Family History Lifestyle Study

Study Title:	Randomised comparison of two remotely delivered diet and physical activity weight loss programmes vs written diet and physical activity advice amongst overweight women at increased risk of breast cancer attending a Family History Clinic: A phase 3 efficacy study
Protocol Short Title/Acronym:	The Family History Lifestyle Study (FHL)
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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, the Sponsoring Trust's R&D Office (or a regulatory authorities, and members of the Health Research Authority or Local Research Network).

Contents

Glossary

AE	Adverse Event
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
AUDIT	Alcohol Use Disorders Identification Test
B-AHEAD	Activity
BC	Breast Cancer
BCPP	Breast Cancer Prevention Programme
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Report Form
CVD	Cardiovascular Disease
DER	Daily Energy Restriction
ECG	Echocardiogram
EudraCT	European Clinical Trials Database
FHC	Family History Clinic
FHL	Family History Lifestyle Study
GAD-7	General Anxiety Disorder-7
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care professional
IAPT	Improving Access to Psychological Therapies
ICF	Informed Consent Form
IER	Intermittent Energy Restriction
MDPP	Multiple Disease Prevention Programme
MDT	Multi Disciplinary Team
MGD	Mean Glandular Dose
MFT	Manchester University NHS Foundation Trust
MUFA	Monounsaturated fat
PI	Principal Investigator
PIC	Participant Identification Centres
PIS	Patient Information Sheet
PROCAS	Predicting Risk of Breast Cancer at Screening
PUFA	Polyunsaturated fat
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SD	Standard Deviation
SFA	Saturated fat
SNP	Single Nucleotide Polymorphisms
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TC	Tyrer-Cuzick
TGH	Tameside General Hospital
TMF	Trial Master File
TMG	Trial Management Group
UHS	University Hospital Southampton
WA	Written Advice

1. Trial Summary

Title:	Randomised comparison of two remotely delivered diet and physical activity weight loss programmes vs. written diet and physical activity advice amongst overweight women attending a Family History Clinic at increased risk of breast cancer: A phase 3 efficacy study
Short title	Family History Lifestyle Study (FHL)
Phase of trial:	Phase III
Objectives:	To compare the efficacy of two remotely delivered weight loss programmes compared to written diet and physical activity advice in terms of : **Primary objectives:** Percentage weight loss **Secondary objectives:** Change in self-reported lifestyle behaviours, quality of life and mammographic density
Type of trial:	single-blind randomised
Trial Participants:	Women at increased risk of breast cancer attending UK Family History Clinics
Trial design and methods:	Individually randomised controlled trial with assessments at baseline, 3, 6 and 12 months
Planned Sample Size:	209
Trial duration per participant:	12 months
Estimated total trial duration	22 months
Planned trial sites:	Three recruiting centres: Wythenshawe Hospital at Manchester University NHS Foundation Trust (MFT), University Hospital Southampton (UHS), Tameside Hospital (TGH) and one Participant Identification Centres (PIC) site; St Marys Hospital Manchester
Main inclusion/exclusion criteria:	Women at increased risk of breast cancer (≥15% lifetime risk) Overweight BMI ≥25 kg/m^2
Statistical methodology and analysis:	Intention to treat analysis using ANCOVA and GEE regression modelling with multiple imputation methods for missing values

2. Context, background and rationale

2.1. Context and purpose of the study

Observational data suggests weight control, physical activity and alcohol limitation reduce breast cancer (BC) risk in women at high risk of the disease (4, 5). Unhealthy lifestyle behaviours are common amongst family history clinic (FHC) attendees and increase the risk of BC, other cancers, cardiovascular disease (CVD), type 2 diabetes (T2DM) and dementia. Current standard care involves general written advice which is likely to have a minimal effect on lifestyle behaviours. It is highly likely that current approaches do not adequately manage risk in the FHC and are missing an opportunity to prevent BC and other diseases. NICE familial BC guidelines CG 164 recommend that women should be advised on the probable increased postmenopausal risk of BC from being overweight and the potential benefits of physical exercise on BC risk (86).

This study aims to test the hypothesis that a remotely delivered programme which aims to change diet and physical activity behaviours will be effective for weight loss for women who have an increased risk of BC in the FHC when compared with receiving written diet and physical activity information.

The objectives of this study are to test three diet and physical activity weight loss strategies. Group 1 will receive written diet and physical activity advice only (WA). Groups 2 and 3 will have diet and physical activity weight loss programmes delivered by phone, email and a designated Family History Lifestyle web site. These will be framed as either: (group 2) A BC prevention programme (BCPP) which communicates BC risk to promote healthy lifestyle; (group 3) A multiple disease prevention programme (MDPP) that in addition to a BC prevention programme also includes an NHS health check (lipids, blood pressure blood sugar and personalised risk feedback on CVD, T2DM and dementia risk).

Importantly, this three arm randomised phase 3 efficacy study also aims to identify which of the BCPP and MDPP programme(s) should be tested in a future trial to identify the relative clinical and cost effectiveness of the relevant intervention across the UK FHC network.

2.2 Background and Rationale

Lifestyle and breast cancer risk amongst high risk women

Expert reports estimate weight control, physical activity and alcohol limitation can reduce BC risk by 30–40% for women in the general population (1) (2, 3). Recent cohort studies suggest that optimal lifestyle can bring about comparable relative risk reductions amongst high-risk women with both moderate (15-30%) lifetime risk (4, 5) and those with high penetrance BRCA1/2 mutations (60–80% lifetime risk) (6-8). High BMI and weight gain from the age of 30 years and older increases the risk of both pre and postmenopausal BC (9, 10), particularly amongst women with a family history who appear predisposed to storing high risk abdominal fat (11-14) (7, 15-17). Losing ≥5% of weight and maintenance of weight loss amongst overweight women has been linked to 25-40% reduced BC risk (18, 19). Healthy lifestyles can reduce the risk of pre/postmenopausal and oestrogen responsive and unresponsive BC (20). Thus lifestyle programmes have the potential for widespread BC protective effects amongst FHC attendees who are typically aged >30 years. High risk women are likely to achieve a greater absolute risk reduction with healthy lifestyle than women in the general population, therefore they have more to gain from adherence to lifestyle recommendations and so it is especially important in this group that we are targeting here.

Current provision of lifestyle advice in UK Family History Clinics

There are around 90 FHCs for high/moderate-risk women in the UK, which provide BC risk assessment, surveillance, advice on chemoprevention (tamoxifen/raloxifene), prophylactic mastectomy and oophorectomy but do not provide lifestyle advice. This is a major omission of these services. BC prevention via lifestyle change potentially provides an important risk reducing strategy for the large proportions of clinic attendees who do not want to consider chemoprevention (~90%) or surgery (~95%) (21). It may also enhance the efficacy of chemoprevention (15);(22). In addition, lifestyle change can reduce risk of CVD, T2DM, dementia and other cancers (ovarian, pancreatic, bowel, oesophagus). This is important since 60 - 85% of high/moderate-risk women and 40-50% of gene carriers will not develop BC (23).

A recent survey of 38 FHCs highlighted that lifestyle advice was either not given (35%), or was provided from generic NHS healthy lifestyles leaflets or information websites, with no support or follow up (65%). This "information only" approach is likely to have a minimal impact on behaviour change (24). Fifteen percent of participants in our leaflet only groups successfully change behaviours and lose weight compared with 55% in our supported weight loss programme (25), thus there is a need to develop and test tailored, supported lifestyle prevention programmes in FHCs.

Unhealthy lifestyles and CVD risk factors amongst women in the FHC

Obesity rates have increased over the past 30 years within our FHC; 11% in 1987 – 1997, 15% in 1997 – 2006 and 20% since 2007. Amongst 130 women (aged 30 – 45) in our recent study of tamoxifen prevention (TamPrev study, ISRCTN53844391), 60% were overweight, 24% obese, 30% had high alcohol intakes (>14 units/week) and 40% failed to meet recommendations for physical activity (≥150 minute/week). These figures were comparable to the general population, although FHC women had lower smoking rates (8%) compared with the national norm of 17% (26). Significant numbers in the Tam Prev study had elevated CVD and T2DM risk markers: total: HDL cholesterol >3.8 (46%), systolic blood pressure >140mmHg (20%) and raised glucose (9%) (Pegington et al, manuscript in preparation). These CVD and T2DM risk markers were previously unknown to the women since they had not undergone a recommended NHS Health Check (27) which has poor coverage (28). Thus our data are consistent with reports that FHC attendees are motivated to attend breast screening but are not adhering to cancer prevention lifestyle recommendations (29, 30). Provision of information about their genetic risk alone is unlikely to change their health-related behaviours in the absence of additional support (31). These considerations indicate that effective weight loss / lifestyle programmes should be offered in the FHC, not only to reduce risk of BC but also as a model for disease prevention for women in the general population.

Our lifestyle weight loss disease prevention programmes

We have found Intermittent energy restriction (IER) to be superior to daily energy restriction (DER) for weight loss, weight maintenance (32) and reducing insulin resistance (32, 33).

We have developed two effective lifestyle weight loss programmes based on IER (2 days per week) and supported with telephone, web and e-mail follow up. One is a BC prevention which is framed in BC risk (BCPP), and the other a multiple disease prevention programme framed in MD risk (MDPP). Both are currently being tested amongst women at high, average and below average BC risk from the NHS breast screening programme in our ongoing PROCAS Lifestyle study (ISRCTN91372184) (34). Preliminary data amongst the first 100 participants indicates somewhat greater uptake in women informed about multiple risks (MDPP) compared with BC risk only (BCPP) (27% vs. 21%). Both programmes are highly successful and associated with substantial reductions in weight. Preliminary data shows mean (SD) weight loss at 12 months for the both groups is -7.3 (6.5) kg; i.e. 16 (14) pounds or -9.3 (7.8) % weight loss.

About 65% and 59% of women commencing the MDPP and BCPP achieved a clinically significant weight loss of ≥5% which is likely to be associated with reductions of risk of BC and other diseases. These programmes were based on our intermittent diet which produced a weight loss of -4.9 (4.1) kg or -6.3 (4.4) % over 4 months in a previous study (32).

This study aims to build on this work and test whether these programmes are effective amongst women who have an increased risk of BC in the FHC, and whether there are differences in the efficacy of the BCPP and MDPP programmes for weight loss in these women. Compared to women who attend NHS BC screening, women in the FHC have greater objective BC risk, and hence are more likely to be more motivated to reduce their BC risk and to have well-developed beliefs about BC, even if these beliefs are not necessarily correct (35). Given this, a comparison of BCPP and MDPP is needed in the specific context of FHC.

