

SUPPLEMENTARY INFORMATION 1

Screening procedures

Table 1: Screening procedures commenced at baseline appointment	
Study Procedure	Screening
Review & discuss study participation	✓
Review inclusion/exclusion criteria	✓
Obtain informed consent	✓
Height	✓
Weight	✓
BMI	✓
Body fat & fat free mass (bioelectrical impedance)	✓
Waist/hip circumference	✓
Blood pressure	✓
Blood progesterone/oestrogen	✓
Study bloods	✓
Urine pregnancy test (if relevant)	✓
Urine sample for metabolomic analysis	✓
Mammogram	✓
Alcohol use (AUDIT)	✓
Self-Efficacy (WEL-SF)	✓
Binge Eating (BES)	✓
Patient Health (PHQ-9)	✓
Anxiety (GAD-7)	✓
Quality of life score (OWL-QoL)	✓
7-day paper food diary/Nutritics app	✓
Physical activity score (IPAQ)	✓
Physical activity readiness questionnaire (PAR-Q)	✓
Demographic questionnaire	✓
Tyrer-Cuzick Breast Cancer Risk Questionnaire/Score	✓

SUPPLEMENTARY INFORMATION 2

Multi-disciplinary TDR Weight Loss Programme

PHASE	Dietitian advice/support	Clinical Psychologist support for a subset	Diet	Exercise
Total Diet Replacement (TDR) 12+/-4 weeks	Initial advice 60-90 minutes covering TDR, resistance exercises, use of the Oviva app video/standard call or face-to-face. 15-20 minute weekly support via video/standard call. Weekly support focussed on adherence to the TDR & resistance exercises, side effects, motivational interviewing and promoting self-monitoring on the app.	Enhanced psychology support for participants with baseline scores indicating moderate scores for binge eating (score 18-26 on BES), depression (score 10-14 on PHQ-9), anxiety (score 10-14 on GAD-7), low self-efficacy (score <45 on WEL-SF) or increasing risk of alcohol dependency (score 8-15 on AUDIT).	7 days/week TDR 850 Kcal / day (3xOptifast® and 8 portions of non-starchy vegetables (~150 kcal) and 1 dessertspoon of vegetable oil (60 kcal). A minimum of 2-2.5 additional litres of energy-free liquids (i.e. water, diet drinks, black tea/coffee) Or a nutritionally equivalent food based LED if women are unable to tolerate the 12-week TDR.	Advised to undertake progressive resistance exercise 3 days/week. Week 1-4, 1 set of 10 reps. Week 5-8, 2 sets of 10 reps. Week 9-12, 3 sets of 10 reps.
Diet Reintroduction Phase (DRP) 4 weeks	Initial advice 40-60 minutes by video/standard call or face-to-face. 15-20 minute weekly support via App or phone.	Clinical psychologist support where required.	Gradual re-introduction of an energy restricted Mediterranean-based diet over 4 weeks. Participants may either follow a total food based approach or they can continue to include 1 or 2 Optifast® products per day. Energy intake will be increased in the following manner over the 4 weeks: a. 1 st week 1000kcal b. 2 nd week 1200 kcal c. 3 rd week 1400kcal d. 4 th week 1500kcal	Advised to continue with resistance exercise 3 days/week. Build up to moderate intensity physical activity of 150-300 minutes/week.

<p>Continued Weight Loss Phase (CWLP) 36 weeks</p> <p>or</p> <p>Weight Maintenance Phase (WMP) » if attained target weight.</p>	<p>10 minutes per week via video/standard call.</p> <p>Promoting self-monitoring motivational interviewing/ managing relapse.</p> <p>Preparing for future weight loss maintenance.</p>		<p>Intermittent food based diet: 850 kcal 2 days per week and Mediterranean diet 5 days per week or daily energy restricted Mediterranean diet.</p> <p>Intermittent food based diet: 850 kcal 1 day per week and Mediterranean diet 6 days per week or isoenergetic Mediterranean diet 7 days per week.</p>	<p>Advised to continue with resistance exercise 3 days per week. Moderate intensity physical activity of 150-300 minutes/week.</p>
<p>Relapse intervention if weight increases ≥ 2kg assessed from self-monitoring during the CWL/WM phase.</p>	<p>Advice 40-60 minutes via video/standard call or face-to-face. Relapse management will include an exploration of the reasons for weight regain, with appropriate signposting for psychological support with the trial psychologist.</p>		<p>Up to 2 relapses; 2 weeks of TDR followed by 2 weeks of food reintroduction (Optifast® and non-starchy vegetables) ~850 kcal/day</p> <p>OR</p> <p>Replace one meal per day with Optifast® shake.</p>	<p>Continue with resistance exercise 3 days per week. Moderate intensity physical activity of 150-300 minutes per week.</p>
<p>Total weeks of programme</p>	<p>52 weeks</p>			

