EASE-CF

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

(Short title: EASE-CF: Weight loss in people with cystic fibrosis)

Statistical analysis plan

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1.0	02.07.2026	Original

Contents

1 Introduction

1.1 Purpose and scope of plan

This statistical analysis plan (SAP) will cover the main statistical analysis as stated in the protocol. The SAP will be approved by the Study Management Group (SMG) and signed off by the Chief Investigator (CI) and statistician prior to database lock and data analysis.

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the NIHR-funded study named "*Weight loss intervention with specialist dietitian behavioural support for people with cystic fibrosis who have excess weight: the EASE-CF randomised controlled feasibility trial*". The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analyses (for e.g. to decide cut off points for categorisation of continuous variables), nor to prohibit accepted practices (e.g. data transformation prior to analysis), but they are intended to

establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged. Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The purpose of the plan is to describe the analysis of the primary and exploratory outcome measures as stated in the protocol. No interim analysis is planned. This document follows published guidelines regarding the content of statistical analysis plans for clinical trials (1). The ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9 (5 February 1998) was reviewed in order to complete this SAP.

2.0 Background and objectives

Please see sections 3.0 (synopsis) and 5.0 (background) in the protocol

2.1 Brief synopsis and Objectives

This trial is a study of an intervention intended to support patients with cystic fibrosis who have excess weight. The primary study objective is to assess the feasibility of progression to a definitive randomised controlled trial that will examine whether a supported weight loss intervention aimed at adults with cystic fibrosis who have excess

weight can help them lose weight. Exploratory and process objectives are detailed in the study protocol.

3 Study methods

3.1 Trial design

Please see the "Study Design", "Synopsis", "Description of the Statistical Methods "sections of the protocol.

This is a multi-centre unblinded parallel randomised controlled feasibility trial with an embedded qualitative study.

The timing is as follows

Total trial length: 4 years

Planned sample size : 30

Recruitment period: 12 months (planned for January 2026 to December 2026)

Individual participant's involvement: 24 weeks active participation and then follow-up interview at 48 weeks.

Long-term follow-up via medical records: Up to 2 years.

Target population: People with cystic fibrosis and body mass index ≥ 27 kg/m^2. Detailed inclusion/exclusion criteria are listed in the protocol.

Participants will be recruited from hospitals across England. Participants are expected to be involved in the study for 24 weeks. They will be asked to attend remote follow-up assessments at 4 weeks, 12 weeks and 24 weeks. They will take part in a semi-structured qualitative interview over video. The study flow-chart is included in the appendix.

3.2 Randomisation and blinding

Please see the section "Study procedures" Protocol

Participants will be randomised by a delegated member of the local research team through Sealed Envelope™ which can be accessed at sites via a secure login. A member of the local study team will enter the participant details to the randomisation system, 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.

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.

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. 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.

3.3 Sample size

Please see the section "Sample Size Determination" Protocol

As this is a feasibility study, it is not powered to detect a clinically and statistically significant difference between groups(2). 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.

3.4 Statistical interim analysis, Data review and Stopping guidelines

Please see the section "Decision Points", "Stopping Rules" Protocol

No interim analysis is planned and the final analysis will take place at the end of the study. The Study Steering Committee (SSC) may formally recommend early termination if needed in line with the SSC charter.

3.5 Statistical Analysis Outline

The data to be analysed for this feasibility study is intended to derive estimates, not to conduct formal statistical testing between groups. The data to be summarised and described includes the baseline demographic and clinical characteristics, primary outcomes (referred to as "trial progression criteria") and the exploratory and process outcomes. These data are treated as follows:

3.5.2 Primary outcomes (referred to as "trial progression criteria")

Progression criteria (as defined in Table 1) will be summarised descriptively as counts and proportions for all participants [and by study group, study site]. The recruitment rate will be reported as number of people randomised per site per month. We will additionally report on the recruitment rate as a proportion of the number of people randomised divided by the number of eligible people approached, but this will not be a formal progression criterion.

Table 1: Primary outcomes (referred to as 'trial progression criteria'.

