Study Title: Weight loss intervention with specialist dietitian behavioural support for people with cystic fibrosis who have excess weight: the EASE-CF randomised controlled feasibility trial

Internal Reference Number / Short title: EASE-CF: Weight loss in people with cystic fibrosis

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Conflicts of interest

DAK is an investigator in two investigator--led publicly funded (NIHR) trials where the weight loss intervention was donated by Nestle Health Sciences and Oviva to the University of Oxford outside the submitted work. None of these associations led to payments to these authors. No other conflicts of interest are reported.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

Study Title: Weight loss intervention with specialist dietitian behavioural support for people with cystic fibrosis who have excess weight: the EASE-CF randomised controlled feasibility trial

Protocol Date and Version No: 17th October 2025 v2.0

Protocol signature page

The undersigned has read and understood the study protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

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1. KEY CONTACTS

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2. LAY SUMMARY

In the UK, 11,000 people are living with cystic fibrosis (CF), a genetic condition that damages their lungs and digestive system. New medications help them improve their health and quality of life and will likely help them live longer. Before these new medications, people with CF often had low body weight and were advised by specialist dietitians to try and gain weight to a target that was linked to better lung health. Since taking these new medications, 4 in 10 people with CF have now significantly exceeded their target weight, which could harm their future health. People with CF are at higher risk of heart disease and cancers than the general population and these may also be linked to excess weight as they get older.

As this is a new issue for people with CF, there has been no research on adapted programmes that could help them lose weight. There are concerns about whether weight loss (a) is safe for people with CF, (b) can fit within their complicated treatment plan and, (c) is possible as it is different to the long-held advice for a high-calorie diet.

We plan to test whether it is practical for people with CF to follow a weight loss programme.

They will receive one-to-one remote support from a specialist dietitian to help them eat less calories and lose weight over 12 weeks and then maintain this weight loss over the next 12 weeks. Individuals will be placed at random in 2 groups: the weight loss programme (20 patients) or routine dietitian care (10 patients). We will monitor participants' lung and overall health to ensure their safety. We will find out whether there are enough people who are willing to take part, lose weight and complete their follow up assessments.

We will speak to participants to understand their experiences of the programme. We will discuss how they felt about the study and gather feedback on anything they found easy or difficult to help us make changes to the programme. We will also speak to clinicians to find out if they would use the programme in day-to-day practice.

We designed the research with a group of 4 people living with CF who all wanted to lose their excess weight. They felt they needed more guidance from their clinical teams to help them lose weight and welcomed this study. They suggested ways to make it easier for people to join the study, stick to the programme, and attend the follow-up assessments. They will continue to be involved in all stages of the research. They will help to interpret the results that we will publish in research journals and will work with the CF Trust charity to communicate these to people with CF and health professionals.

3. SYNOPSIS

Study Title	**Weight loss intervention with specialist dietitian behavioural support for people with cystic fibrosis who have excess weight: the EASE-CF randomised controlled feasibility trial**
Internal ref. no. (or short title)	EASE-CF: Weight loss in people with cystic fibrosis
Study registration	ISRCTN17298282
Sponsor	University of Oxford
Funder	National Institute for Health Research (NIHR)
Study Design	Multi-centre unblinded parallel randomised controlled feasibility trial with embedded qualitative study
Study Participants	Adults with excess weight and cystic fibrosis and healthcare professionals involved in the study.
Sample Size	30 participants with cystic fibrosis in study and interviews and 10 clinical staff participants in interviews only

Planned Study Period	1/1/2026 – 1/1/2030 Total trial length: 24 months + 2 years follow up in medical notes Individual participant's involvement: 48 weeks Long-term follow-up via medical records: up to 2 years		
Planned Recruitment period	January 2026 to December 2026		
	Objectives	Outcome Measures	Timepoint(s)
Primary objective	To assess the feasibility of progression to a definitive RCT.	i. Recruitment rate ii. Engagement rate iii. Adherence rate iv. Retention rate v. Adverse events profile	i. Screening ii. During the intervention iii. During the intervention iv. End of study assessment at 24 weeks v. Throughout the trial
Exploratory objectives	To report between group differences from baseline to 24 weeks in 1. Body weight 2. Body composition 3. Health-related quality of life (HRQoL) 4. Lung function	i. Weight ii. Fat-free mass iii. Fat mass iv. EQ-5D-5L v. AWESCORE (Validated CF specific quality of life scale) vi. Forced expiratory volume	Baseline,4 weeks, 12 weeks, 24 weeks

		predicted (FEV1%) Forced vital capacity predicted (FVC %)	
	5. Fitness	i. Time for sit to stand test	
	6. Respiratory exacerbation rate	vii. Respiratory exacerbations	
	7. Blood pressure	viii. Blood pressure	
	8. Glycaemic control	ix. HbA1c	
	9. Blood Lipid profile	x. Total cholesterol, HDL, LDL, and triglyceride levels.	
	10. Adverse events	xi. Adverse events	
Process objectives	To examine the 1. Experience of the intervention	i. Analysis of qualitative interviews with intervention participants	At 12 weeks or 24 weeks At 24 weeks

	2. Experience of the trial	ii. Feedback questionnaire for intervention participants	
		iii. Analysis of qualitative interviews with all participants	At 24 weeks
	3.Contamination of the control group (presence of weight loss practices)	iv. Feedback questionnaire at the end of trial period for all participants	
		v. Analysis of qualitative interviews with control group participants	
	4.Fidelity of delivery	vi. Feedback questionnaire at the end of trial period for control group participants	Throughout the trial
		vii. Recording of trial delivery consultations	Throughout the trial
	5. Data availability for outcome measures	viii. Observation of consultations	
	6. Data availability for Health Resource use	ix. Review of data available on trial database	

	6. Barriers for involvement in the trial	x. Review of health resource use from electronic care records xi. Reasons for declining participation	At Recruitment
Intervention(s)	Structured weight loss programme with behavioural support from a specialist dietitian		
Comparator	Care as usual		

4. ABBREVIATIONS

AE	Adverse event
BMI	Body Mass Index
CF	Cystic Fibrosis
CI	Chief Investigator
eCRF	Electronic Case Report Form
ETI	Elexacaftor-Tezacaftor-Ivacaftor
EQ-5D-5L	EuroQoL-5D 5-level version
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
NHS	National Health Service
PI	Principal Investigator

PIS	Participant Information Sheet
REC	Research Ethics Committee
RCT	Randomised controlled trial
R&D	NHS Trust R&D Department
RGEA	Research Governance, Ethics & Assurance Team
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSC	Trial steering committee

5. BACKGROUND AND RATIONALE

Cystic Fibrosis

Cystic fibrosis (CF) is a rare, genetic, life limiting disease that affects over 11,000 people in the UK of whom 63% are aged ≥ 16 years (1). People living with CF have progressive lung disease and can experience problems with the gastrointestinal and endocrine systems. CF care is delivered in the NHS by CF centres comprising of a highly specialist multidisciplinary team with patients attending for appointments every 3 months(2). The medical treatment is complex and involves a high burden of medication, daily physiotherapy, and nutritional care(3).