There are plausible reasons to believe that either BCPP or MDPP will produce better uptake and efficacy, so a competitive test is needed now, so that the definitive effectiveness and cost-

effectiveness trial can evaluate the programme that performs best at engaging women in the FHC and helping them lose weight.

There may be better engagement and behaviour change with the BCPP than the MDPP as BC risk may be more personally relevant to women who attend the FHC for BC risk. Personal relevance of risk information increases the likelihood of that information being attended to, and hence increasing engagement (36). In addition, personal relevance of information leads to more stable and positive attitudes, positive intentions and greater intention-behaviour consistency (37).

Alternatively, there may be greater engagement and behaviour change with the MDPP rather than the BCPP. Behaviour change is increased in response to risk information where participants believe that changing their behaviour reduces their risk of disease (response efficacy). A recent survey (n = 100) in our FHC reported a greater proportion believed that lifestyle would reduce their risk of CVD (88%), than their risk of BC (21%) which they perceive to be under more genetic control. Likewise our 2015 interview study of FHC women in a weight loss programme reported their motivation to lose weight was primarily for general health, with BC risk as a secondary motivation. Some viewed their BC risk as unchangeable because of their family history, yet valued disease risk management information about other conditions (38). Thus the relative efficacy of the BCPP and MDPP needs to be tested in the context of the FHC.

The effect of the weight loss programmes on mammographic density

Mammographic density is a proven imaging biomarker for BC risk (39). Volume of dense breast tissue has been positively linked to weight in our own (Brentnall, manuscript in preparation), and other studies (40), but there are few reliable data on changes in breast density with weight loss due to differences in imaging parameters and radiographic technique (i.e. degree of compression, positioning) between successive mammograms.

We will determine the effects of the BCPP and MDPP (i.e. weight loss) vs. WA on changes in the volume of dense breast tissue (Volpara) (41) (Volpara Health Technologies Limited, Wellington, New Zealand), and the image texture (mathematical measurements of the mammographic

pattern - the organisation and distribution of density) using Densitas (42) (Densitas Inc. Nova Scotia, Canada). Mammographic density will be measured in a sub group of patients using methods which correct for differences in radiographic technique between two time points (baseline and 12 months). Adding two different measures of density to the planned study will provide novel information on changes in amount and texture of dense breast tissue with weight loss, and whether breast density measures can be used to evaluate risk reduction with weight loss in the planned follow up cost effectiveness study.

Breast derived plasma proteins

Our previous mechanistic studies have reported increased expression of genes which produce the breast derived proteins lactalbumin, casein and cell surface mucins which indicate an increase in differentiation of epithelial cells and a lower risk of BC (43). We are currently evaluating whether we can measure changes in these breast derived proteins (e.g. milk proteins lactalbumin and casein, cell surface mucins and secreted proteins such as secretoglobulin and mammoglobin) in plasma when women lose weight. Hence whether a simple blood test which assesses changes in plasma proteins can indicate BC risk reduction with weight loss. This biomarker study will be completed by December 2017. We plan to collect and store plasma samples at baseline and 12 months in the current weight loss study and subsequently assess changes in any relevant plasma proteins identified, and would seek additional external funding for this.

2.3 Risks and benefits

This trial has been categorised as Type A risk i.e. no higher than the risk of standard medical care.

The recruiting researcher will discuss the potential risks and benefits with patients prior to trial entry and they will be outlined in the participant information sheet.

Benefits:

Potential weight loss and successful lifestyle change and increased cardiovascular fitness. This

will in turn reduce risk of BC, T2DM, CVD, other cancers and dementia and increase well-being.

Risks:

The additional burden and time commitment of trying to adhere to a healthy diet and physical activity plan. The potential disappointment if they do not achieve their weight loss / lifestyle goal. Potential increase in anxiety if the procedures involved result in them having a higher estimated BC risk. There is a small risk of radiation-induced cancer developing later in life, due to exposure to x-rays (mammography).

Study participants will have annual or 18 monthly mammograms due to their increased risk of breast cancer. There are no additional mammograms as part of the study. During the study period participants may have one or two bilateral two-view mammography procedures, around baseline and around 12-18 months.

Local dose audits at Manchester University NHS Foundation Trust, Wythenshawe Hosiptal(MFT) and Tameside General Hospital indicate a mean glandular dose (MGD) for a two view mammogram of approximately 3 mGy per breast. This gives a maximum total MGD to participants at these sites of approximately 6 mGy, all of which is standard care. Doses at University Hospital Southampton (UHS) are likely to be similar, although they may vary according to local equipment.

For a participant in normal health, there is an extra risk of cancer induction due to exposure to radiation. Younger patients are at slightly higher risk than older patients. Participants in this study are aged 30 to 75 years old. For a 30 year old adult (worst case for this study), the estimated lifetime risk of fatal cancer associated with the total study dose (6 mGy) is approximately 1 in 9250. This is calculated using the lifetime risk of radiation-induced breast cancer for UK women (aged 30) of 18 per million per mGy, taken from NHSBSP Report 54.

This level of dose places the study in Category IIb (ICRP 62) considered to involve a level of an intermediate risk and requiring a moderate level of societal benefit. It should be stated that none of the exposures are in addition to standard care.

ICRP 62 "Radiological Protection in Biomedical Research" Annals of the ICRP 22 (3) 1991: Categories of risk and corresponding required levels of benefit

Category and Level of risk	Total risk of detrimental radiation effect	Corresponding effective dose range (adults) (mSv)	Level of social benefit required
I Trivial	~10^{-6} or less	<0.1	Minor
IIa Minor	~10^{-5}	0.1-1	Intermediate
IIb Intermediate	~10^{-4}	1-10	Moderate
III Moderate	~10^{-3} or more	>10	Substantial

3. Trial Objectives and design

3.1 Trial objectives

This study is an individually randomised trial to test the efficacy for weight loss over 12 months of two different remotely delivered diet and physical activity weight loss programmes compared to only receiving written diet and physical activity information amongst 209 overweight/ obese women in UK Family History Clinics. Women will be allocated to:

1. A standard group (written advice, WA) (n=35): Women receive personalised BC risk information and are given written diet and physical activity advice for weight loss to reduce BC risk.
2. A BC prevention programme (BCPP) (n=87): Women receive personalised BC risk information and a 6 month health care professional (HCP) supported telephone, web based and e-mail diet and physical activity programme followed by 6 months of web / e-mail support.
3. A multiple disease prevention programme (MDPP) (n=87): Women receive personalised BC, CVD, T2DM and dementia risk information from an NHS Health Check followed by a 6 month health care professional (HCP) supported telephone, web based and e-mail diet and physical activity programme followed by 6 months of web / e-mail support.

3.1.1 Primary objective

To test the hypothesis that a remotely delivered 12 month diet and physical activity weight loss programme will lead to a $\geq$ 4% greater weight loss compared to a group receiving written diet and physical activity information amongst women who have an increased risk of BC in the FHC and that there will be a 3% difference in % weight loss between the BCPP and MDPP weight loss programmes.

3.1.2 Secondary objectives

1. To assess changes in body composition, diet and physical activity behaviours, quality of life and disease risk perception between the three groups.
2. To quantify the impact of the three interventions on measures of health status and well-being
3. To quantify the use of healthcare resources for each of the three interventions
4. To identify the fidelity of the delivery of the BCPP and MDPP programmes
5. To conduct a process evaluation of the interventions to understand the process of behaviour change.
6. To determine the effects of the programmes on mammographic density, a biomarker of BC risk in a sub group of patients (sub study 1).
7. To explore the views of women using the BCPP and MDPP programmes (sub study 2).

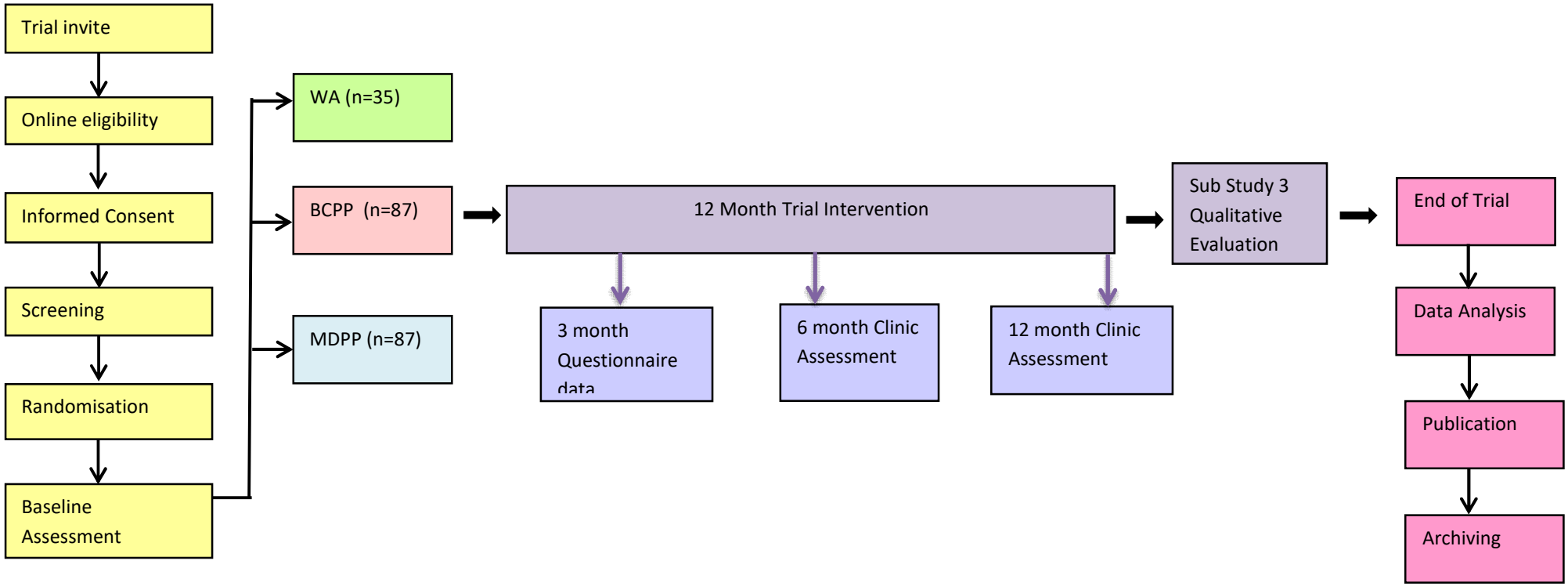
3.2 Exploratory endpoints

We plan to collect plasma samples for a possible future validation study to see if breast derived plasma proteins correlate with weight loss in a sub-group of patients (sub study 2).

