with CI/PI contact details in the Participant Information Sheet and will have the opportunity to request results from their PI if they so wish. Participants will be advised upon requesting results that these will be made available once data analysis has been completed and/or the final study report has been compiled.

The main study documentation - study protocol and full study report – will be made accessible to the wider research community on international study registry websites such as clinicaltrials.gov or EudraCT within 1 year of study opening.

12.1 Authorship eligibility guidelines and any intended use of professional writers

Key contributors to the protocol and final report will be noted as authors, as will study clinicians / researchers who contribute significantly to the running/management of the study at site. All will be provided with a draft copy of the final report for review prior to publication. Criteria for individually named authors or group authorship will adhere to that of The International Committee of Medical Journal Editors.

13. Ethical Consideration

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

Favourable ethical opinion will be sought from an appropriate REC before participants are entered into this study. Participants will only be allowed to enter the study once they have provided informed consent. Consent forms will be either returned via email with electronic signature or returned via mail as signed hard copies.

The Co-PIs will be responsible for updating the Ethics committee of any new information related to the study.

14. Finance and Indemnity

The study is funded by the National Institute for Health Research, COV-LT2-0059.

The study is sponsored by NHS Greater Glasgow & Clyde. The sponsor will be liable for negligent harm caused by the design of the study. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

15. Publications

Findings from the study will be published in peer–reviewed publications as well as executive summaries being made available to research participants.

16. References

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Appendix 1: Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
				See related Summary of Changes Doc

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.

Appendix 2: Drugs for Diabetes during Weight Management

Weight loss is a potent treatment for type 2 diabetes: blood glucose falls during active weight loss, and often falls rapidly on starting TDR. Hypoglycaemia is possible without medication dose reduction or withdrawal. Requirement for insulin or other glucose-lowering drugs often falls rapidly but may rise somewhat when the patient has stabilized at a new lower weight.

Type 2 Diabetes on oral anti-diabetic drugs

All anti-diabetic medications ***(Exceptions see below **)*** should be **stopped** on the day TDR is commenced, because blood glucose levels fall rapidly on the diet. This is a safety measure, to avoid hypoglycaemia, but also an important incentive to achieve remission.

- Monitor BG fasting each day initially, until clearly falling or stable.
- Where possible, measure fasting BG at each subsequent appointment
- If glycaemic control deteriorates, the usual explanation is poor adherence to dietary advice, and weight loss below expected: discuss resuming anti-diabetes medications
- If weight loss is satisfactory but blood glucose control is still inadequate, e.g. BGs consistently above 10mmol/l, consider reintroducing medication. **See order for reintroduction (below).**
    - Start at the lowest dose and increase gradually.
    - Subsequently, if control remains poor, add further agents
- Encourage and support efforts for further weight loss at each visit

***** Exceptions***

If diabetes remission considered less likely (e.g. > 10yrs duration of diabetes). All oral hypoglycaemic (sulphonylureas) drugs can still be stopped on the day TDR is commenced, and the patient managed as above. Some achieve remission after much longer durations.

Patients receiving multiple medications for diabetes are less likely to achieve remission. Blood glucose usually still falls with TDR, but it is safe to start TDR and remain on a drug which does not cause hypoglycaemia: metformin, glitazones, GLP-1 analogues, DPP-4 Inhibitors.

These drugs may become unnecessary after major weight loss. A therapeutic trial of drug withdrawal, monitoring BG over a few days, can be done either at the start of TDR, or later if weight loss is achieved. Stopping GLP-1 agonists may be less successful, as the patient may have more advanced diabetes, or be more dependent on the weight-loss effect of the drug.

Metformin, glitazones, GLP-1 analogues and DPP-4 Inhibitors have some small metabolic benefits for people with type 2 diabetes aside from glucose-lowering and assist with weight loss and maintenance. However, they are not licensed for these purposes without diabetes (this may change very soon: currently under review at SMC).

- **SGLT2 inhibitors (gliflozins)** must be stopped before starting TDR, because they can cause ketoacidosis.