Life expectancy for people living with CF has been increasing, with median predicted survival estimates improving from 36 years in 2013 to 64 years in the latest registry data predictions(1). This is partly due to the availability of new treatments that restore the function of the cystic fibrosis transmembrane conductance regulator (CFTR) proteins. These medications are known as CFTR modulators; eligibility for these treatments is based on genotype and the most commonly prescribed is Elexacaftor-Tezacaftor-Ivacaftor (ETI)(1). Patients taking CFTR modulators on average increase their lung function, have reduced frequency of infective chest exacerbations and a requirement for intravenous antibiotics to treat these. Improvements in CF related quality of life scores have also been demonstrated(4). CF centres are now adjusting care models to address the challenges of managing a heterogenous ageing population of CF patients(5).

Overweight and obesity in cystic fibrosis

Previous nutritional care for people with CF focused on achieving optimal body mass index (BMI) targets linked to higher lung function, as most patients were either underweight or managing to maintain these targets. Since 2020 there has been widespread availability of CFTR modulators in the UK and the

prevalence of people with CF recording a BMI classified as overweight or obese (BMI ≥25kg/m^2) has increased. In the latest UK CF Trust registry data, 39% of adults with CF recorded a BMI ≥25kg/m^2 (10% with a BMI ≥30kg/m^2), with the prevalence in the over 50's age group being above 50% (1). This increased prevalence is also seen in registry data from other countries(6-8).

As this remains an emerging issue, cystic fibrosis clinical care guidelines (2, 9-11) provide minimal guidance on options for assessing and treating people with cystic fibrosis who are living with overweight and obesity. Several reviews comment on potential solutions and the appropriateness of using weight management treatments that are well tested in other populations (12-14) but there is no consensus about whether these treatments are safe, effective, and acceptable for people with CF.

CF Clinicians have highlighted the need for research in this area (15, 16), but there are currently no published or registered randomised control trials investigating weight management interventions in people with cystic fibrosis. The 2023 James Lind Alliance Priority Setting Partnership identified the question 'How can overweight and obesity be effectively managed in people with CF?'(17).

Possible benefits of intentional weight loss in cystic fibrosis

The risks, if any exist, associated with overweight and obesity in CF are not well described. There may be additional risk factors in people with CF who are overweight or obese compared to people with CF who are not overweight or obese. These include evidence of worsening cardiometabolic risk parameters (hypertension, hyperlipidaemia, and insulin resistance) shown in observational studies of people with CF who have a higher weight, especially in those who are prescribed ETI (18, 19).

There is also evidence of significantly higher cardiovascular risk in people with CF compared to age matched controls without CF (20); this is concerning given that the population in this study was under the age of 50 years and cardiovascular risk increases with age(21). 40% of people with CF over age 30 years have diabetes related to their pancreatic damage caused by CFTR dysfunction and are taking insulin(22). Studies have shown increased insulin resistance in people with CF who have excess weight compared to those of a healthy weight (19, 23). Increased risk of gastrointestinal cancers has been demonstrated in people with CF (24)and this type of cancer can also be linked to obesity. It is important to test whether weight loss may lead to similar benefits for people with CF and excess weight as it does in other chronic disease populations(25). People with CF are recommended to participate in regular physical activity as part of their physiotherapy treatment for airway clearance and ability to do this may be compromised by carrying excess weight(26).

Possible risks of intentional weight loss in people with CF

Studies demonstrating a positive association between weight and lung function in people with CF has driven the focus on achieving optimal BMI. Although overweight has been associated with higher lung function (FEV1) in some studies(27-29), these findings are prone to confounding from other clinical factors and there is no conclusive data showing additional benefit to FEV1 beyond a BMI of 25kg/m^2(9). Given that there are no data showing the effect of intentional weight loss on lung function in people with CF, it is important to consider that there may be beneficial effects especially in forced vital capacity (FVC) (a measure of lung capacity) as seen in other respiratory conditions(30). In healthy populations, ongoing weight gain is associated with accelerated lung function decline and the same may be true in people with

CF(31). There are potential concerns about muscle mass loss as reduced muscle mass has been linked to poorer lung function in people with CF(32).The extent of muscle mass loss expected during intentional weight loss in people with CF is unknown, but in other populations who are more frail than the CF population, these reductions have been shown to be small and not clinically meaningful (33).

Proposed trial of weight loss intervention in cystic fibrosis

People with CF have been exposed to different nutritional messaging to the general population and advised to eat a high-fat, high-energy diet with minimal focus on diet quality measures(16). It is therefore unclear if they will be willing and able to change their dietary habits to reduce energy intake and lose weight due to cognitive dissonance from the inconsistency and change in dietary advice. However, people with CF are used to adhering to specific nutritional advice when they needed to gain significant amounts of weight so it is likely that they will be able to adhere to advice to lose weight. Intensive dietetic support is a fundamental part of CF care. Therefore, it is appropriate for this programme to be delivered by specialist CF dietitians who have existing rapport with patients. A programme supported by dietitians is required because people with CF have additional complexities when adjusting their eating habits. 90% are pancreatic insufficient and are prescribed pancreatic enzyme replacement with every meal to optimise their digestion. The doses of this medication need to be adjusted to the fat content of the food, and they may require dietetic support with this if they are changing the types of food they consume. Around 40% of people with CF are treated with oral agents or insulin for CF-related diabetes. This will also need adjusting with different eating habits. It is recommended in people with type 2 diabetes treated with insulin, that they receive dietetic support when trying to lose weight(34). This programme will include meal replacement products and portioned ready prepared meals. Using these in a behavioural weight management intervention has been shown to lead to greater weight loss at 1 year compared to programmes not utilising meal replacements (35). The prescriptive nature of these interventions is likely to be familiar to people with CF who may have used oral nutritional supplements in the past to achieve weight gain. Given the high clinical treatment burden that exists for people with CF, having a prescriptive intervention may be easier for them to combine with their other care needs. A dietetic led programme using meal provision may lead to weight loss and improve cardiometabolic parameters and stabilise lung function in people with CF, but this requires testing.

A feasibility trial with an embedded qualitative component is needed to assess the feasibility of recruitment, engagement, adherence, and retention to confirm if it is feasible to move to a trial to test the intervention's effectiveness.

6. OBJECTIVES AND OUTCOME MEASURES

Please refer to objectives and outcomes in section 3. More detail on the feasibility measures is presented in progression criteria table in section 11.

7. STUDY DESIGN

This study is a randomised controlled feasibility trial with an embedded qualitative interview with participants and staff delivering the intervention and the trial. The aim of the study is to assess the feasibility of progression to a definitive RCT.

Participants will be recruited from CF centres in a range of geographical locations across the UK and will be expected to be involved in the study for 24 weeks. Assessments will be conducted remotely via video on MS teams. The assessments will take place at baseline, 4, 12 and 24 weeks All participants will be invited to take part in a semi-structured interview about their experience in the study. Of the intervention group some participants (n=10) will be interviewed at 12 weeks and some participants (n=10) will be interviewed at study conclusion. This two time points for interviews are to collect data about participant views of concurrent acceptability of the intervention and retrospective acceptability of the intervention, as resources do not allow for two interviews for each intervention participant. The control group participants all (n=10) will be interviewed at study conclusion.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Adults with cystic fibrosis who have a BMI ≥ 27 kg/m^2 (or BMI ≥ 25 kg/m^2 for people of Black, Asian, or minority ethnic origin) for involvement in the randomised study and healthcare professionals involved in the trial (for interviews only)

8.2. Inclusion Criteria

- Aged 18 years or above.
- BMI ≥ 27 kg/m^2 (or BMI ≥ 25 kg/m^2 for people of Black, Asian, or minority ethnic origin).
- Participant is willing and able to give informed consent for participation in the study.
- Access to the internet and an internet enabled device (smartphone, tablet, computer)
- Established diagnosis of cystic fibrosis including those who have previously received a lung or liver transplant.
- Forced expiratory volume (FEV1) ≥ 25% predicted recorded in the last 6 months.

- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.

- Able to communicate in English or has a relative/friend/carer acting as interpreter.

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Female participant who is pregnant, lactating or planning pregnancy during the course of the trial.

- Currently participating in a structured weight loss programme or ≥10% self-reported weight loss in the 6 months before the screening visit.

- Documented decompensated liver disease.

- Documented stage 4-5 kidney disease.

- Actively using enteral feeding.

- Currently taking part in other interventional studies unless agreed in advance by all trial teams (participation in observational studies is allowed).

- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

8.4. Health care professional inclusion criteria (interviews only)

- Health care professional participant is willing and able to give informed consent for participation in the study.

- Involved in the trial either through recruiting and/or completing study assessments for participants, through delivery of the intervention or providing clinical care to participants.

9. PROTOCOL PROCEDURES

9.1. Recruitment

Participants will be recruited from NHS Trusts that have adult CF services from across the UK. We will aim to choose sites to reflect different geographical areas to increase diversity of participants. The study team has badging from the Clinical Trials Accelerator Platform (CTAP) run by the Cystic Fibrosis Trust who provide support with recruitment and research co-ordinators for research trials in CF centres. CTAP are also aware of other clinical trials taking place in CF centres.

Sites should have available staff and resources to be able to recruit participants, conduct study assessments, and collect specified research data.

CF centres have established cohorts of patients, and due to this it will be possible for clinical teams to screen their databases and identify potentially eligible participants at the start of the recruitment period as detailed information exists on the clinical parameters required to assess eligibility.

A member of the CF team will screen potentially eligible participants and discuss the study with them at routine CF appointments or by phone/email/letter and provide them with a participant information sheet (PIS) and a member of the CF clinical team will request verbal consent to pass on the participant's details to the research team. The site research team will then contact the potential participant to confirm if they wish to participate in the study. Alternatively, the potentially eligible participant will be able to contact the research team directly if they wish via contact details provided.
For those who are eligible but decline to participate in the study, the research team will ask them if they are happy to choose their reason for declining from the following list. The information will be recorded in the site screening log and retained without any identifying information. These data will be used to assess the feasibility of recruitment to the study.

1. I would find it difficult to follow the weight loss programme

2. I do not like the idea of using a meal replacement and/or ready prepared meals

3. I am worried about potential side effects from the diet

4. I do not think I can commit to this study due to my current treatment regime

5. I do not think I can commit to this study due to my current family or work commitments

6. I am uncomfortable with the idea of randomisation

7. I feel uncertain that I will benefit from the research study

8. I was not given adequate information

9. Other (not specified)

The number of patients who are assessed for eligibility will be recorded on a pre-screening log. To allow comparison of the demographics of those who decline to participate against those who enrol, summary anonymised statistics (age, sex, BMI) of all those approached will be recorded.

9.2. Screening and Eligibility Assessment

Patients who agree to participate after the initial recruitment process described in section 9.1 will be booked for a screening/ baseline video assessment and equipment will be sent to them. At the start of this visit the link to the e-informed consent form will be emailed to them using the email address they will provide at the time of booking the visit. The participant will complete the e-consent form at the start of the call (see further detail in section 9.3). Following the completion of the e- informed consent form the participant will then undertake screening/baseline assessments.

During the video appointment the participant will check their weight on the scales provided and the researcher will confirm they meet the BMI inclusion criteria and all approved inclusion and exclusion criteria in the protocol; no exceptions will be made regarding eligibility. If they do not meet all the criteria then they will fail the screening and will not be recruited into the study and equipment will be returned.
At the screening/baseline visit, the baseline assessments will be carried out including recording of the current concomitant medication and the participant will complete the blood test vial following the instructions provided and post it to Medichecks. If the time between initiation and completion of screening is more than 2 months (60 calendar days), the participant must repeat all screening procedures before proceeding to randomisation.

Rescreening will be permitted if the participant becomes eligible over the period that the study is running at the site. The most likely reason for this will be participants who were not initially eligible on BMI criteria but record weight gain making them eligible during the period that the study is open for recruitment.

9.3. Informed Consent

The participant must personally sign and date the latest approved version of the e- informed consent form before any trial specific procedures are performed.

The link to the written electronic version of the e-informed consent form will be emailed via REDCap at the start of the baseline visit. The e-informed consent form will be presented to the potential participant by the research team member detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The potential participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP, or other independent parties to decide whether they will participate in the trial. The participant will mark each box on the e-informed consent form and then provide an e-signature which will form their e-informed consent. The researcher who is presenting and obtaining the informed consent will also fill in a form on REDCap to confirm that they have confirmed the validity of the consent. The person who verifies the validity of the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. The completed e-consent form will be emailed directly from REDCap to the participant's email address. The original signed form will be retained electronically on REDCap and an electronic copy or paper copy will be added to the participant's medical records.

Informed consent will be sought from research and clinical staff who are approached to take part in qualitative interviews. A consent form will be sent to the participant along with the relevant participant information sheet prior to the start of the interview and the researcher conducting the interview will confirm it has been completed, signed and returned by email before the interview commences.

9.4. Randomisation

Eligible participants will be randomised 2:1 into the intervention group or usual care stratified by presence of CF-related diabetes (yes/no) and age over or under or equal to 40 years.

Randomisation can be performed following the baseline assessment once all baseline data including blood sample results have been received.

The unique randomisation codes will be generated using a central computer software (Sealed Envelope™) which can be accessed by a member of the study team at sites via a secure login. There will be no requirement for a back-up paper randomisation system as randomisation is not time critical and can be delayed should the randomisation software be temporarily unavailable e.g., because of internet connection issues.

Once the screening assessment has been completed, if the participant meets the eligibility criteria and is keen to proceed with the study, the participant should be randomised. Queries on eligibility must be resolved before randomisation and participants who do not meet all the eligibility criteria must not be randomised. A member of the local study team will enter the participant details to the randomisation system (initials, participant ID and research site code, confirmation of eligibility, confirmation of completion of baseline assessments, date of informed consent, and stratification factors).

The system will allocate the participant, and the researcher will be informed of the allocation. The researcher will then inform the participant of their allocation. There will be no maximum duration between completion of the screening assessment and randomisation. Allocation concealment is achieved as randomisation occurs after the baseline visit, the randomisation algorithm is unmodifiable and concealed from investigators and the local research teams, and the local research teams have no access to the total number of participants randomised to each group.

The recruiting site will receive notification of a new participant/randomisation via a message from Sealed Envelope™.

Following randomisation, the research team will send a letter to the participant's GP informing them about trial participation and group allocation.

9.5. Blinding and code-breaking

Due to the nature of the intervention in this study it is impossible to blind the participants and research teams. Therefore, procedures for breaking the allocation code are not applicable.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

9.6.1. Description of study intervention(s)

The intervention is a structured weight loss programme with behavioural support from a specialist cystic fibrosis dietitian.