Sufficient levels of	**Criterion**	Green (progress to definitive RCT)	Amber (Progress to definitive RCT with changes)	Red (Stop- don't progress to definitive RCT)

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 10 or more sessions during the 24 weeks (60% 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			

3.6 Exploratory outcomes

All other exploratory outcomes detailed below will be summarised descriptively by study arm. Further details regarding the exploratory outcomes will be provided at a later date, (provisionally in a supplementary document) prior to database lock. Data will be reviewed to see whether planned analysis is still appropriate (for example, in the case of recruitment targets not being met). 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. To explore associations, linear regression will be used for continuous variables and logistic regression for categorical variables as

appropriate for outcomes measures at one or two time points. Outcomes measured at 3 or more time points will be analysed with mixed effects models. Table 2 details the planned statistical model for each exploratory variable assuming that assumptions will be met and sufficient data will exist to allow for the model to be run.

Table 2 : Intended statistical model for each exploratory variable

Exploratory variable	**Type of outcome**	**Time point**	**Intended statistical model**	**Summary measure/estimate**
Body weight	Continuous	Baseline, 4, 12 weeks, 24 weeks	Mixed effects model with participants as random effects and treatment arm, timepoint, and a multiplicative interaction between treatment and timepoint as fixed effects.	Adjusted mean difference between groups at 24 weeks; 95% CI
Proportion achieving 5% weight loss between randomisation and 12 weeks	Binary	Baseline and 12 weeks	Logistic regression with achievement of 5% weight loss as the dependent variable; group as the independent variable; baseline weight included as a covariate	Odds ratio for achieving 5% weight loss between groups; 95% CI
Absolute fat free mass (kg) Relative fat free mass(%)	Continuous	Baseline, 4, 12 weeks, 24 weeks	Mixed effects model with participants as random effects and treatment arm, timepoint, and a multiplicative interaction between treatment and timepoint as fixed effects	Adjusted mean difference between groups at 24 weeks; 95% CI
Absolute fat mass (kg) Relative fat mass(%)	Continuous	Baseline, 4, 12 weeks, 24 weeks	Mixed effects model with participants as random effects and treatment arm, timepoint, and a multiplicative interaction between treatment and timepoint as fixed effects	Adjusted mean difference between groups at 24 weeks; 95% CI
EQ-5D-5L utility score index (0-1)	Continuous	Baseline and 24 weeks	Linear regression model with 24-week outcome as dependent variable;	Adjusted mean difference

			group as independent variable; baseline value included as covariate	between groups at 24 weeks; 95% CI
EQ-5D-5L VAS (0-100)	Continuous	Baseline and 24 weeks	Linear regression model with 24-week outcome as dependent variable; group as independent variable; baseline value included as covariate	Adjusted mean difference between groups at 24 weeks; 95% CI
AWESCORE (0-100)	Continuous	Baseline and 24 weeks	Linear regression model with 24-week outcome as dependent variable; group as independent variable; baseline value included as covariate	Adjusted mean difference between groups at 24 weeks; 95% CI
FEV_1 (L), FEV_1 (% predicted)	Continuous	Baseline, 4, 12 weeks, 24 weeks	Mixed effects model with participants as random effects and treatment arm, timepoint, and a multiplicative interaction between treatment and timepoint as fixed effects	Adjusted mean difference between groups at 24 weeks; 95% CI
FVC (L), FVC (% predicted)	Continuous	Baseline, 4, 12 weeks, 24 weeks	Mixed effects model with participants as random effects and treatment arm, timepoint, and a multiplicative interaction between treatment and timepoint as fixed effects	Adjusted mean difference between groups at 24 weeks; 95% CI
Time for sit-to-stand test (seconds)	Continuous	Baseline, 4, 12 weeks, 24 weeks	Mixed effects model with participants as random effects and treatment arm, timepoint, and a multiplicative interaction between treatment and timepoint as fixed effects	Adjusted mean difference between groups at 24 weeks; 95% CI
Systolic blood pressure (SBP, mmHg)	Continuous	Baseline and 24 weeks	Linear regression model with 24-week outcome as dependent variable; group as independent variable; baseline value included as covariate	Adjusted mean difference between groups at 24 weeks; 95% CI
Diastolic blood pressure (DBP, mmHg)	Continuous	Baseline and 24 weeks	Linear regression model with 24-week outcome as dependent variable; group as independent variable; baseline value included as covariate	Adjusted mean difference between groups at 24 weeks; 95% CI
HbA1c	Continuous	Baseline and 24 weeks	Linear regression model with 24-week outcome as dependent variable; group as independent variable; baseline value included as covariate	Adjusted mean difference between groups at 24 weeks; 95% CI
Total cholesterol, LDL cholesterol, non-HDL	Continuous	Baseline and 24 weeks	Linear regression model with 24-week outcome as	Adjusted mean difference

cholesterol, HDL cholesterol, Total cholesterol: HDL , Triglycerides (analysed separately)			dependent variable; group as independent variable; baseline value included as covariate	between groups at 24 weeks; 95% CI

4. Statistical Principles

4.1 Statistical Significance and Multiple Testing

See protocol section "" Please see the section "Level of Statistical Significance"

Protocol

P-values will not be reported given the feasibility nature of the study 95% confidence intervals will be nominal and descriptive. As the study is not powered to detect changes in exploratory outcomes, there will be no adjustment for multiple testing(3).