4. Trial Design

4.1 Trial Overview

Figure 1. Study Schema



WA = Written Advice
BCPP = Breast Cancer Prevention Programme
MDPP = Multiple Disease Prevention programme

4.2 Study setting

This multicentre study (n=4) will recruit participants from Family History Clinics, Genetics Clinics and those enrolled on high risk mammographic surveillance protocols at MFT, TGH, and UHS. Patient identification, informed consent and face to face trial assessments will take place in the recruiting centres. The weight loss programmes will be delivered to trial participants by research dietitians working at MFT. St Marys Hospital Manchester will act as a PIC and will display leaflets, posters and give a patient information sheet and cover letter to interested patients. Informed consent and face to face trial assessments will take place at MFT. Targets for recruitment in TGH and UHS will be 20 – 40 patients from each site.

Table 1 Recruiting centres

Centre	Identification of patients	Recruitment / informed consent	Trial assessments	Remote delivery of weight loss programme
MFT	✓	✓	✓	MFT
Tameside	✓	✓	✓	MFT
UHS	✓	✓	✓	MFT
St Marys	PIC site	MFT	MFT	MFT

4.3 Trial timelines

Month 1 – 8: Recruitment period - recruitment target of 6 patients per week

Month 1 – 20: Delivery of the telephone, web and e-mail programme

Month 7 – 20: Follow-up measurements

Month 12 – 22: Qualitative interviews

Month 22 – 28: Analysis, write up and redesign of web site based on feedback from FHC users in the study.

4.4 Selection of Trial Participants

Identification and selection of patients in the recruiting centres

We will aim to recruit women around the time of their routine mammogram appointment in the recruiting centres in a number of ways:

Invite letter sent prior to mammogram appointment

Women will be sent an invite letter and a patient information sheet (PIS) prior to their routine mammogram appointment by the clinical team in their recruiting centre. The PIS outlines the rationale, purpose and design of the study, and contact details of their local FHL study research team should they wish to discuss the study further. The invitation letter will invite women to check their eligibility using an eligibility screening tool on the FHL study website. (Appendix 1: FHL study Eligibility Screening Questions). Potentially Eligible and interested women will be contacted by their local FHL study research team to reiterate what the study involves and to book a screening / baseline appointment.

The invite letter will advise that they can phone the local FHL study research team to find out more about the study and check their eligibility if they do not readily have immediate access to the internet. These women will be informed that they will not be able to join the study unless they can find a way to regularly access the internet, e.g. at a local library.

Approached when attending routine mammogram or FHC appointments

Women will also be asked about their interest in joining the study when they attend clinic for their mammogram or FHC appointments by staff in the FHC, FHL study research team or radiographers undertaking mammography and through recruiting posters and flyers in the FHC/mammography waiting areas. Women who express interest when they attend the clinic will be given a copy of the PIS and directed to the eligibility screening tool on the FHL study website to check their eligibility. Eligible women will subsequently be contacted by their local FHL study research team to reiterate what the study involves and to book a screening / baseline appointment.

In order to streamline recruitment and keep recruitment proximal to the time of screening, women who are interested and potentially eligible will be booked for a consent and baseline appointment at their recruiting centre either on the day of their routine mammogram or another date at the convenience of the participant. Thus participants are likely to be recruited to the study and randomised to their study group before they receive their mammogram results. We anticipate that only 0.5% of booked women i.e.1-2 out of 209 booked women would subsequently be diagnosed with BC at this mammogram. These women will be offered the option of continuing in the trial within their allocated group or leaving the trial. The diet and physical activity programmes in the study are appropriate for women who have been diagnosed with BC and the research dietitians at MFT have experience of supporting BC patients with diet and physical activity weight control programmes in our B-AHEAD 1 and B-AHEAD 2 studies (66) (67).

4.5 Women who are not interested in the Trial

The invite letter will invite women who are not interested in joining the study to tell us why they are not interested. This provides valuable insights into factors which influence uptake to weight loss programmes and therefore the generalisability of our study findings within the FHC clinic. Women who are not interested to join can inform us of the reasons by returning a tear off slip to the FHL study research team at MFT in a prepaid envelope or not respond at all.

4.6 Eligibility

4.6.1 Inclusion criteria:

1. Identified as being at moderately increased/ high risk of breast cancer (i.e. $\geq$ 17% lifetime risk

Receiving annual or 18 monthly mammograms in the FHC (aged > 30 years) , or as part of a mammographic surveillance programme for increased familial risk of BC or scheduled to commence mammographic screening in the future.

2. Have previously received information on their risk of developing BC within the FHC
2. Overweight / obese (BMI ≥ 25 kg/m^2).
3. Access to the internet and telephone

4. Ability to understand English and complete trial paperwork as successful participation requires engagement with weekly tailored e-mails and an interactive patient forum.
5. Participants must be willing to follow a diet and physical activity plan with the aim of losing weight
6. Agree that results of any NHS Health Checks conducted in the study can be communicated back to their GP. This is a requirement of NHS Health Checks to allow patients with undiagnosed CVD or T2DM or high risks of these diseases to receive appropriate follow up tests and medical management.
7.
8. Women taking chemoprevention for BC, e.g. tamoxifen, raloxifine or aromatase inhibitors are eligible to join the trial

4.6.2 Exclusion criteria:

1. Only one woman per family is able to join the study to avoid contamination between the groups.[1]
2. Previous diagnosis of cancer with the exception of previous non-melanoma skin cancer or cervical intra-epithelial neoplasia.
3. Previous diagnosis of cardiovascular disease, e.g. stroke, transient ischaemic attack (TIA), angina, heart attack, heart failure or ventricular or aortic aneurysm
4. Currently prescribed medication for raised cholesterol.
5. Current diagnosis of diabetes (type 1 or type 2)
6. Patients with on-going difficulties relating to a diagnosis of borderline personality disorder or bipolar affective disorder (not in remission), psychotic illness, post-traumatic stress disorder as well as those with evidence of current self-harm/suicidal behaviour, substance abuse or harmful alcohol use .The following patients may be eligible to be invited to baseline screening subject to approval from the GP or relevant health care professional : patients with a diagnosis of bipolar disorder or borderline personality disorder with evidence of a

[1] Recruited women will be advised they can share the diet and physical activity advice with other subsequent family members where appropriate. However, these family members would be precluded to join the study.

stable mood for at least two years, patients with a previous history of self-harm, substance abuse, harmful alcohol use or dependency whose condition is under control and stable

7. Currently prescribed antipsychotics, e.g. Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone as these can cause excessive weight gain
8. Current alcohol or drug dependency.
9. People requiring highly specialist medical diets which cannot be adjusted to fit with a weight loss diet, e.g. phenylketonuria, maple syrup urine disease, glycogen storage diseases, and urea cycle disorders advanced kidney disease, advanced liver disease.
10. Currently pregnant, breast feeding or planning pregnancy in the next 12 months[2].
11. Patients who are currently on treatment with Orlistat for weight loss or who have previously had bariatric surgery for weight loss including gastric bypass and sleeve gastrectomy or are planning to have this surgery in the next 12 months.
12. Current diagnosis of kidney disease.
13. Patients with a diagnosis of an eating disorder (e.g. binge eating or bulimia)
14. Currently successfully following a diet and/or physical activity plan and have lost more than 2 lb (1 kg) of weight in the last 2 weeks

4.6.3 Ineligible and non- recruiting Participants

Women who are not eligible to join the study will be able to download our standard weight loss / lifestyle advice leaflet outlining the IER diet or request a postal copy from the study team. We plan to collect anonymised data on the numbers who visit the eligibility website, telephone enquiries to the office and reasons for non-eligibility or lack of interest. Women who are either “not interested“ or “not eligible“ will be given the option of answering some anonymous additional questions on the eligibility web site or on a tear off slip which ask about key demographic factors. This is to inform if there is any bias in the uptake to the study, i.e. age, ethnicity, post code (to provide an index of multiple deprivation) (68), whether a known gene carrier or not.

[2] This will be based on self-report.

4.7 Informed consent

Potential participants will be invited to attend the screening / baseline assessment in their recruiting centre and to provide written informed consent after which their eligibility will be confirmed as follows:

1. Asking them to confirm the answers they have previously given on the online screening questionnaire (Appendix 1)
2. Measuring their weight and height to ensure BMI >25kg/m^2

Consent will be taken by a member of the FHL research study team in the recruiting centre who is GCP trained, experienced, and has been delegated by the Principal Investigator in the recruiting centre to undertake this activity. The participant will have been given the PIS and given adequate time for consideration and discussion. The person taking consent must be satisfied that the participant understands the information given to her, the demands of the trial including the risks involved and benefits. This trial excludes patients lacking mental capacity or children under the age of 18. The original, signed copy of the consent form will be retained in the investigator site file and a copy will be placed in the patient notes, a copy is given to the patient to keep and a copy will be sent to their GP with the study confirmation letter.

4.8 Randomisation

Participants eligible to enter the trial after confirmation of eligibility assessments will be registered and randomised on the site trial register (Randomisation Log).

Women will be randomised to either:

Group 1: A group receiving written advice (WA) on diet and physical only (n=35)

Group 2: A BC Prevention Programme (BCPP) (n=87)

Group 3: A Multiple Disease Prevention Programme (MDPP) (n=87)

Randomisation will be stratified by four factors:

1. BMI < and ≥ projected median BMI of 30kg/m^2
2. Age < or ≥ median age of 45 years

3. Defined as moderate or high risk of BC by the local FHC (i.e. lifetime T-C risk 17–30% or >30%)
4. Recruiting centre

Randomisation will be undertaken using a minimisation programme produced by the trial statistician (Julie Morris) at MFT. The programmes will be located on a department computer in each of the recruiting centres.

4.9 Participant Registration

Baseline CRF information for recruited participants will be sent securely to the main trial researchers at MFT within 2 working days. MFT researchers will book an initial diet and physical activity phone consultation for groups 2 & 3 within 10 working days of their baseline appointment where possible.