Participants will be supported to reduce their energy intake to approximately 1200kcal per day with three main eating occasions. Participants will be asked to replace one of their meals with a formula product (shake/porridge/bar) which will provide 200kcal/day that conforms to the total diet replacement regulatory guidance regarding its composition, and a second meal with a ready prepared portioned meal that will provide approximately 500kcal and 30-40g protein. The participant will select the third meal using guidance on portion size and meal ideas provided during the initial consultation with a specialist cystic fibrosis dietitian. On one day a week the participant will select 2 meals themselves and continue with the shake/porridge/bar). Guidance will be given if participants want to include snacks, they will be advised to consume a piece of fruit and one high protein, low energy snack.

Participants will be advised to drink energy-free fluids (e.g., water, coffee, tea with skimmed milk, diet soft drinks) and avoid energy dense drinks (e.g., alcohol, milkshakes, sugar-sweetened beverages) during the programme.

Following randomisation to the intervention group, participants will have a 60 min initial consultation via video call (using MS teams). This consultation will take place with a specialist cystic fibrosis dietitian at the site or the lead study site and will include an initial assessment of current diet including food allergies or intolerances and weight history to ensure the programme is tailored to the individual participant and potential issues are discussed. Specific CF issues such as pancreatic enzyme dosing and diabetes treatments will be addressed. The participant will be sent an email detailing how to order the meal replacement product and the ready portioned meals. Weekly video calls with the specialist cystic fibrosis dietitian will continue until 12 weeks when the frequency of these sessions will drop to fortnightly until

the end of the trial at 24 weeks. All intervention sessions will be recorded using Microsoft teams and will used to assess fidelity of the intervention delivery.

Following the initial appointment, the intervention will commence, and the participant will be provided with an initial 4-week supply of formula meal replacement products to be used in one of the meals. Participants will have further products delivered to their home address by a courier company. The portioned ready meals will be delivered to the participants home each week by an external company. During the last session of the programme, they will be supported to gradually transition back to a self-selected energy-controlled and healthful diet and guided by the dietitian to support food choices and meal planning. The intervention will finish at the end of study assessment at 24 weeks.

Participants will not receive any further support from the study team following this, but summary information will be provided to their clinical team so that new eating habits established during the programme can be maintained.

The aim of the dietitian supported consultations is to maintain motivation to follow the programme and to help to solve any problems that arise. The participants will be supported with habit formation using appropriate behaviour change techniques. Advice on avoiding and managing lapses and coping with social situations will be given as appropriate to the individual situation. This type of support will be familiar to participants as they attend regular dietetic reviews as part of their usual care.

Participants will receive the intervention on top of the local standard care pathway of regular 3 monthly clinic appointments in a multidisciplinary cystic fibrosis clinic that may include dietetic review. As part of the standard care the dietitian may provide advice and support regarding diet and lifestyle changes.

Medication adjustment

Cystic fibrosis related diabetes

Based on current UK CF registry data(1), it is anticipated that up to 40% of participants will be on treatment for CF related diabetes, typically insulin. People with CF are used to self-management of insulin treatment and will be guided to adjust their insulin as they would normally do when eating different foods. Participants in the intervention group will be asked to make an initial reduction of 25% of total daily baseline insulin doses at the start of the intervention, this is in line with other trials testing a calorie reduction and has been shown to be safe and effective in reducing the risk of hypoglycaemia(36). They will be advised to monitor their glucose levels regularly, typically done using a continuous glucose monitoring device that they will already have. If they experience hypoglycaemia or hyperglycaemia, they will be advised to discuss this with the clinical team. The doctor providing oversight to the dietitians delivering the intervention will also be available to discuss insulin management. Participants will be required to continue attending their diabetes review appointments /monitoring as usual.

Pancreatic Enzyme Replacement Therapy adjustment

Around 85% of people with CF are classified as pancreatic insufficient(1) meaning that they need to take pancreatic enzyme replacement therapy (PERT) with every fat containing meal and snack. In routine

clinical care, patients are taught how to adjust dosage according to their dietary intake with some using a fat dosing method (i.e.; ratio of fat (g) to each enzyme capsule) and some using a fixed dosing depending on the size of meal (9). It is important that PERT dosing is adequate otherwise patients are at risk of malabsorption and/or distal intestinal obstruction syndrome (a common condition where the small intestine becomes partially blocked with faecal material).

Participants will be informed that their PERT dosing may need to change (most likely to reduce), and they will discuss at the intervention sessions with the specialist dietitian how they can achieve this.

CFTR modulator treatment

Around 90% of people with CF are eligible for cystic fibrosis transmembrane conductance regulator (CFTR) modulators. These are medications that target the underlying defect in the CFTR protein that leads to the development of CF. These medications must be taken twice a day with fat containing food to optimise absorption(37). The exact amount of fat varies according to the individual situation, but participants will receive guidance from the dietitian to ensure they are still having adequate fat with their CFTR modulator treatment.

9.6.2. Description of comparator(s)

Usual care group participants will follow the local standard care pathway attending their routine 3 monthly cystic fibrosis appointments where they will see a dietitian as part of their multidisciplinary care. The dietitian may provide advice and support regarding weight management and behavioural changes. To incentivise trial participation, control group participants will be offered a one-off 30 min weight loss consultation at the end of the trial with a specialist CF dietitian.

9.7. Description of study procedure(s)

All equipment required for the remote study assessments will be provided to the participants. This will include blood pressure monitor, spirometer and scales. If there is loss or accidental damage to equipment the research team will arrange repair or replacement as needed.

Demographic questionnaire – 2 mins (Baseline)

Basic demographic characteristics including date of birth, sex, and ethnic group will be recorded using standardised questions. Contact details (home address, contact number(s), GP practice address, next of kin) will be extracted from medical records and verified by the participant. This information will be stored on REDCap.

EuroQoL-5D 5-level version (EQ-5D-5L) questionnaire – 5 mins (Baseline and 24 weeks)

This is a commonly used and validated general HRQoL instrument which assesses five areas; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The participant is asked to record the most appropriate answer for each domain using a 5-level scale. They are also asked to provide a score from 0-100 for overall self-rated health. The questionnaire will be self-completed by the participant via REDCap.

Alfred Wellness Score (AWESCORE) – 5 mins (Baseline and 24 weeks)

Patients will be asked to complete the AWESCORE CF-specific HRQoL instrument which has been validated specifically for patients with cystic fibrosis and used in clinical trials and clinical care(38), it assesses CF specific functional status and symptoms. The questionnaire will be self-completed by the participant via REDCap.

Concomitant medication (5 min) (Baseline, 4 weeks, 12 weeks and 24 weeks)

Participants will be asked to bring their prescription or a list of their medication at the screening/baseline assessment so the medications can be recorded at baseline and updated at 4, 12 and 24 weeks.

Weight and body composition – 3 mins (Baseline, 4 weeks, 12 weeks and 24 weeks)

The participants will measure their own weight whilst advised to be barefoot and wearing light clothing. Weight will be recorded down to the nearest 0.1kg. The calibrated digital scale (Tanita) used will also use bioelectrical impedance to estimate body composition (fat mass and fat free mass). This device and instructions for use will be provided to the participant for use at home during the trial. This device has CE marking and will be used for its intended purpose.

Height – (Baseline)

The participants' height will be taken from medical records or if missing in records by self-report.