- **Sulphonylureas or repaglinide/nateglinide** should be stopped because of higher risk of hypoglycaemia during TDR.
- **Statins**. There is no direct evidence over the withdrawal of statins, prescribed to reduce cardiovascular risks for people with type 2 diabetes, when there is remission of diabetes. These risks remain elevated in the 'prediabetes' range (HbA1c 43-48 mmol/mol), so statins should be continued.

Protocol for patients who have osmotic symptoms (thirst, polyuria) and/or pre-meal BG >10mmol/l (When these values are not falling with weight loss).

GP/PN/ Diabetic Nurse Practitioner (liaise with Counterweight Practitioner) to:

- Exclude intercurrent illness (e.g., viral infection, urinary tract infection etc.).
- Check HbA1c. (reflects blood glucose over previous 3 months).
- If weight loss is satisfactory (according to charts held by Counterweight Practitioner), re-introduce anti-diabetic medication, and increase dosage gradually (see below for suggested order of reintroduction of medications).
- Subsequently, if control remains poor, add further agents according to usual guidelines.

Counterweight Practitioner (liaise with GP/PN/ Diabetic Nurse Practitioner) to:

- Check if weight loss is as anticipated (see page 24 Counterweight-Plus Flipchart).
- If weight loss is below expected, discuss TDR compliance with the patient: re-check at next visit.
- If weight loss is adequate, refer to GP/PN.

Order for reintroduction of anti-diabetic medications (may vary with national or local guidelines).

1. Reintroduce metformin (500mg twice daily). If this has previously not been tolerated for the individual, try the slow-release preparation. If needed, increase to 1g twice daily over 2-4 weeks.
1. If a second agent is required, add sitagliptin 100mg once daily.
2. If control is still inadequate, consider liraglutide, in a dose up to 3mg/day for optimal weight control.
3. Add gliclazide, starting with 80mg once daily (or other sulphonylurea if preferred). **PLUS advice and support to avoid weight gain.**
4. If glucose control remains inadequate, follow current guidelines. **PLUS advice and support to avoid weight gain.** Insulin may be considered, but this would result in withdrawal from the trial.

Appendix 3: Hypertension Treatment during weight management

- Weight loss is a potent treatment for hypertension.
- The combination of Counterweight-Plus and either diuretic or antihypertensive medications can produce postural hypotension which is potentially hazardous**.** Practitioners should advise patients about the risk of postural hypotension, and its symptoms (light-headedness on standing).
- **If antihypertensive and diuretic medications are continued during TDR, monitor blood pressure regularly (as per protocol below), and seek medical advice if blood pressure falls or if dizziness develops.**
- **From the safety evidence in the DiRECT trial, we recommend stopping all antihypertensive and diuretic medications on day one of Total Diet Replacement (TDR ~850cals) When antihypertensive drugs are stopped, re-emphasise the importance of weight loss and avoiding sodium (salt).**
- Reassure patients that their treatment of hypertension is not stopping, rather it is being replaced with Counterweight-Plus. The most potent hypotensive element is acute negative energy balance during TDR, so BP can fall before there is significant weight loss.
- Antihypertensive drugs given for other reasons (e.g. angina, heart failure) should be continued.
- **When two or more drugs are prescribed for hypertension, BP may not fall so markedly, and reintroduction of some medication is often needed when weight loss ceases.** It is reasonable to remain on treatment during TDR, perhaps with one drug, and monitor lying and standing BP weekly or if there are symptoms of light-headedness. If systolic BP falls below 120 mmHg, at any stage of Counterweight-Plus, we suggest that BP is reviewed by GP.

This protocol lays out a "standard approach" to follow, but different clinical decisions may be necessary for some patients. To simplify decision making, systolic pressure only is used as a guide to therapy. The level of 140mmHg is chosen to allow safe decisions during the weight loss period for those who have stopped their antihypertensive medications.