4.10 Blinding

It is not possible to blind participants or the clinical staff delivering the intervention to group allocation for a dietary intervention. However the statistical analysis will be performed by staff that are independent from the research team delivering the intervention and will be blinded to group allocation to minimise any potential bias.

4.11 Assessing suitability for the home based moderate intensity physical activity programme

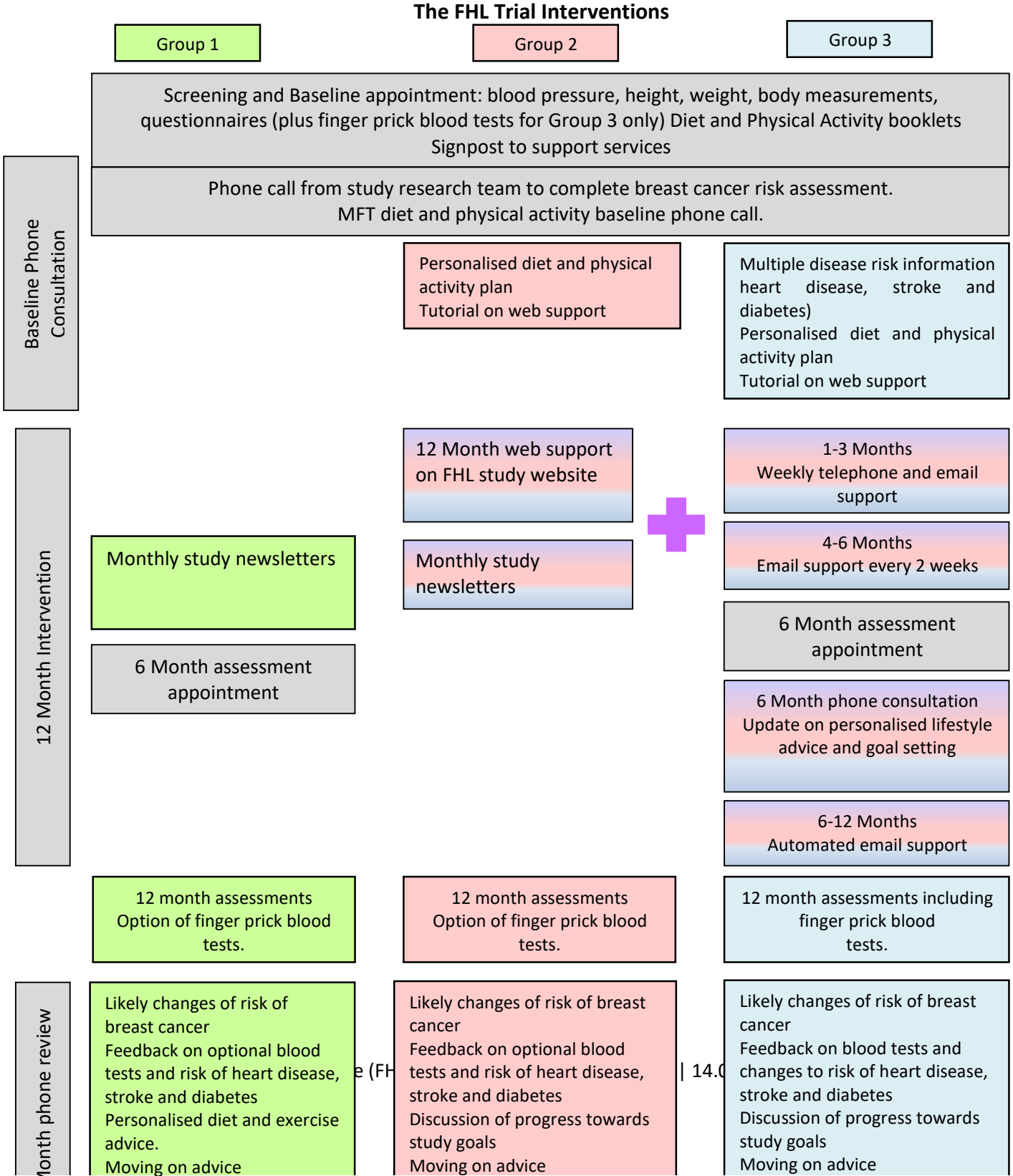
This will be assessed in two ways.

Firstly from the PAR-Q questionnaire (69) and where appropriate the opinion of the patients general practitioner.During the baseline assessments the participant will be asked to complete the PAR-Q questionnaire. If they answer yes to one or more of the seven physical activity screening questions they will be asked to consult with their GP regarding any physical activity restrictions they may have. A GP letter of authorisation will need to be completed as appropriate before any study related physical activity can commence.

Secondly from resting blood pressure and pulse regularity assessed at their baseline or follow up trial appointments Women who are found to have a resting blood pressure > 140 / 90 bpm or an irregular pulse at any of their FH lifestyle trial appointments will be referred back to their GP for further investigations and for the GP opinion of their safety to enter/ continue with the home based moderate intensity physical activity programme. Ongoing assessment of raised blood pressure or other conditions highlighted by the PAR – Q by their GP after joining the study may mean that they will be able to undertake physical activity once they have successfully lost weight. Analysis of our recent PROCAS lifestyle study showed that after 6 months of weight loss 75% of women with a baseline blood pressure of > 140/90 bpm became normotensive (< 140 bpm/ 90), largely as a result of weight loss. Thus they were then able to safely embark on the home based physical activity programme.

5. Trial Intervention

The FHL Trial Interventions



5.1 Diet and physical activity written information group (WA)

5.1.1 Baseline phone consultation

Women will be phoned by an FHL researcher preferably within 15 working days of their baseline assessment[3]. This consultation will include the following elements:

1. Women will be informed of their BC risk in a standardised manner as follows. They will be informed of their clinic risk category i.e. high or moderate risk as defined in Table 1 , and also their Tyrer-Cuzick (TC) estimated lifetime and 10 year risks as determined by current reported risk factors using the TC model version 8 (43). We do not foresee any issues with patients receiving this more detailed and updated TC BC risk information. The minority of women for whom the recalculated TC risk has redefined their risk to a different risk category (i.e moderate, high or population risk) to their previous clinic risk category will be referred back to their FHC who will review their clinic risk and contact the patient to discuss their BC risk. If BC risk has already been recalculated and fed back in the last 12 months and there is no obvious change in major risk factors the BC risk may not need updating. In this case the FHL researcher will remind the patient of their most up to date risk

   Many of the patients would have previously discussed their TC risk scores with clinicians in the FHC. However a proportion of the patients will not have done, and some patients may have had their previous risk assessment a number of years previously. The FHL researchers discussing the TC BC risks will have undergone standardised training on risk communication for BC.

[3] This period may be longer for patients who have to have their risks rechecked and communicated by their FHC or at the convenience of patients who may be unavailable

Table 1. NICE definitions of moderate and high risk (86)

	Breast cancer risk category		
	Near population risk	Moderate risk	High risk1
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3-8%	Greater than 8%
1 This group includes known BRCA1, BRCA2 and TP53 mutations and rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (STK11),Cowden (PTEN) and familial diffuse gastric cancer (E-Cadherin).			

2. Women will be informed that modest weight loss (≥5%) and lifestyle change can reduce their BC risk by 25-30%, but they <u>will not</u> receive any information on their current individual T2DM, CVD or dementia risk . The written information that they receive will reiterate that they can reduce their BC risk by 25-30% and will also inform them that lifestyle change can reduce T2DM by ~ 60% and CVD by ~ 30%,

5.1.2 Diet information

Women will be given written advice which outlines two different weight loss diets.. The two diets are: 1. An IER diet with two energy restricted and five unrestricted Mediterranean diet days per week to lose weight and reach their target weight and one day/week to maintain a healthy weight or 2. A DER Mediterranean diet.

The IER includes two days of a low carbohydrate low energy diet and five days following a less restrictive, healthy Mediterranean-type diet each week. The two low carbohydrate days include generous amounts of poultry, fish, eggs, tofu, monounsaturated (MUFA) and polyunsaturated fats (PUFA), limited lean red meat (max of 100g / day), low fat dairy foods, 5 portions of

vegetables and 1-2 portions of fruit, and at least 2 litres of low energy fluids. We have shown that low carbohydrate days self-limit to approximately 1000 kcal, 70-90 g protein, <60 g fat and <15g saturated fat (SFA) per day. The Mediterranean-type diet provides 30% energy from fat (15% MUFA, 8% PUFA, 7% SFA), 25% energy from protein and 45% from low glycaemic load wholegrain carbohydrates and includes at least 5 portions of vegetables, 2 portions of fruit/day and low fat dairy products. Calorie controlled Mediterranean diets are considered optimum for reducing weight, blood pressure and improving lipid profiles (45-47).

The IER and DER diets both include good dietary sources of calcium and vitamin D to provide a daily total of 700-1000mg calcium and 10µg vitamin D per day. This will help limit any reductions of bone density which can occur alongside weight loss (48). The diets limit alcohol to less than 10 units/week, and restricts sodium intake to less than 2.4g/day.

5.1.3 Physical activity information

Women will be given standard written advice which outlines the benefits of cardiovascular and resistance physical activity and encourages them to undertake ≥30 minutes of moderate intensity cardiovascular activity at least five days per week such as cycling or brisk walking (60–80% maximum heart rate) and resistance physical activity three times per week (~40 minutes/week). The moderate intensity physical activity target can be met by either 150 minutes of moderate physical activity / week or the equivalent amount of vigorous physical activity, i.e. 75 minutes per week and resistance physical activity for the trunk, legs and arms three times / week. This information is only provided if patients are considered to safe to undertake the physical activity plan so according to their baseline PAR-Q and blood pressure, pulse assessment.

5.1.4 Referrals to NHS smoking cessation and alcohol services.

Approximately 10% of women in the FHC are current smokers. Although smoking has weak links with the risk of BC (49), smoking cessation is important for overall health in our cohort to reduce risk of CVD (50), lung cancer and 15 other cancers [72]. Smokers identified at baseline will be advised to self-refer to available NHS smoking cessation services, e.g. group or one-to-one support via their GP, local pharmacy or specialist smoking cessation services and nicotine

replacement therapies. Recent randomised trials show that multiple lifestyle behaviour changes, i.e. smoking cessation, diet, physical activity and weight control can be achieved when tackled either concurrently or sequentially (51, 52). The success of concurrent or sequential approaches depends on the participant's preference for attempting multiple behaviour changes and their readiness to change the different behaviours (53).