Blood pressure – 5 mins (Baseline and 24 weeks)

Participants will be provided with a home blood pressure monitor and provided with paper instructions on how to correctly perform a home blood pressure reading using a validated device (Omron) (39) . This device has CE marking and will be used for its intended purpose.

HbA1c and Lipid profile – 5 mins (Baseline and 24 weeks)

Participants will be given an HbA1c and lipid profile test at baseline and 24 weeks. This will be done at the participants' home, with a finger-prick blood sample kit, which they will post to an established provider. The kit contains lancets and vials, to collect 3 drops of blood to be sent to the laboratory. The participant will be sent an email detailing the blood sample collection process. It will be permitted to use a blood test result recorded at the CF centre if it is within a month of baseline visit or within a month of the 24-week visit.

Spirometry (lung function)– 5 mins(Baseline, 4 weeks, 12 weeks and 24 weeks)

Spirometry will be performed according to British Thoracic Society guidelines(40). Participants will record their lung function using their home spirometer. Patients with cystic fibrosis are typically trained in how to do this at home as part of their routine clinical care. If any participants are not familiar with the technique they will be provided with training. If any lung function measure drops by more than 10% from the previous visit, the clinical team will be notified by the study team.

Patients who do not already have access to a home spirometer will be given a Spirobank Smart device. This device has CE marking and will be used for its intended purpose. In order to use this device, they will need to download an app on a smartphone, they will add their participant number to the details section on this app rather than their name. Once they have used this device to measure their lung function, they will be able to read the relevant results (FEV1 and FVC) to the researcher on the video call or send a PDF of the results generated from the app directly to the study email address. Spirometry data is only stored on the app on the participants phone and does not go to any external servers.

Sit to stand- 5 mins (Baseline, 4 weeks, 12 weeks and 24 weeks)

Participants sit in a standard straight-backed stable chair (without wheels) positioned by a wall. They then stand fully and sit back down, without using the hands, five times, as quickly as possible. This will be completed over video call.

Adverse events (AEs) (Baseline, 4 weeks, 12 weeks and 24 weeks)

Potential adverse events will be reported by the participants using a pre-defined list of expected adverse events (see section 10.0). This list will be based on previous trials of dietary interventions and will include the option for free text to record any additional adverse events.

Feedback questionnaire- all patient participants – 5 mins (24 weeks)

A 10-item study-specific questionnaire will assess how satisfied all participants were with trial processes, any potential contamination of the usual care group, and satisfaction with the intervention for the intervention participants. The questionnaire will be self-completed by the participant via REDCap.

Feedback questionnaire- intervention participants only – 5 mins (24 weeks)

An 8-item questionnaire will assess intervention acceptability, it uses adapted questions from the Theoretical Framework of Acceptability questionnaire (41).

Overview of embedded qualitative interviews

All interviews will be conducted over MS teams and will be transcribed using intelligent verbatim at the same time as the interview using Microsoft Team's embedded transcription feature, which has been approved for use at Oxford.

Qualitative interviews with intervention participants at 12 weeks – ~45min

The interviews conducted with the intervention participants will ask for their views on the following areas. The interviews will be conducted by a researcher from the central study team. The topic guide is provided

in the document 'EASE-CF Qualitative interview topic guides' and will be piloted prior to study commencement, changes may be made as required to fully explore unanticipated topic areas. Participants will be guided by the researcher to explore any particular areas that are individual to them. Attempting to interview all intervention participants will maximise the data collected to inform the feasibility objectives, as below

(a) The delivery of the programme
(b) Barriers to engagement to the programme
(c) Barriers to adherence to the programme including specific factors related to their cystic fibrosis
(d) Facilitators to adherence to the programme

Qualitative interviews with intervention participants at 24 weeks – ~45min

The interviews conducted with the intervention participants will ask for their views on the following areas. The topic guide is provided in the document 'EASE-CF Qualitative interview topic guides' and will be piloted prior to study commencement, changes may be made as required to fully explore unanticipated topic areas. Participants will be guided by the researcher to explore any particular areas that are individual to them. Attempting to interview all intervention participants will maximise the data collected to inform the feasibility objectives, as below

(a) The delivery of the programme
(b) Barriers to engagement to the programme
(c) Barriers to adherence to the programme including specific factors related to their cystic fibrosis
(d) Facilitators to adherence to the programme

Qualitative interviews with usual care participants at 24 weeks – ~45min

The interviews conducted with the usual care participants will ask for their views on the following areas. The topic guide is provided in the document 'EASE-CF Qualitative interview topic guides' and will be piloted prior to study commencement, changes may be made as required to fully explore unanticipated topic areas. (REF). Participants will be guided by the researcher to explore any particular areas that are individual to them.

They will be asked about the following areas

(a) *Experience of being in a clinical trial*
(b) *Experience of being in the usual care group*
(c) *Potential contamination*

Qualitative interviews with research and clinical staff – ~45min

The interviews conducted with 10 clinical staff taking involved in delivering the intervention or providing care to the participants will ask for their views on the following areas. The topic guide is provided in the document ' EASE-CF Qualitative interview topic guides' and is informed by the RE-AIM Framework(42), a commonly used framework compromising of five dimensions (reach, effectiveness, adoption,

implementation and maintenance) that can be used to explore barriers and facilitators when considering the potential scale up of an intervention for a full RCT.

Reach

- Reasons for discussing (or not discussing) the trial with potential participants beyond the inclusion/exclusion criteria
- Factors influencing recruitment and retention
- Perceived participant attitudes to randomisation

Effectiveness

- Specific concerns regarding clinical equipoise for intentional weight loss in this population
- Clinical staff understanding of the trial intervention and comparison to other weight loss strategies available.
- Beliefs about observed benefits to health outcomes from the intervention and usual care.

Adoption

- Professional concerns about the trial design, intervention and procedures including organisation specific factors contributing to adoption of the trial.
- Perception of patients' reactions to the trial and the intervention.

Implementation

- Ease of implementing the intervention as intended.
- Factors that made delivering the trial easier
- Barriers that health professionals encountered during implementation and strategies that were used to overcome these challenges.
- Challenges reported by intervention participants and how dietitians supported participants to overcome challenges.

Maintenance

- Relevance to clinical practice and likelihood of adopting the intervention or principles of the intervention in routine clinical practice
- Potential barriers to fitting into routine care models and potential adaptations would need to be made.

Fidelity of delivery

To assess the fidelity of delivery of the intervention, the intervention sessions will be recorded via MS teams. The data from these sessions will be coded using a pre-specified criteria to assess fidelity of delivery.

Qualitative interview with intervention participants at 6 months after the end of their active participation in the study (optional).

Intervention participants will be asked to provide consent for the research team to reapproach them 6 months after the end of their active participation in the study. This interview will explore their experience and reflections after finishing the intervention and check whether they were able to continue to follow any changes they made during their participation in the intervention. The topic guide is provided in the document 'EASE-CF Qualitative interview topic guides' and will be piloted prior to study commencement, changes may be made as required to fully explore unanticipated topic areas. Participants will be guided by the researcher to explore any particular areas that are individual to them

9.8. Baseline Assessments

The baseline assessment will be conducted remotely during screening. The assessments will take approximately 1 hour and will include the following as detailed in section 9.4

- Height (taken from medical records/self-report)
- Weight and body composition
- Spirometry
- Demographic questionnaire
- Concomitant medication
- EQ-5D-5L questionnaire
- Alfred Wellness Score (AWESCORE)
- Sit to stand
- HbA1c and lipid profile – one blood sample kit

9.9. Subsequent Visits

Subsequent assessments will take place in week 4, 12 and 24. The study schedule is available in Appendix B.