During TDR

Evidence from the DiRECT trial shows that when patients start Counterweight-Plus and stop their diuretic and antihypertensive drugs, blood pressure does not change for 4 weeks, and then it starts to fall

- **Monitor BP weekly/fortnightly (as per appointment schedule)**: make changes only for persistently elevated BP (on repeat testing) as defined below:
- **If systolic BP is over 165 mmHg** on repeated measurement In the first 2 weeks after stopping antihypertensives and diuretics:
- Restart one drug, using the order set out below.*
- **Thereafter, if systolic BP is repeatedly >140 mmHg** –
  Restart one drug as per order listed below.* Increase dose weekly to achieve systolic BP<140mmHg.
- If systolic BP remains repeatedly >140mmHg on the first drug – add a second, as per order listed below. * Increase dose weekly to achieve target <140mmHg.
- Repeat as necessary with third, fourth or more drugs (increasing each to maximum dose).

During FR

As body weight stabilises at a lower level, most patients with previous hypertension do need some antihypertensive medication, but usually less than before weight loss.

After Food Reintroduction, Measure BP 4-weekly and follow usual guidelines for management of hypertension.

*** Order of reintroduction of previously used drugs (protocol based on current NICE/SIGN guidelines). Note the previous drugs which the patient had been taking and choose from these in the following order:**

- Advise salt avoidance
- ACE inhibitors (ramipril, lisinopril, perindropril, etc.)
- Angiotensin receptor blockers (irbesartan, candesartan, etc.)
- Thiazide type (bendroflumethazide, indapamide, etc.)
- Spironolactone
- Calcium channel blocker (nifedipine, amlodipine, etc.)
- Beta blocker (atenolol, labetolol, etc.)
- Alpha blocker (doxazosin, prazosin, etc.)
- Others

Supporting information when Managing Blood Pressure for patients with hypertension on Counterweight-Plus

- The Counterweight Practitioner will communicate with the patient and patient's GP/Prescribing nurse when guidance is required on medication adjustment as indicated per protocol.
- The Doctor / Prescribing Nurse will deal with each patient individually, to weigh up BP control against other aspects of care and personal situations.
- Blood Pressure will fall during active weight loss, especially if antihypertensive drugs or diuretics are being taken. This can cause unpleasant symptoms of dizziness, postural hypotension, and sometimes blackouts and falls.
- No SAEs or other problems have been reported. And Q-risk (risk of a cardiac event in the next 10 years) falls from 16% to 8% in patients who achieve remission of type 2 diabetes.
- The evidence from clinical trials is that BP does not rise after stopping antihypertensive or diuretic medications, provided the patient is on the programme and losing weight.[1]
- BP tends to rise after weight loss has stabilised, so some patients need to go back onto medication.
- To help keep the BP lower, and avoid the need for drugs, all patients should be advised to limit salt intake. Avoid adding salt to foods in cooking and at the table.
- BP should be monitored at each appointment weekly/fortnightly, until stable (measured by Counterweight practitioner or self-monitored by participant, with appropriate training)
- Measure BP Lying (rested) and Standing (for 2-3 minutes). If there is no postural drop (>20mmHg) at baseline or after 1-2 weeks, continue monitoring as per protocol, see last bullet point.
- If there is a postural drop of >20 mmHg, at baseline or 1-2 weeks, advise caution when rising to stand, and check that the patient has stopped antihypertensive or diuretic drugs during weight loss.
- **How often should you monitor BP? When to take action?**
  The timing is not critical, and changes in medication must be on the advice of the doctor or prescribing nurse only.
  As a general guideline: For people previously on antihypertensive medications, check BP at 1 week, then 2 weeks, then fortnightly thereafter. If it remains under 140mmHg systolic for 3 or 4 weeks, then monitoring may be reduced to 4 weekly. If it is elevated once, it should be repeated in 1 and 2 weeks (after encouraging further weight loss). (Re-)starting medication should be considered if there are 3 consecutive BP measurements above 140 mmHg, or 2 above 160mmHg.

[1] Leslie WS et al. Antihypertensive medication needs and blood pressure control with weight loss in the Diabetes Remission Clinical Trial (DiRECT). *Diabetologia* 2021; 64: 1927-1938