The standard dietary information recommends limiting alcohol intake to achieve weight loss and reduce risk of BC. In addition women reporting harmful levels of drinking on their baseline questionnaires defined as ≥35 units per week and/or an AUDIT score of 16 or above (Alcohol Use Disorders Identification Test Score: 0-7 Lower risk, 8-15 Increasing risk, 16-19 Higher risk, 20+ possible dependence) (54) will prompt a discussion regarding the likelihood of problem drinking and a referral letter to their GP if this is appropriate and with the patients' consent.

5.1.5 Other components of the WA group

- This group will receive a standard monthly trial newsletter which covers the progress of the trial.
- This group will be offered an NHS Health Check at their 12 month appointment (i.e. personalised information on their risk of CVD ,T2DM and dementia)
- 12 month phone diet and physical activity advice consultation with one of the study dietitians after their 12 month trial assessments to discuss their final weight, any associated likely changes to their risk of BC, feedback on results from their optional 12 month NHS Health Check; and moving on advice and referral to other weight loss or behaviour change support agencies where appropriate. Results from the optional NHS Health Check will be communicated to their GP.

5.2 Breast Cancer Prevention Programme (BCPP)

5.2.1 Initial phone consultation. Prior to the call, women will have received their written diet and physical activity information so they have a chance to look at the information and formulate specific questions. Women will be phoned by their allocated FHL research dietitian at MFT. This consultation will include the following elements:

- Disease risk information and referrals to NHS smoking cessation and alcohol services as for the WA group described above.
- **Lifestyle advice and goal setting**
    - Discussion of their current weight, BMI and dieting history, current diet and physical activity patterns; readiness and safety to physical activity (PAR-Q), and agreed realistic target for weight loss.
    - Explanation of the IER and DER diets[4]. All participants receive a portion guide and meal plans for their diet plan from the research dietitian.

Personalised physical activity advice to build up to the recommended amount of cardiovascular activity (≥150 minutes of moderate physical activity / week or the equivalent amount of vigorous physical activity, i.e. 75 minutes per week

- and resistance physical activity for the trunk, legs and arms three times / week. The plan is tailored to each participant's preferences, co-morbidities and abilities using the demonstration videos on the web site https://www.physiotec.ca/.

This information is only provided if patients are considered to safe to undertake the physical activity plan so according to their baseline PAR-Q and blood pressure, pulse assessment.

-
- Goal setting and action planning for diet and physical activity
- Plans for coping with setbacks / relapse prevention
- Inform patients of the dietetic and web support in the programmes and tutorial on using the web site
- Sign-post to any relevant support services in their locality, i.e. physical activity.

5.2.2 Phone and web support

FHL study website

[4] Women are encouraged to try the IER diet but can opt to follow the DER diet. Eighty percent of women in our current PROCAS Lifestyle study chose to follow the IER diet.

Patients will have access to the FHL study website for the 12 month programme. The web site includes the following key features:

- Detailed information about our recommended diets and the key food groups, e.g. fruit and vegetables, fat , fibre, alcohol
- Tools for self-monitoring of weight, diet and physical activity
- Information on weight, diet and physical activity and risk of BC, other cancers, cardiovascular disease, T2DM and dementia
- Separate moderated forums for participants in the BCPP and MDPP groups to avoid contamination between the groups.
- Recipes and meal plans for the recommended diets
- Suggested cardiovascular and resistance physical activity programmes with demonstration videos (https://www.physiotec.ca/)
- An 'ask the expert' function for ongoing queries.
- Enhanced monthly newsletters which cover the progress of the trial and recent news stories on lifestyle and risk of BC and other relevant conditions.

5.2.3 Months 1-3: weekly telephone and e-mail support.

Diet and physical activity advice will be reiterated and reinforced by their designated trial dietitian in three follow up calls at weeks 1, 4 and 8. These calls will cover: participants' understanding of their diet and physical activity advice and BC risk; remind patients of their diet and physical activity goals; trouble-shoot any issues with these goals and/or use of the website; encourage patients to self-monitor their weight, diet and physical activity and remind them that they can use the patient forum on the website.

Patients will also receive weekly tailored e mails in weeks 2, 3, 5-7 and 9-12 from the dietitian which will include feedback on; their progress based on self-reporting from the website; praise (feedback) for good behaviours/outcomes; prompts to self-report if they are not doing this; and additional diet and physical activity advice where appropriate.

5.2.4 Months 4-6: e-mail support only

Tailored e-mails from the dietitian every two weeks as described above but no phone calls.

5.2.5 6 Month phone review

- **Lifestyle advice and goal setting following on from 6 month assessments**

- Discussion of their current weight, BMI, current diet and physical activity patterns and updated target for weight loss.
- Updated diet plan with portion guide and meal plans.
- Goal setting and action planning for diet and physical activity.
- Plans for coping with setbacks / relapse prevention
- Sign-post to any relevant support services in their locality, i.e. physical activity.

5.2.6 Months 6-12: automated e-mail and web support only

Participants will be encouraged to continue to self-monitor their weight, diet and physical activity on the trial website and they will receive automated e-mail feedback (not tailored) on this. The e-mails will prompt a return to dieting after 1kg regain and offers a specific diet plan to do so [5]**.** Participants can still access the other features of the web site, e.g. the patient forum and 'ask the expert' functions.

5.2.7 12 month phone review

This group will be offered an optional NHS Health Check (i.e. personalised information on their risk of CVD ,T2DM and dementia) when they attend their 12 month face to face appointment in the recruiting centre. After the appointment, patients will receive a final call from their allocated dietitian to discuss their final weight and progress towards their initial weight loss diet and physical activity goals, any associated likely changes to their risk of BC, other cancers, CVD,

[5] Observational data from the US weight registry showed few people (11%) recover from weight regains of even 1-2kg. Similarly those with greatest weight regain after 1 year were least likely to re-lose weight the following year, suggesting early prevention of weight regain is important (55, 56).

T2DM and dementia, feedback on results from their optional 12 month NHS Health Check; and moving on advice and referral to other weight loss or behaviour change support agencies where appropriate. Results from the optional NHS Health Check will be communicated to their GP.

5.3 Multiple Disease Prevention Programme (MDPP)

The MDPP group will receive an NHS Health Check at their baseline appointment, i.e. systolic blood pressure, heart rate, pulse rhythm (30 seconds manual), non-fasting total and HDL cholesterol, total: HDL cholesterol ratio and HbA1c (point of care testing Alere Ltd, Stockport, UK). Personalised estimates of CVD risk will be determined using the Joint British Societies CVD risk calculator (http://www.jbs3risk.com/pages/risk_calculator.htm) to present a heart age, remaining lifetime and 10 year risk of CVD which uses BMI, non-fasting total: HDL cholesterol ratio, systolic blood pressure, smoking and family history of heart disease (57) .If the participant is suspected to have diabetes (HbA1c ≥ 48 mmol/mol) then the JBS3 QRISK calculator cannot be used. Even if a participant's diagnosis has not been confirmed with their GP use the UK Prospective Diabetes Study (UKPDS) calculator to calculate their 10-year CVD risk. People with diabetes have a CVD risk up to 3 times greater than the general population (UKPDS website, 2014).

The risk calculator can be downloaded from: https://www.dtu.ox.ac.uk/riskengine/download.php.

Personalised risk of T2DM will be estimated using HbA1c to screen for diabetes and the QDiabetes® 2018 risk calculator (http://www.qdiabetes.org/2018/)which assesses 10 year risk of T2DMbased on age, ethnicity, smoking, family history of diabetes, use of steroids, hypertension and history of CVD (58) . If the patient is either diagnosed with diabetes, has BP meds prescribed or statins prescribed following the baseline assessments then the risks will be recalculated to take this into consideration. These updated risk estimations will be used as baseline risk estimations for data entry.

5.3.1 Initial phone consultation

As with the BCPP group, women will have received their written diet and physical activity information prior to the call. The initial phone consultation is identical to the BCPP described

above but patients also receive feedback on their personalised risk of CVD and T2DM based on the NHS Health Check measurements above.We will also discuss their potential risk of dementia which aligns to unhealthy lifestyle (excess weight, smoking, alcohol, sedentary behaviour, and cardiovascular risk factors: www.healthcheck.nhs.uk/document.php?o=327).

We will ask about their hierarchy of concerns regarding BC, T2DM, CVD and dementia. The group will be informed that a weight loss of ≥5% weight loss and lifestyle change can reduce their risk of BC by 25-30%, T2DM by 60% and CVD by 30%.

Participants identified with hyperlipidaemia will be encouraged to include all aspects of The Portfolio Cholesterol Lowering Diet, e.g. plant sterols/stanols, nuts and soy protein which can yield reductions in cholesterol comparable to first line statins (-20%) (59).

5.3.2 Feedback to GP

Risks of CVD, T2DM and biomarker results will be communicated to their GP after this phone call. Results of NHS Health Checks must be fed back to GPs as a requirement of NHS Health Checks, which enable patients with risk factors to receive appropriate additional follow up diagnostic tests (e.g. repeat HbA1c, or ECG at GP surgery for irregular pulse and / or medical management, e.g. statins or anti–hypertensives).

5.3.3 Phone and web support

Web and phone support for 12 months is identical to the BCPP group, as detailed above.

5.3.4 12 Month NHS Health Check

The NHS Health Check will be repeated at 12 months to assess changes in CVD and T2DM risk markers in this group, and results communicated to their GP.

5.4 Achieving behaviour change in the BCPP and MDPP groups

Behaviour change techniques we will use in both BCPP and MDPP programmes include goal setting, self-monitoring of weight, diet and physical activity programmes on the website and

timely personalised feedback on these records, rehearsing successful performance of behaviour, action planning, planning for how to deal with setbacks (60). Both programmes communicate how weight loss reduces disease risk as a gain framed message to increase response efficacy (61). This is based on their personal risk of BC in the BCPP and their personal risk of CVD, T2DM, dementia as well as BC in the MDPP.

The BCPP and MDPP programmes also both use established behaviour change techniques to increase self-efficacy, i.e. the belief that individuals have the capability to change behaviours which we and others have found key for dietary change (62), to overcome dietary temptations (63), maintain weight loss (64) and engage in physical activity (65).