Assessment 1: Week 4 (± 1 week) – video - Assessment of outcome measures

- Concomitant medications
- Adverse events
- Weight and body composition
- Spirometry
- Sit to stand

Assessment 2: Week 12 (± 1 week) - video- Assessment of outcome measures

- Concomitant medications
- Adverse events
- Weight and body composition
- Spirometry
- Sit to stand
- Qualitative interview for n=10 intervention participants

Assessment 3: Week 24 (± 1 week) - video- Assessment of outcome measures

- Concomitant medications
- Adverse events
- Weight and body composition
- Spirometry
- Sit to stand
- HbA1c
- Lipid profile
- EQ-5D-5L
- AWESCORE
- Feedback questionnaire for intervention participants only
- General Feedback questionnaire for all participants
- Qualitative interview for n=10 intervention participants and all usual care group participants

Healthcare resource use and long-term follow-up data through the hospital medical records

Informed consent will be sought from participants allowing the study team to access medical records to collect long term follow up data. Providing informed consent for long term data follow up is optional. We will extract relevant data collected as part of routine care at each study site for up to 2 years after each participant completes their active participation. The type and timing of relevant data collected will depend on data availability based on each participant's routine clinical care. This is likely to include weight, lung function and health resource use data. Relevant guidance will be provided to sites at the end of the study.

9.10. Sample Handling

Participants in both groups will have blood samples taken for lipid profiles and HbA1c at baseline and 24 weeks. As this trial is delivered fully remotely, this will be done at the participants' home using a finger prick blood sample kit provided from an established provider. They will use the lancet in the kit to obtain 3 drops of blood to complete the test kit and then post this to the provider (Medichecks). The kit will be

pre-registered online by the study team using a unique identifier to ensure confidentiality of the participant. The sample results will be received online directly by the study team who will communicate them to the participant's GP via a letter and to the participant. Medichecks is compliant with GDPR rules and is a registered provider for the University of Oxford. The samples will be used only for this project, destroyed after testing by Medichecks and will not be stored for long term use.

9.11. Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to withdraw early from the trial treatment at any time. This may happen for a number of reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with trial procedures
- Participant decision

Participants in the intervention group:

They may stop the intervention and/or study assessments but may remain on study follow-up and will be encouraged to do so.

Participants in the care as usual group:

They may opt out of study assessments but may remain on study follow-up.

All participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. In the case of withdrawal from both treatment (intervention) and active follow up consider the following options for a tiered withdrawal from the study will be given to participants and be covered in the participant information sheet.

According to the design of the study, option 1 below will be the default. Participants can explicitly opt for option 2.

1) Participants may withdraw from active follow-up and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., CT-Scans, blood results and disease progression data etc.

2) Participants can withdraw from the study but their data including data from samples already analysed before withdrawal will be retained for use in the study analysis.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Pregnancy

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-adherence with the intervention regimen or study requirements
- An adverse event which requires discontinuation of the study intervention or results in inability to continue to comply with study procedures
- Disease progression which requires discontinuation of the study intervention or results in inability to continue to comply with study procedures

The follow-up of participants that have withdrawn from the intervention but not from active follow-up will continue with the standard follow-up assessments of the study. Participants who withdraw from the study will not be replaced.

The type of withdrawal and reason for withdrawal will be recorded in the CRF if available.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for frequent telephone calls until the AE has resolved or stabilised and up to the point that the participant completes the study.

If a participant is withdrawn from treatment due to pregnancy, the pregnancy will be followed up to outcome. See the Safety Reporting section below.

9.12. Definition of End of Study

The end of study is the point at which all the data has been entered and queries resolved.

10. SAFETY REPORTING

This intervention is low risk, and adverse events are expected to be limited to those related to the underlying disease. The safety reporting window will start from randomisation and continue until the 24 weeks of the active study participation, AEs/SAEs will not be recorded during the two-year long term follow up.

10.1. Recording Adverse Events

Participants may report potential AEs at study assessments, during intervention contacts for those in the intervention group, or at any other time by contracting the research team.

AEs will only be recorded if they are judged by the investigator to be possibly related to the study intervention or study procedures as follows:

AEs possibly related to the intervention: Based on the discretion of the investigator, these may include but not limited to the following events in the intervention group:

- Constipation

- Fatigue
- Dizziness
- Hypoglycaemia
- Upper abdominal pain
- Headache

- AEs possibly related to study procedures: Based on the discretion of the investigator, these may include but not limited to the following events in either group:

- Dizziness
- Syncope
- Bruising
- Distress

AEs will be reviewed by an investigator (an appropriately qualified individual and delegated member of the study team) at the local site. The review should include details of the nature, seriousness, severity, causality and expectedness of the event. The participant's clinical team, including the dietitian, will manage potential adverse events.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

Non-serious AEs considered related to the study intervention will be followed up until the event is considered stable or up to the end of the safety reporting window, whichever is earlier.

AEs meeting the seriousness criteria (SAEs) will be reported to the sponsor delegate (CI) via RedCap within 24 hours of the study team becoming aware of the event. SAEs will be followed up by local site staff until the event is considered stable or up to the end of the safety reporting window, whichever is earlier.

10.2. Expected adverse events

The following events are generally prevalent in CF population and may require hospitalisation. It is likely that some participants may experience one or more of these events during the study period and such events are classified as expected due to the illness but (possibly) unrelated to the intervention. All AEs detailed below that meet the SAE definition will be recorded on REDCap but not require SAE reporting.

- **Episodes of lung infection and haemoptysis –** these can be severe and are referred to as 'infective exacerbations' of CF. They typically require treatment with antibiotics either at home or at hospital.

- **Episodes of distal intestinal obstruction syndrome (DIOS) -** these are common in people with CF and may require intensive laxative treatment as an outpatient or inpatient.

- **Episodes of pancreatitis -** these are a common complication of CF and may require treatment in hospital.

10.3. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant taking part in the research study, including occurrences which are not necessarily caused by or related to the intervention or research procedures. For the purposes of this study, only those AEs which are in the opinion of the local investigator related to the study intervention or study procedures will be recorded and reported.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.4. Reporting Procedures for Serious Adverse Events

Sites will complete the SAE form on REDCap and the system will automatically notify the central team, including the CI and trial manager of the event. A medically qualified researcher will assess whether the AE is an SAE and, if so, assess its causality and expectedness.

A serious adverse event (SAE), excluding the ones on section 10.2, occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event.

11. STATISTICS AND ANALYSIS

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be reviewed and signed off prior to final database lock, and, if an amendment is deemed necessary, then this will be documented.

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be reviewed and signed off prior to final database lock, and, if an amendment is deemed necessary, then this will be documented.