4.2 Definition of Analysis Populations for exploratory analysis

Given the feasibility nature of the study, the primary analysis population will include all randomised and eligible participants in the group they were originally assigned regardless of withdrawal or non-adherence. No imputation will be undertaken; analyses will use observed data only.

A per-protocol analysis will be performed to explore the impact of the intervention among the most adherent participants. It will include 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.

5. Trial population and Descriptive analyses

This is a summary of flow of trial participants through the trial and baseline stratification, demographic and clinical characteristics of each group.

5.1 Representativeness of Study Sample and Patient Throughput

See also the protocol appendix "Study Flow Chart"

The flow of participants through each stage of the study including screening data, numbers consented and randomised and completing the study will be detailed in a CONSORT flow diagram. Information on number of participants screened, found to be ineligible (with reasons where available), declined to participate (with reasons where available) will be included as applicable.

5.2 Withdrawal from treatment and/or follow-up

Please see the "withdrawal section" of the protocol .

The numbers (and percentages) of withdrawals will be reported by treatment group along with the reasons for these withdrawals. The potential reasons for withdrawal are detailed in the study protocol.

5.3 Baseline characteristics

Please see the "Baseline assessments" section of the protocol .

The baseline demographic and clinical characteristics will be presented in a table(s) and reported by group (intervention or usual care).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. There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

5.4 Reliability

The REDCap database will incorporate range and logic checks and data will be checked manually and any queries raised with study sites for resolution.

6 Analysis

6.1 Outcome definitions

Please see the "Synopsis" section of the protocol .

The primary variables for this trial are referred to as "trial progression criteria"(see Table 1) and a list of those primary outcomes is given below.

Table 2: List of primary variables and their measurement

Type	Objectives	Outcome measures	Definition
Primary (Recruitment)	1a Recruitment variable	Recruitment rate	n of patients recruited per site per month.
Primary (Recruitment)	1a Recruitment variable	Total number of participants recruited	Integer (0-n)
Primary (Engagement)	Engagement variable	Proportion of participants who attended 6 or more sessions during the 24 weeks (60% of sessions) and at least one of the last 3 sessions/total number eligible and randomised to this group	Percentage (0-100%)

Primary (adherence)	Adherence variable	Proportion of participants in the intervention group who finished the programme with ≥5% weight loss at 12 weeks	Percentage (0-100%)
Primary (retention)	Retention variable	Proportion of randomised participants completing a 24 week follow up visit	Percentage (0-100%)
Primary (safety)	Safety profile	Based on related adverse events and expected related and unexpected related serious adverse events	Type, number of and percentage of each event category.

6.2 Analysis Methods

See section 3.5 “Statistical Analysis Outline”

6.3 Missing data

The proportion of missing data for each outcome measure will be reported to inform the feasibility outcomes. This is likely to only apply to the adherence criteria which requires weight data. Given the small scale of the study, imputation will not be meaningful and so it will not be done.

6.4 Sensitivity analysis

No sensitivity analyses are planned.

6.5 Pre specified subgroup analysis

No subgroup analyses are planned.

6.6 Supplementary/Additional analyses and outcomes

No supplementary analyses are planned.

6.7 Harms

Safety is an outcome variable and its analysis is detailed elsewhere in this document in sections such as the section 3.5 “Statistical Analysis Outline”

7. Validation of the primary analysis

To validate the primary outcomes, a statistician not involved in the trial will independently review the code for the analyses detailed in this SAP.

8 Specification of statistical packages

Any specific statistical analysis will be carried out using appropriate validated statistical software such as STATA, SAS, or R.

9 Publication

Deviations from the original SAP will be reported and justified at publication following the CONSORT guidelines(4).