5.5 Standardisation of delivery of the programmes

The researchers delivering the programmes will have undergone standard training and assessments to ensure they have adequate knowledge and competence in risk feedback, knowledge of BC, CVD, T2DM and dementia and links with lifestyle, behaviour change and diet and physical activity advice for weight loss. They will follow Standard Operating Procedures (SOP'S) for the delivery of advice and support, including protocols to guide the procedure for missed calls. The researchers will have 2 weekly case review meetings which can also include our department exercise specialist to discuss any issues arising with patients and Multi Disciplinary Team (MDT) decisions on appropriate advice for participants.

6. Withdrawal of subjects

Possible reasons for withdrawal include:

- Pregnancy during the trial
- Patient subsequently diagnosed with BC who chooses to withdraw from the trial
- Patient whose recalculated TC risk indicates their BC risk is below the moderate risk threshold and they subsequently chose to withdraw from the trial.
- Patient choice to withdraw from the trial for other reasons
- Unplanned loss of contact for ≥8 weeks

- Development of severe disease where weight loss and diet and physical activity are no longer feasible or appropriate.

The right of the participant to refuse to participate in the study without giving reasons will be respected. All participants are free to withdraw at any time. We will not recruit additional patients to replace those who withdraw.

Data from participants who withdraw from the study will be retained for use, unless participants specifically withdraw consent for use of existing data. Participants who withdraw from the programme protocol, or who fail to return for follow-up assessments, will continue to have their weight and mammographic density data collected from their routine FHC visit unless they specifically withdraw consent for this. Data analysis will use best available follow-up weights within 3 months before or after the planned study visits.

7. Trial procedures

7.1 visit schedule

There will be three face to face appointments in the recruiting centres an initial screening/ baseline appointment and reviews at 6 and 12 months. Additional questionnaire data will be collected at 3 months.

Table 2

	Screening	**Baseline**	**3 M**	**6 M**	**12 M**
Informed consent	✓				
PAR-Q readiness to exercise		✓			
Resting blood pressure		✓		**MDPP**	✓
Weight Body composition Body measurements	✓	 ✓ ✓		✓ ✓ ✓	✓ ✓ ✓
Demographics		✓			
Binge eating, anxiety and depression scales (BEAD): - Binge eating , PHQ-9, GAD-7		 ✓			
Health behaviours:					

	Screening	Baseline	3 M	6 M	12 M
- Med Diet score		✓	✓	✓	✓
- IPAQ		✓	✓	✓	✓
- Alcohol and Smoking		✓	✓	✓	✓
- 7-day actigraph [6]		✓		✓	
Quality of life:					
- EQ-5D-5L(73)		✓		✓	✓
- ICE-CAP-A (74)		✓		✓	✓
- Health resource use		✓		✓	✓
Questionnaires to assess hypothesised mediators:					
- Disease risk perception (including susceptibility, severity and response efficacy)		✓	✓		
- Hierarchy of concern		✓			✓
- Self -efficacy scales (initiation of change in physical activity and diet)		✓	✓		
- Initiation (physical activity and diet)					
- Planning behaviour				✓	✓
- Self-reported habit				✓	✓
- Satisfaction with programme		✓	✓	✓	✓
- Self-efficacy scales (recovery and maintenance self-efficacy for physical activity and diet)		✓	✓	✓	✓
Tyrer-Cuzick breast cancer risk assessment [7]		✓			
NHS Health Check		**MDPP**			✓
Weight & dieting history questionnaire		✓			
Food frequency and diet habits questionnaire		**MDPP BCPP**			
Study Feedback Questionnaire			✓	✓	✓
Sub study 1 (optional) [8] Mammographic density		✓			✓
Sub study 2 (optional) Plasma biomarker		✓			✓
Sub study 3 (optional) Qualitative evaluation					**MDPP BCPP**

[6] in a sub set of 45 patients (15 patients in each group)

[7] Tyrer Cuzick project risk feedback will be provided after the baseline assessment. It will be provided by the FHL study researchers at the start of the three different weight loss programmes.

[8] Sub study in a sub set of patients

7.2 Assessments

7.2.1 Patient demographics

Recorded on the CRF from hospital notes:

Age, postcode (to determine index of multiple deprivation) and the number of years they have attended the FHC.

Recorded on the CRF at baseline appointment:

Ethnicity, marital status, employment, number of children living at home, highest level of education.

Recorded on the weight and diet history questionnaire:

Weight at the age of 20 and adult weight gain [9].

7.2.2 Estimation of lifetime and 10 year risk of breast cancer

We will collect information on BC risk factors for assessment of personal BC risk using the Tyrer-Cuzick (TC) risk model which includes family history, hormonal risk factors and BMI (44) (appendix 3). The TC BC risk estimation based on this information will be undertaken by FH lifestyle researchers of FHC clinic staff in the centres after the baseline appointment and prior to their initial telephone consultation. The "research" TC risk assessment will be done to the same standard QC as in the clinics by researchers who have had training, support and supervision from the family history clinics.

The TC remaining lifetime risk will be fed back to all participants by the study research team as part of the weight loss programmes. Risk feedback will follow the MFT standardised protocol and the researchers will have all had training in disease risk communication.

In the unexpected situation of a TC risk defining women to a different broad risk category than their previous clinic risk category, i.e. defining them as high rather than moderate risk or visa versa, or as below the threshold for moderate risk, patients will be referred back to their FHC team to have their clinic risk and care pathway, i.e. frequency of screening, re-assessed.

[9] Adult weight gain is consistently linked to breast cancer risk

Women will be reassured that if they are confirmed to now be below the moderate risk threshold they will still be able to remain in the study and partake in the programmes since women of all levels of BC risk can reduce their risk of BC and other diseases by adhering to a healthy lifestyle.

7.2.3 Weight and body composition

All sites will measure: weight, height, body composition (body fat and fat free mass) measured by bioelectrical impedance [10], waist, hip, bust and back circumferences following standard SOPs from the Lifestyle Research Team, MFT.

7.2.4 Resting systolic and diastolic blood pressure and pulse

This is measured at the initial screening appointments in all subjects to determine safety to physical activity, following a standard SOP from the Lifestyle Research Team MFT. Patients do not see their measurements when they are taken and are only informed of adverse results which require either further investigations by their GP (all groups) or possible modification to the physical activity programme (BCPP or MDPP groups).

7.2.5 Health behaviours

- Diet quality; Mediterranean score (75)
- Physical activity (IPAQ short form) (76)
- Alcohol; 7 day recall (77)
- Smoking behaviour: never / ex- smoker / current
- Current smoker: number of cigarettes / day
- Objective measurement of physical activity:

A subset of 50 patients (19 BCPP, 19 MDPP, 12 control) will be provided with an Actigraph® accelerometer (physical activity monitor on a waistband) and asked to wear it for 7 days before

[10] Body composition will be assessed using different impedance devices in the three centres (MFT Tanita 180, Tameside Hospital Tanita 420, UHS Seca multi-frequency mb1a515). Measurements at the different time points will be conducted on the same machines for each trial participant.

receiving their initial phone consultation with the study researcher and for 7 days before their 6 month face to face assessment.

7.2.6 Health and well-being measures

All patients will be asked to complete two measures to record their current health status and well-being and the impact of the intervention on their health and well-being. Health status will be measured using the EQ-5D-5L(73), which is the measure recommended within the NICE methods guide for technology appraisal to capture the consequences of healthcare programmes and technologies. The EQ-5D-5L has been extensively validated and has gained widespread use due to its simplicity. It imposes minimal burden on the respondent. An additional measure, the ICECAP-A (74) is also included to capture the impact on well-being. The patients who will be recruited to this study are likely to be generally healthy and it may be unlikely to see a quantifiable change in health status as a result of the interventions in this study. The ICECAP-A is a capability measure which defines wellbeing in terms of an individual's ability to 'do' and 'be' the things that are important in life. It is being included as an outcome measure in this study as weight loss may have an immediate impact on the patient's capability.

7.2.7 Use of healthcare

All patients will be asked to record their health resource use over the past 6 months (in-patient, out-patient, accident and emergency primary and community based health service, prescription, diet aids. At baseline, participants will be asked to record their use of healthcare resources in the last six months prior to recruitment. There are no published standardised questionnaires to record resource use but an on-line resource (https://www.Dirum.org) has been used to inform the design of a study-specific healthcare resource use questionnaire.

Healthcare resources used to provide each intervention will also be calculated. Examples of relevant healthcare resources include: the resources required to set up the website; telephone reminders and text alerts; staff time to deliver the interventions; monitoring of weight using scales; other monitoring e.g. using Alere point of care testing for the NHS health check. Staff

time to deliver the interventions will be recorded for a sample of patients in each study arm (n=10) by asking relevant healthcare staff to make a note of how it takes them to deliver relevant aspects of each programme e.g. telephone consultation length and relevant grade of NHS staff.

7.2.7 Behaviour change questionnaires

Disease risk perception (including susceptibility, severity and response efficacy)(78)

Hierarchy of concern

Self -efficacy scales (initiation of change in physical activity and diet)(78)

Initiation (physical activity and diet) (78)

Planning behaviour (79)

Self-reported habit(80)

Satisfaction with programme(81)

Self-efficacy scales (recovery and maintenance self-efficacy for physical activity and diet)(82)

7.2.8 NHS Health Check

This includes the following additional assessments:

- CVD risk is based on the Joint British Societies CVD risk calculator (http://www.jbs3risk.com/pages/risk_calculator.htm) which requires additional personal and family medical history questions and point of care tests for total and HDL cholesterol.
- T2DMrisk is based on Qrisk diabetes http://qdiabetes.org/2018 which involves additional personal and family medical history questions. We will also assess whether subjects have normal blood glucose control, or have suspected prediabetes or diabetes using point of care testing for HbA1c.

The clinic researchers will adhere to the departmental protocol used by the MFT research dietitians when undertaking these assessments. Key abnormal values i.e. Hba1c >, blood

pressure > 140 / 90 or total cholesterol > 7.5 will be discussed with the patient who will be given a letter for their GP to undertake further investigations of these abnormal values. Patients will be informed that their test results will be collated in the assessment clinic and communicated to FHL researchers at MFT who will subsequently discuss the results with the patients at their initial information/advice call in the following 10 days.

7.2.9 Weight and dieting history

The short questionnaire will provide information about their personal weight and dieting history, e.g. patterns and reasons for weight gain over adult life, whether they have ever advised and helped to lose weight by a health care professional and recent supported or unsupported attempts to lose weight.