11.2. Description of the Statistical Methods

The primary objective of the study is to assess the feasibility of progression to a definitive RCT. Progression criteria (as defined in Table 3) will be summarised descriptively as counts and proportions for all participants [and by study group, study site]. Uncertainty in the progression criteria will be expressed with 95% confidence intervals. The baseline demographic and clinical characteristics will be presented in a table. Continuous variables will be summarised using means, standard deviations. For non-normally distributed continuous data medians with interquartile ranges will be presented. Categorical variables will be summarised using counts and percentages. All other exploratory outcomes detailed in the study synopsis will be summarised descriptively by study arm. Where appropriate, the effect size and 95% confidence intervals will be estimated with regression models adjusting for treatment group, baseline value (where applicable), and stratification variables. Both absolute and relative effect sizes will be reported. Data will be analysed using appropriate statistical software.

Table 3: Progression criteria.

Sufficient levels of	Criterion	Green (progress)	Amber (Progress with changes)		Red (Stop)
Recruitment	1a Rate (*n* of patients per site per month) 1b Total *N* participants recruited	≥ 0.6 ≥30 patients	0.35 - 0.59 16-29 patients	Add sites to progress	≤ 0.35 15 patients
Engagement	Proportion of participants who attended 6 or more sessions during the 24 weeks (25% of sessions) and at least one of the last 3 sessions.	≥ 60%	36-59%	Consider making changes from process evaluation to progress	≤ 35%
Adherence	Proportion of participants in the intervention group who finished the programme with ≥5% weight loss at 12 weeks	≥50%	36-49%		≤ 35%
Retention	Proportion of randomised participants completing a 24 week follow up visit	≥75%	51-74%		≤ 50%
Safety	Safety profile	Adjudicated by the Study Steering Committee, based on related AEs and on related expected and related unexpected SAEs			

11.3. Sample Size Determination

As this is a feasibility study, it is not powered to detect a clinically and statistically significant difference between groups(43, 44). The sample size of 30 patients was not arrived at using a statistical method. CF is a rare disease, and this sample size is in keeping with other feasibility studies in CF (45). The sample size will provide sufficient data to test the feasibility objectives in this study. The sample size has been derived after taking into account potential withdrawals which are expected to be low.

11.4. Analysis populations

All randomised and eligible participants will be included in the main analysis on an intention-to-treat principle regardless of withdrawal or non-adherence.

A per-protocol analysis will be performed including intervention participants who adhered to the intervention (as defined in the adherence criterion) against those in the control group who lost <5% of their body weight from baseline to 12 weeks.

The adverse event analysis will include the participants in the control group and the participants commencing the intervention in the intervention group.

11.5. Decision points

No interim analysis is planned

11.6. Stopping rules

The Study Steering Committee (SSC) may formally recommend early termination if needed in line with the TSC charter.

11.7. The Level of Statistical Significance

The level of statistical significance will be set at 0.05 and 95% confidence intervals will be nominal and descriptive. P-values will not be reported given the feasibility nature of the study(46). There will be no adjustment for multiple testing(47).

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

The proportion of missing data for each outcome measure will be reported to inform the feasibility outcomes. Given the small scale of the study, imputation will not be meaningful.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Deviations from the original SAP will be reported and justified at publication following the CONSORT guidelines(46).

11.1. Qualitative Analysis

Interviews will be video and audio recorded and will be transcribed using intelligent verbatim at the same time as the interview using Microsoft Team's embedded transcription feature, which has been approved for use at Oxford. Appropriate software will be used to collate data, and deductive analysis will be undertaken as the interviews are conducted. The following steps of the framework method will be used; familiarisation, coding data to a pre-defined list based on the theoretical framework of acceptability and combined with some open coding to ensure important aspects are not missed(48). A final analytical framework will then be used to chart the data and then move into the interpretation stage, organising themes into categories and mapping linkages. To validate the coding a second coder (a member of the research team) will re-code a random 10% sub-sample.

12. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

Audio recordings will be collected using Oxford Nexus 365 MS teams.

12.2. Access to Data

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

Names and contact details (address and phone number) of participants receiving the intervention will be shared with the company providing the meal replacement and ready prepared meal products and the delivery company for the sole purpose of selecting and delivering the products to the participants.

12.3. Data Recording and Record Keeping

All Study data, except the audio recording files, will be entered on REDCap, which will host the eCRF. The validation process with be in line with the SOPs and include naming variables, eCRF design, data verification and validation (range and logic tests), test data entry, and data export verification. Identifiable, personal data will be retained centrally on REDCap (i.e. by the sponsoring organisation). The participants will be identified by a unique study specific number and/or code in any database for analysis outside REDCap (i.e., they will be excluded from any data exports for data analysis). Electronic forms with personal information, such as e-consent forms, will be held securely at the University of Oxford until the end of the study to allow for the long-term follow-up through medical records to occur. They will then be securely deleted. Following review to ensure participant anonymity is safeguarded and subject to any reasonable and necessary delay, anonymised research data will be securely archived to a repository following publication of the results where they will be stored indefinitely. These data may be used in future research, here or abroad, and may involve commercial organisations.

The recordings of the intervention sessions and interviews will be transcribed using intelligent verbatim at the same time as the interview using Microsoft Team's embedded transcription feature, which has been approved for use at Oxford. Transcripts will be uploaded to the file, checked for accuracy, and pseudonymised by an approved member of the research team. The audio and where recorded, video files will be securely stored in Nexus 365 OneDrive for Business. The recordings will be linked to the rest of the data using the unique study specific ID number in the file name. The copy of the MS Teams recordings held at the University will be retained until completion of relevant analyses and they will then be securely deleted. The de-identified transcripts will be retained in line with the rest of the de-identified research data. Prior to database lock, the database will be reviewed to ensure all queries have been resolved and the dataset is complete. The Data Management will be compliant with the University of Oxford's policy (https://researchsupport.admin.ox.ac.uk/policy/data). No study data will be stored on personal laptops in line with this policy.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.2. Study monitoring

All data entry will be conducted on the online database, with remote monitoring conducted by the study management group. The REDCap database has an integrated system for reviewing data queries and errors, which will be monitored throughout and discussed with the respective recruiting sites.

13.3. Study Committees

Study Management committee

The trial management committee will comprise of all named investigators, the study manager, relevant staff from the Oxford Respiratory Trials Unit, patient and public involvement representative and other key personnel involved in the study. In line with the committee's Charter, it will be responsible the day-to day management of the trial. Meetings will be monthly and adjusted as needed as the study progresses.

Independent Study Steering Committee (SSC)

This study is unblinded and as such does not require a separate Data Monitoring and Ethics Committee. The SSC will also assume the role of the Data Monitoring and Ethics Committee. The group will compromise of an independent chair (academic respiratory consultant), an independent CF dietitian and a patient and public representative.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the study subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

Clinical equipoise

In other clinical populations, a 5-10% weight loss has been associated with improvements in existing obesity related comorbidities but also in reducing the risk of these comorbidities(49). It is unknown if following an energy restricted diet to achieve intentional weight loss is possible in people with CF and at what rate weight loss might occur compared to other clinical populations. There is no evidence to show what the effect of intentional weight loss on clinical parameters is likely to be. There is clinical equipoise in relation to whether interventions targeting intentional weight loss in people with CF who have a higher BMI are necessary. A randomised study is required to test this, but whether a definitive study is feasible is unclear which justifies the need for this feasibility study.