SUPPLEMENTARY INFORMATION 3

Schedule of Assessments

Table 3: Schedule of assessments – Control group							
Appointment	Screening	1 0 Baseline	2 ~3 months	3 ~6 months	4 ~9 months	5 ~12 months	6 ~15 months
Review & discuss study participation	✓						
Review inclusion/exclusion criteria	✓	✓					
Obtain informed consent	✓						
Height	✓						
Weight	✓		✓	✓	✓	✓	✓
BMI	✓		✓	✓	✓	✓	✓
Body fat & fat free mass (bioelectrical impedance)		✓	✓	✓	✓	✓	✓
Waist/hip circumference		✓	✓	✓	✓	✓	✓
Blood pressure		✓	✓	✓			
Blood progesterone/oestrogen		✓		✓			
Study bloods		✓	✓	✓	✓	✓	✓
Urine pregnancy test (if relevant)		✓	✓				
Urine (metabolomics)		✓	✓	✓	✓	✓	✓
Breast VAB		✓	✓				
Endometrial pipelle		✓	✓				
Mammogram		✓	✓				✓
Alcohol use (AUDIT)	✓		✓	✓	✓	✓	✓
Self-Efficacy (WEL-SF)	✓		✓	✓	✓	✓	✓
Binge Eating (BES)	✓		✓	✓	✓	✓	✓
Patient Health (PHQ-9)	✓		✓	✓	✓	✓	✓
Anxiety (GAD-7)	✓		✓	✓	✓	✓	✓
Quality of life score (OWL-QoL)		✓	✓	✓	✓	✓	✓
7-day paper food diary/Nutritics app		✓	✓	✓	✓	✓	✓
Physical activity score (IPAQ)		✓	✓	✓	✓	✓	✓
Physical activity readiness questionnaire (PAR-Q)		✓					
Demographic questionnaire	✓						
Tyrer-Cuzick BC risk		✓					
Adverse events screening		✓*	✓*	✓*			

Table 4: Schedule of assessments – Intervention group						
Appointment	Screening	1 0 Baseline	2 ~3 months	3 ~6 months	4 ~9 months	5 ~12 months
Review & discuss study participation	✓					
Review inclusion/exclusion criteria	✓	✓				
Obtain informed consent	✓					
Height	✓					
Weight	✓		✓	✓	✓	✓
BMI	✓		✓	✓	✓	✓
Body fat & fat free mass (bioelectrical impedance)		✓	✓	✓	✓	✓
Waist/hip circumference		✓	✓	✓	✓	✓
Blood pressure		✓	✓	✓	✓	✓
Blood progesterone/oestrogen		✓	✓			
Study bloods		✓	✓	✓	✓	✓
Urine pregnancy test (if relevant)	✓	✓	✓			
Urine (metabolomics)		✓	✓	✓	✓	✓
Breast VAB		✓	✓			
Endometrial pipelle		✓	✓			
Mammogram		✓				✓
Alcohol use (AUDIT)	✓		✓	✓	✓	✓
Self -Efficacy (WEL-SF)	✓		✓	✓	✓	✓
Binge Eating (BES)	✓		✓	✓	✓	✓
Patient Health (PHQ-9)	✓		✓	✓	✓	✓
Anxiety (GAD-7)	✓		✓	✓	✓	✓
Quality of life score (OWL-QoL)		✓	✓	✓	✓	✓
7-day paper food diary/Nutritics app		✓	✓	✓	✓	✓
Physical activity score (IPAQ)		✓	✓	✓	✓	✓
Physical activity readiness questionnaire (PAR-Q)		✓				
Demographic questionnaire	✓					
Tyrer-Cuzick BC risk		✓				
Adverse events screening		✓*	✓*	✓*		

SUPPLEMENTARY INFORMATION 4

Medicines Management

Background: Antihypertensive and diuretic drugs will be stopped on the day Total Diet Replacement (TDR) is commenced. This is a safety measure, because blood pressure is likely to fall on the diet. This protocol lays out the standard approach to be followed, as taken from the DiRECT study. Individual clinical decisions may be necessary for a person's best interest. The level of 140 mmHg is chosen to allow safe decisions during the weight loss period. After the Food Reintroduction period follow usual guidelines for management of hypertension. To simplify decision making, systolic pressure only is used as a guide to therapy even though both systolic and diastolic are relevant to long term benefit.

Protocol: When antihypertensive drugs are stopped, re-emphasise the importance of avoiding sodium (salt)

1. In the first 2 weeks after stopping antihypertensives and diuretics: If systolic BP over 165 mmHg on repeated measurement - restart one drug, as below.
2. Thereafter, if systolic BP is >140 mmHg - restart one drug as below.
3. Increase dose weekly to achieve target.
4. If systolic BP remains >140 mmHg on the first drug - add a second drug, as below.
5. Increase dose weekly to achieve target.
6. Repeat as necessary with third, fourth or more drugs (increasing each to maximum dose).

Order of reintroduction of previously used drugs:

1. ACE inhibitors (ramipril, lisinopril, perindopril, etc.)
2. Angiotensin receptor blockers (irbesartan, candesartan etc.)
3. Thiazide type (bendroflumethazide, indapamide etc.)
4. Spironolactone
5. Calcium channel blocker (nifedipine, amlodipine etc.)
6. Beta blocker (atenolol, labetalol etc.)
7. Alpha blocker (doxazosin, prazosin)
8. All others