7.2.10 Food frequency,diet habits and physical activity questionnaire (BCPP and MDPP groups only)

This provides a simple overview of current dietary intake and patterns of eating and physical activity to highlight areas which currently meet or do not meet recommendations in order to inform the personalised advice provided.

7.3 Sub study 1: Mammographic density

This will assess changes in mammographic density between the baseline and 12 month mammograms. This sub study will **only** include women if their baseline mammogram is ≤6 weeks before or ≤2 weeks after they commence their treatment allocation in the study, if they have annual mammograms, and if they have consented to enter this sub study. Women who have had a double mastectomy or have breast implants will be excluded from the study. To allow the full 12 months following the allocated FHL study programme, the routine mammogram at 12 months can safely be delayed by a maximum of 6 weeks. We will assess density using a range of automated methods (volumetric and area-based) and visual assessment by experts.

7.4 Sub study 2: Breast derived plasma proteins

This sub study will include women who consent to providing a blood sample at their baseline and 12 month appointments. We will collect two 4ml EDTA tubes of blood for a potential future proteomic analysis. After collection the tube should be inverted 8-10 times and spun within 30 minutes. Centrifugation will be for 10 minutes at 2000g with plasma removed from the upper layer. After preparation the sample will be split into 2 x 2ml aliquots and stored at -80 in the recruiting centre. Samples will be transported under dry ice to ensure samples don't thaw and stored at -80°C in freezers in the Nightingale Centre, MFT. Analysis of these samples will be undertaken at the Stoller Biomarker Discovery Centre, Manchester. Samples can be collected at any time of day and in the fasting or fed state.

7.5 Sub study 3: Qualitative evaluation of the BCPP and MDPP programmes

We will undertake 20 semi-structured interviews with women from the BCPP and MDPP groups at the end of the 12 month programme, staggered throughout the eight month period when women are reaching this point. Sampling will be purposive, aiming to obtain women with a range of ages and BC risks. Interviews will examine perspectives of the telephone/web-based support, how personalised advice impacts on the ability to make lifestyle changes in light of BC or multiple disease risk, and perspectives on how women with a family history of BC maintain lifestyle changes in the 6-12 months of the programme when they are no longer receiving direct support from a health care professional. We will explore their experiences, giving insight into disease risk perceptions and beliefs surrounding response efficacy and behavioural intentions.

Interview data will be digital audio-recorded and transcribed verbatim and analysed using thematic analysis (83). Analysis will be inductive: open-ended, exploratory, and driven by the data. The interviews will be conducted by Dr Louise Gorman (qualitative health psychology researcher) or Helen Ruane (Research Assistant) with the topic guide being produced in conjunction with Professor David French (Health Psychologist) and Dr Michelle Harvie (Dietitian). Data will be analysed using thematic analysis. Thematic analysis is arguably the foundation of all qualitative analyses. It is free from theoretical bonds and is therefore adaptable to a wide range of methodologies. This freedom of epistemology means that the

qualitative data from this study can provide a parallel and complimentary perspective to the other methods of data collection being used in this study. Thematic analysis can account for both individual and group consensus, so that both convergent and divergent experiences across the corpus of the data can be taken into account as the process of analysis involves searching for all salient themes that emerge from the data. Primary analysis will be conducted by Dr Louise Gorman, secondary analysis will be conducted by Helen Ruane. Codes will be discussed, revised and refined in conjunction with Dr Michelle Harvie, and Prof David French.

7.6 Co-redesign of the website

The BCPP and MDPP groups will be invited to suggest refinements at the end of their 12 month programme. We will assess usage of the different website functions and invite questionnaire feedback (weeks 12, 26 and 52) on how the website could be improved for a future effectiveness/cost effectiveness trial (84).

8.0 Trial Data

8.1 Data Monitoring Plan

8.1.1 Source Data

Clinic assessments of weight, anthropometric measurements, blood pressure, will be collected on paper CRFs. Data recorded from automated instruments will be stored in patient records, i.e. print outs from bioelectrical impedance meters, lipid and HbA1c results from Alere® machines and screen shots of T-C BC risk assessment from on line form http://www.ems-trials.org/riskevaluator/. All CRFs will include the patient ID, date and visit, i.e. baseline, 6 or 12 months.

Questionnaire data will be collected either on paper or electronically either in the assessment clinic or immediately prior or after clinic assessments to increase convenience for the patients. Patient utility and activity on the website (BCPP and MDPP groups only) will be downloaded from the FHL study website in a csv file. There will also be electronic files with copies of transcriptions of qualitative interviews.

8.1.2 Flow of data from recruiting centres

Patient CRF data will be stored at the recruiting sites on a trial case report form during the trial. These semi-anonymised forms (trial ID and patient initials) will be transferred to the FHL researchers at MFT during the trial using secure methods, i.e. nhs.net e-mail or fax. The FHL researchers at MFT will also have patient data; log of review calls and emails from the dietitian. These data are stored in the participants' individual 'Participant Trial Files' kept in a secure area in the R&D department at MFT.

Prior to statistical analysis, all data will be entered from the Participant Trial Files to secure databases that will be anonymous. Researchers in each recruiting site will adhere to their hospital SOP for dealing with participant trial and medical records.

The raw mammographic files used as part of routine care in the recruiting centres will be transferred to MFT via the Image Exchange Portal. This is a secure method for transferring scan images that is widely used within the NHS. The mammographic files will then be anonymised prior to analysis using specialist software.

Anonymous (trial ID only) online questionnaire and web usage data will be downloaded by researchers at MFT.

8.1.3 Data entry

On receipt of the CRFs, the data is entered in the trial database. Data is verified during the data validation process and QC procedures.

We will double data entry the paper CRF data for the main trial endpoints, i.e. weight and body composition and anthropometry, and resolve any differences between databases by reviewing source data.

8.1.4 Data checking

The data manager at MFT will check CRFs within 2 weeks of receipt from the recruiting centres. Any data queries will be resolved with the recruiting centres within 2 weeks of the date of the data check.

The admin team at MFT will undertake sense checking on CRF data for values outside expected ranges and ensure that % fat is correctly recorded by checking fat (kg) / weight (kg). These will be checked with the recruiting centre. All completed data queries and endorsed data corrections received and processed are filed on an ongoing basis and kept secure at all times.

Outcome	**Expected range**
BMI	≥25 and < 70 kg/m^2
Waist circumference	>40 and < 140 cm
Hip circumference	>51 and < 165 cm
Total cholesterol	≥2.59 and ≤ 12.95 mmol/l
HDL cholesterol	≥ 0.39 and ≤ 2.59 mmol/l
HbA1c	≥ 20 and ≤ 140 mmol/mol

IPAQ data will be checked and cleaned according to the IPAQ data cleaning and processing protocol https://sites.google.com/site/theipaq/

Data will be transferred from the main trial database to SPSS or STATA statistical software. We will undertake random QC checks of the SPSS and STATA database to ensure accurate transfer of data.

8.1.5 Data storage

All trial data will be kept strictly confidential according to Good Clinical Practice (GCP) Guidelines. All data will be stored in a secure fashion for 10 years in accordance with the ICH GCP guidelines.

8.2 What to record in medical records

A copy of the signed consent form, PIS and copies of GP letters will be recorded in the patient's medical records.

8.3 Access to Data

The sponsor (MFT) may request trial-related monitoring, audits, and regulatory inspection(s), and direct access to source data/documents.

By participating in the trial, the CI and PI in each centre is confirming agreement with MFT to ensure that:

1. The trial documentation is present, complete and in compliance with ICH GCP and local standard operating system and regulations
2. Source notes match CRF entries for the selected number of the trial participants
3. Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs
4. Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
5. Trial-related monitoring, audits and regulatory inspection(s) are permitted and direct access to source data/documents is provided as required

9.0 Archiving

Data from this non CTIMP will be retained for 10 years at the end of the study. The Trial Management File and patient source documentation will be archived according to MFT SOP 11 and local policies in the other recruiting sites. Electronic data will be backed up on a secure server and on an encrypted safe stick retained securely in the lifestyle research office @ MFT.

10. Data analysis

10.1 Sample size calculation

With 30 controls and 74 subjects in each of the two 'active' treatment regime groups, the study will have 90% power to detect differences in absolute change in percentage weight loss of 4% or more between the control group and an active treatment group, and a difference of 3% or more between the two active treatment groups. A difference in percentage weight loss of > 3% between the active treatment groups has been chosen as this represents a clinically significant difference. Our previous FHC trial reported a 4% difference in percentage weight loss between a programme and control group amongst a population of high risk women (25). Incorporating an estimated drop-out rate of 15%, these sample sizes increase to 35 controls and 87 in each of the two active treatment groups. These calculations are derived using the two sample t-test with estimated SD of 5%, and with a 2% significance level to take account of the multiple testing between the three study groups.

Justification for using unequal randomisation in this trial

Since there are two programme groups and a minimal intervention comparison group, the most efficient design takes account of the different expected differences between the groups. The expected difference of 4% between each programme group and the comparison group (this difference was found in a previous study) is larger than the clinically important difference between the two programme groups (3%). A major objective of the study is to compare the programme groups, therefore to account for the smaller clinically important difference, more patients are required to sufficiently power the programme group comparison. Thus an unequal randomisation allocation is required.

10.2 Statistical analysis plan

10.2.1 Primary outcome analysis

Percentage weight loss between the groups at 12 months will be assessed using analysis of covariance (ANCOVA), adjusted for baseline levels and important confounding factors, with multiple imputation (using an iterative Markov chain Monte Carlo method) being employed to deal with missing data. Appropriate sensitivity analysis will be applied or considered to assess any missing at random assumptions.

A longitudinal linear regression analysis, using generalized estimating equations (GEE) with an autoregressive correlation structure, will also be used to assess differences between the groups in the change in weight over the 6 and 12 month time points.

All analyses will be carried out on an intention to treat basis using SPSS version 22.0.

10.2.2 Secondary outcome analysis

Change in body composition, blood pressure, diet and physical activity behaviours over the study period will be assessed at 12 months using ANCOVA as above for continuous outcomes and logistic regression analysis for binary outcomes. Changes over the whole study period incorporating the 6 month time point will be analysed using regression modelling (GEE with either a binary or normally distributed response as appropriate, and an auto-regressive correlation structure).

Changes in disease risk perception, behavioural and quality of life and health economic scores will be analysed as a per protocol analysis.