10. References

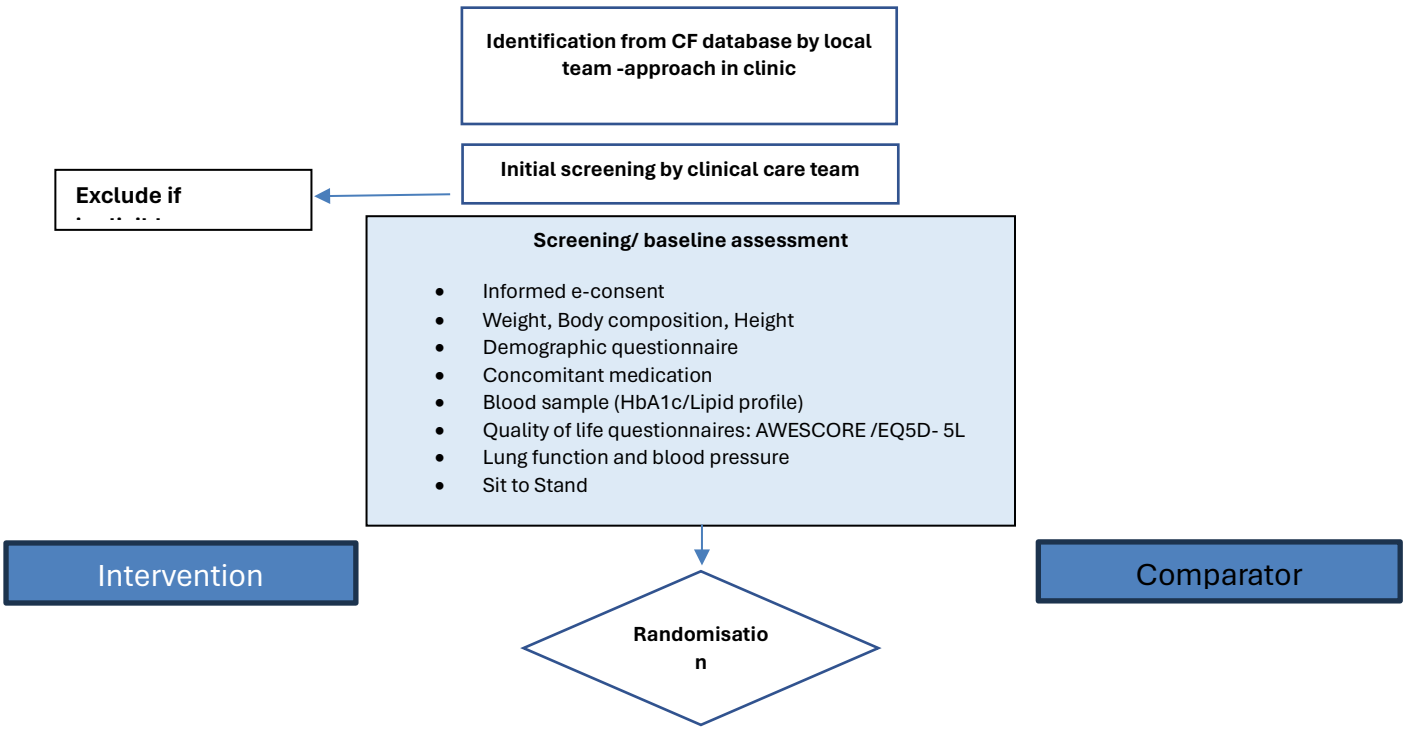
1. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the content of statistical analysis plans in clinical trials. JAMA - Journal of the American Medical Association. 2017;318(23):2337-43.
2. Lewis M, Bromley K, Sutton CJ, McCray G, Myers HL, Lancaster GA. Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back! Pilot and Feasibility Studies. 2021;7(1):40.
3. Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ, Wells GA, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol. 2017;46(2):746-55.
4. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ (Clinical research ed). 2016;355:i5239.