Adverse events

The adverse events expected during the study are likely to be related to underlying cystic fibrosis diagnosis. There is a theoretical concern about excessive loss of muscle mass and potential reduction in lung function, but it is thought that these will be clinically insignificant as there is no physiological basis for steady controlled and intentional weight loss leading to lung function decline. People with CF are closely monitored by their clinical teams, with regular clinic appointments and direct access to their secondary care teams between appointments as needed. As part of their routine clinical care, they are encouraged to report significant adverse events (including apparent deteriorations in lung function) to their clinical teams, who will continue to guide their clinical care throughout the study period.

Mental health concerns

During the design of this study, we have considered appropriate mental health safeguards to mitigate the risks of disordered eating, development of unhealthy weight loss behaviours and potential mental health challenges associated with weight management. The dietitians delivering the intervention will be specialist CF dietitians who will be used to looking out for mental health challenges in their patients across a range of nutritional interventions. During the weekly/fortnightly contacts during the study they will build rapport with the participants and will be advised to be vigilant for participants who experience mental health challenges. Any participants who are deemed to require onward referral will be referred to the CF psychology services at the site as required. Overall, the literature shows that structured weight loss programmes, like the one under test here, improve disordered eating and mental health.

16.5. Reporting

The CI shall submit once a year throughout the clinical study, or on request, an Annual Progress Report to the host organisation, funder and Sponsor (where required). In addition, an End of Study notification and

final report will be submitted to the HRA, the REC, host organisation and Sponsor. A lay summary of results will be produced for participants and members of the cystic fibrosis clinical community.

16.6. Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on ISRCTN, a publicly accessible database.

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

We will offer participants a voucher following the baseline, 4-week, 12 week and 24-week assessments as compensation for their time to attend study assessments. Each voucher will be worth £10 and therefore the maximum reimbursement value for attending all of the assessments will be £40.

To incentivise study participation, control group participants will be offered a one-off 30 min weight loss consultation at the end of the study with a specialist CF dietitian.

17. FINANCE AND INSURANCE

17.1. Funding

This study is funded by the NIHR (Grant Reference Number NIHR304079).

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting

Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute for Health and Care Research (NIHR) under its Doctoral Fellowship Programme (Grant Reference Number NIHR304079). The views expressed will be those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study.

19. ARCHIVING

This will be in line with section 13.3. Anonymised data will be indefinitely archived in a repository. Identifiable data will be stored within the secure network of the University of Oxford for 3 years and then securely deleted.

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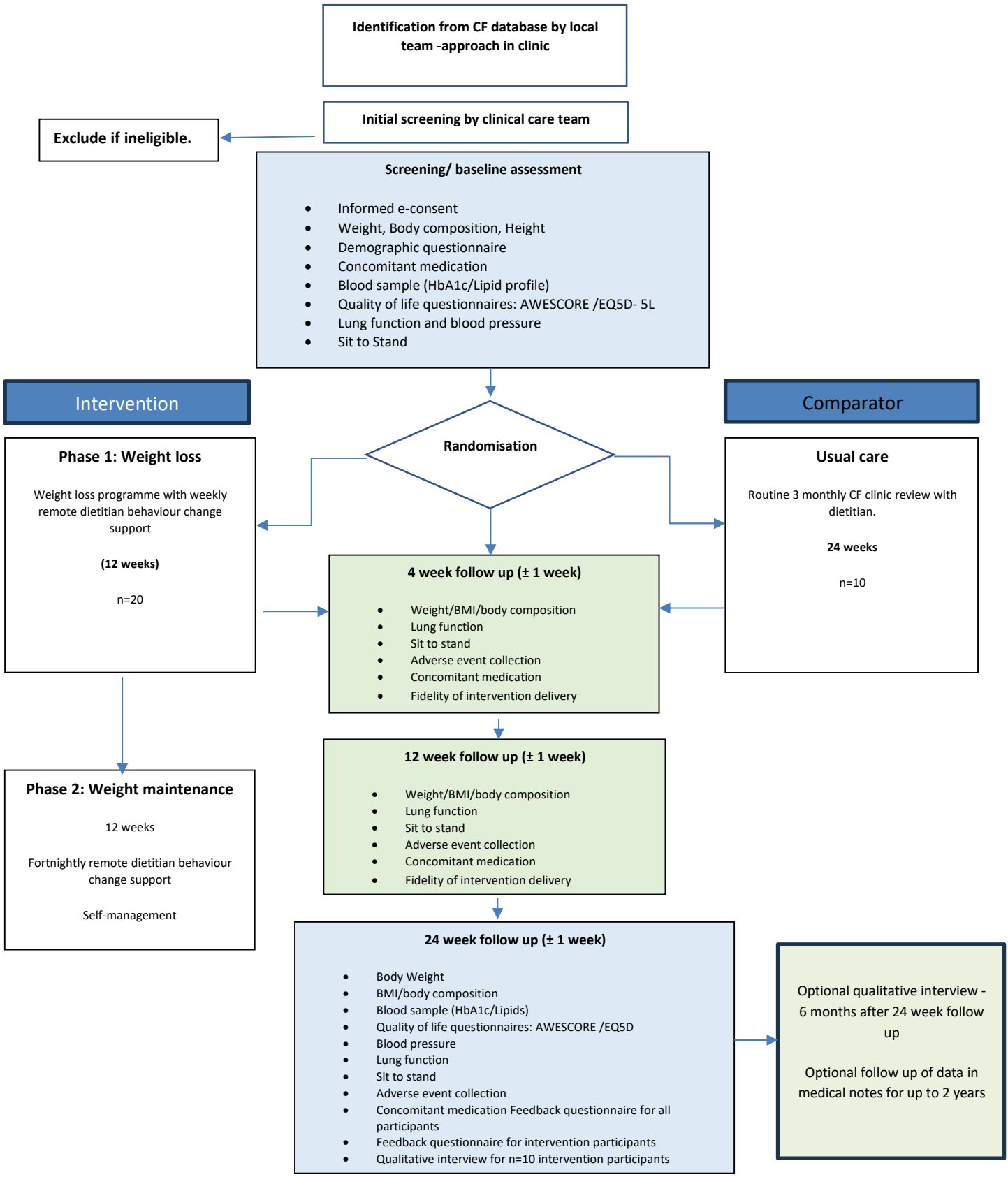
21. APPENDIX A: STUDY FLOW CHART



22. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Assessments**					
	0 weeks	**4 weeks**	**12 weeks**	**24 weeks**	**6 months after last study visit**	**Up to2 years after last study visit**
	Screening/ Baseline	**Assessment 1**	**Assessment 2**	**Assessment 3**		
Informed consent	x					
Eligibility assessment	x					
Demographic questionnaire	x					
Medical history	x					
Concomitant medications	x	x	x	x		
Randomisation	x					
EQ-5D-5L questionnaire	x			x		
AWESCORE questionnaire	x			x		
Weight & fat/fat-free mass	x	x	x	x		
Height	x					
Blood pressure	x			x		
Lung function	x	x	x	x		
Lipid profile	x			x		
HbA1c	x			x		
Adverse events assessments	x	x	x	x		
Qualitative interview with participants			x	x		
Qualitative interviews with staff				x		
Feedback questionnaire end of trial (all participants)				x		
Feedback questionnaire end of trial (intervention participants)				x		
Fidelity of intervention delivery	x	x	x	x		
Additional interview with intervention participants 6 months after the last visit (optional).					x	
Follow up through medical notes						x

23. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

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 and HRA (where required).