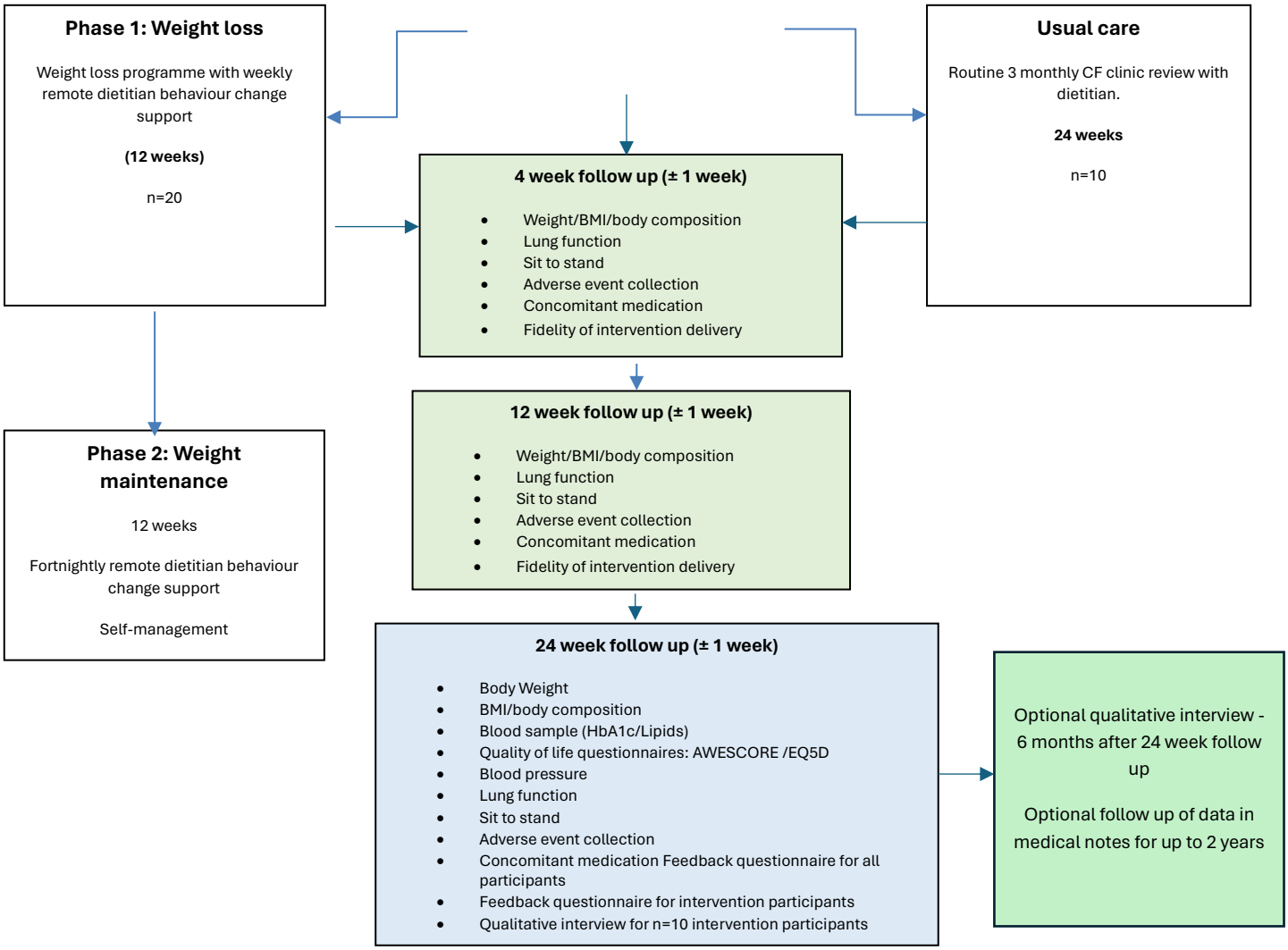
11. APPENDIX: SCHEDULE OF STUDY EVENTS

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

APPENDIX: STUDY FLOWCHART




Phase 1: Weight loss
Weight loss programme with weekly remote dietitian behaviour change support
(12 weeks)
n=20
Usual care
Routine 3 monthly CF clinic review with dietitian.
24 weeks
n=10
4 week follow up (± 1 week)
Weight/BMI/body composition
Lung function
Sit to stand
Adverse event collection
Concomitant medication
Fidelity of intervention delivery
12 week follow up (± 1 week)
Weight/BMI/body composition
Lung function
Sit to stand
Adverse event collection
Concomitant medication
Fidelity of intervention delivery
Phase 2: Weight maintenance
12 weeks
Fortnightly remote dietitian behaviour change support
Self-management
24 week follow up (± 1 week)
Body Weight
BMI/body composition
Blood sample (HbA1c/Lipids)
Quality of life questionnaires: AWESCORE /EQ5D
Blood pressure
Lung function
Sit to stand
Adverse event collection
Concomitant medication Feedback questionnaire for all participants
Feedback questionnaire for intervention participants
Qualitative interview for n=10 intervention participants
Optional qualitative interview - 6 months after 24 week follow up
Optional follow up of data in medical notes for up to 2 years

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