10.2.3 Health economic analysis

The economic analysis in this study is a preliminary analysis that will be used to inform a future definitive trial. The analysis will be conducted in accordance with published guidance (87). A within-trial analysis will quantify the incremental costs (using the trial resource use data), taking the NHS perspective, and incremental benefits (using the trial EQ5D-5L and ICECAP-A data), and analyse these data using descriptive statistics, including measures of variation. A cost

consequences analysis will present two measures of the consequences of the interventions: health status (EQ5D-5L data) and well-being (ICECAP-A).

The data from the EQ5D-5L and ICECAP-A will be transformed using published preference weightings. This will allow the estimation of quality adjusted life years (QALYs) using EQ5D data and the impact on capability for ICECAP-A data. Healthcare resource use will be translated into costs using published sources of unit cost data such as the NHS reference costs, British National Formulary and published staff costs (88, 89, 90, 91).

After accounting for missing data using multiple imputation (92, 93, 94), a full incremental analysis appropriately comparing each programme with usual practice will be conducted taking into account baseline data (95). Appropriate regression-based methods (96, 97, 98, 99), that take into account the distribution of the data, will be used to identify the potential key drivers of relative cost-effectiveness of the two programmes compared with current practice over the trial time-horizon.

10.2.5 Additional analysis

We will also assess:

a. The hypothesised mediators of change in lifestyle behaviours and weight. Specifically, we will examine changes in risk appraisal, self-efficacy, and planning, to assess whether the interventions were successful in changing the intended mechanism of change, and whether this affects lifestyle behaviour, controlling for baseline levels. At 3 months we will also examine which hypothesised mediators (i.e. planning, habit, satisfaction with programme and recovery/ maintenance self-efficacy) predict maintenance of behaviour change and weight loss at 12 months, relative to 6 months.
b. The impact of the FH lifestyle website on weight loss/ change in lifestyle behaviours. The successes of weight loss websites directly correlate with how well they maintain engagement of users over time. Throughout the course of the study we will assess

overall usage of the website and usage of the key functions, e.g. self-monitoring, patient forum, and how this correlates with final weight loss success.

c. A sub group analysis to compare efficacy of the BCPP and MDPP vs WA between women at high vs moderate risk of BC
d. The numbers of women who have increased risk of CVD and T2DMat baseline in the MDPP group. This will inform the prevalence of previously undiagnosed CVD and T2DMrisk amongst women at increased risk of BC.

10.3 Interim reporting

The funding body Prevent Breast Cancer have requested an update on recruitment 10 months after activation of the grant. If recruitment rate is slower than anticipated 6 patients per week, we will review recruitment strategy in the recruiting centres and consider opening an additional recruitment site.

10.4 Subject population and missing data

The primary and secondary analysis will be an intention to treat analysis amongst patients who are randomised to the three groups. The analysis will include **all patients** randomised to each group. It will include all subjects irrespective of whether they received their actual treatment allocation and irrespective of their subsequent level of engagement with the weight loss programmes. We will record the number of patients in the BCPP and MDPP group who fail to receive their treatment allocation, i.e. who do not receive their initial telephone consultation.

10.5 Procedure to account for missing data

We have a number of strategies to maximise follow up. These include reminder letters and e-mails / texts for 6 and 12 month review appointments, a monthly trial newsletter for all trial participants, use of online questionnaires which can be completed prior to 6 and 12 month assessments. Reasons for missing data will be recorded in CRFs and the trial database. The

planned analysis described previously (10.2.1) will use a number of methods for handling missing data.

11 Safety reporting

11.1 Adverse test results within the trial

Participants in the trial will undergo a number of assessments of physical and emotional wellbeing. Adverse results defined as follows will be communicated back to their GP with the patient's permission, following a standard SOP from The Nightingale Centre, MFT. For abnormal lipid and HbA1c results ascertained with point of care testing, a letter will be sent to GPs to inform them of the abnormal result which will need verification by further tests by their GP in order to confirm this result.

11.2 Definitions of terms used for safety reporting for non-CTIMPS

TERM	Definitions for this study
Adverse Event (AE)	An adverse event is any **untoward medical occurrence** in a patient which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	An adverse reaction is any **untoward and unintended response to the** trial treatment administered to that subject. Note: Any adverse event judged by either the reporting investigator or the sponsor as having reasonable causal relationship to the trial treatment qualifies as an AR if there is evidence or argument to suggest a causal relationship.

Serious adverse event (SAE), or unexpected serious adverse reaction	A serious adverse event or reaction in a trial subject that: • results in death, • is life-threatening, • requires hospitalisation • results in persistent or significant disability / incapacity • consist of a congenital anomaly / birth defect, or • Important medical events may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences. Note: For the purpose of this definition, life-threatening refers to an event in which the trial subject was at risk at the time of an event; not an event that might have caused death if it were more severe.
Suspected unexpected serious adverse reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is **not consistent with the information about the trial treatment** in question. For non CTIMP studies like this study an SAE occurring to a research participant should be assessed by the CI as to whether: • Related- That it resulted from administration of any of the research procedures, and • Unexpected- that the type of event is not listed in the protocol as an expected occurrence.
Reference safety information	The information used for assessing whether an adverse reaction is expected. For the purpose of this trial, information revealed in the course of current trials or scientific literature which may have impact on the safety of the participants.

11.3 Pregnancy during study

Women are not eligible if they are currently pregnant or planning to become pregnant in the next year. In the unlikely event of a pregnancy occurring during the study, the participant will be withdrawn from the study and documented in participant's study file. Pregnancies will not be tracked as part of the study. Moderate calorie restriction and moderate intensity physical activity interventions amongst pregnant women have been found to be safe and to improve outcomes for both mother and baby (85), although the effects of more severe daily energy restriction or intermittent diets is not known.

11.4 Reporting of adverse events

PIs at recruiting centres other than MFT will be responsible for reporting of serious adverse events according to their Trust protocols, and for alerting MFT R&D (as study sponsor) and the Chief Investigator to all SAEs according to the flow chart in Appendix 3.

11.5 Trial stopping rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or regulatory authority on the basis of new safety information or for other reasons given by the Ethics Committee. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

12. Trial management group

This group comprises the Chief Investigator, the PIs in the recruiting centres, co-applicants, data manager, patient representative(s), trial statistician, cancer clinical trial manager at MFT and MFT study dietitians. The group will be responsible for the day to day running and management of the trial which includes the following:

- Supervise the conduct and progress of the study, and adherence to the study protocol.
- Assess the safety and efficacy of the interventions during the study.
- Evaluate the quality of the study data.
- Review relevant information from other sources (e.g. related studies).
- Escalate any issues for concern to the Sponsor, specifically where the issue could compromise patient safety or the integrity of the study or quality of the study data.

Trial management group meetings are planned at the initiation of the trial, and at 4, 10, 16, 22 and 28 months.

13. Principal investigator responsibilities

Attendance at the initiation meeting, training of new members of the trial team in the protocol and its procedures, ensuring that the site file is accurately maintained, dissemination of

important safety or trial related information to all stakeholders within their site, safety reporting within the timelines.

14. Authorisation of trial sites

Researchers from MFT the main recruiting site and sponsor will undertake site initiation visits prior to sites starting to recruit to the study. These visits will outline all trial procedures and ensure that the site staff are fully compliant with the trial SOPs for assessments.

15. Public and patient involvement

We have a lifestyle PPI group at the Nightingale Centre to advise on our lifestyle research programme. This group have advised the researchers on the design of the study, patient information sheets, diet resources, the trial web site and preferred methods for inviting and screening potential participants for the trial.

The trial management group involves 1-2 members of this group to advise on the ongoing running of the trial. Dissemination of findings to women at increased risk of BC via the Prevent Breast Cancer web site and the National Hereditary Breast Cancer Help line in conjunction with Wendy Watson
http://www.breastcancergenetics.co.uk/contact-us/.
We will invite all trial participants to provide anonymous feedback on their satisfaction with the study process to inform our future research protocols

16. Ethics and Regulatory Requirements

The Chief Investigator will submit a final report at conclusion of the trial to the Sponsor and the REC within the timelines defined in the Regulations. Annual progress reports will be submitted to the REC, in accordance with their procedures. REC and local R&D approval will be obtained before a site can recruit patients. Sub study 1 utilises mammographic data which is collected as normal standard of care from annual mammograms. The recruiting sites do not therefore

require ARSAC certificates as the trial does not involve additional ionizing radiation above standard care.

17. Quality Control

Trial assessments and delivery of the weight loss programmes across the recruiting centres will be undertaken according to the strict trial SOPs from The Nightingale Centre, MFT. Staff from the main recruiting centre (MFT) will ensure compliance with these SOPs in the recruiting centres through an initial site initiation visit and a review/audit visit after 6 months of recruitment. Weighing scales and blood pressure monitors in each centre will undergo annual calibration in accordance with good clinical practice. Research staff working on the trial must have a GCP training certificate within the past 3 years. Protocol deviations are recorded and reported to the Sponsor. The data manager in the main recruiting centre will produce reports of completeness of data and highlight any issues with data collection / validity of the data across all recruiting sites after 3 months of recruitment which will be repeated at 9, 12 and 18 months.

18. Post-trial care

The FHL study research team will not be able to provide dietetic support to participants beyond their participation in the trial. The WA group is offered an individual phone consultation about diet and physical activity at the end of their 12 month study period. The BCPP and WA groups will be offered an NHS Health Check at 12 months.

All BCPP and MDPP patients will be informed that they can continue to use their respective sections of the trial website, e.g. self-monitoring, chat room functions, until the end of the active intervention phase of the study, i.e. 12 months after the last patient has been recruited.

19. Data protection and patient confidentiality

- All data will be kept strictly confidential according to GCP Guidelines. Representatives of the MFT sponsor and any relevant regulatory authorities will be required to have access to patients notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

- Patient identifiable raw mammographic images will be sent to MFT from the recruiting sites (UHS and Tameside Hospital) via the secure Image Exchange Portal. This data will be anonymised at MFT and copied to an encrypted USB device which will be passed to the mammographic researchers at the University of Manchester for analysis.
- Baseline patient data and contact details for patients who consent to the study from the recruiting sites UHS and Tameside Hospital will be sent to MFT via secure means (nhs.net account / secure fax).
- Participant data collected on CRFs and questionnaires in all recruiting centres will be anonymised; only trial ID number and patient initials will be used to identify the participant. This data will be sent to MFT from the other recruiting centres via secure means (NHS net account / secure fax) for input to the trial database. The data manager at MFT will have a separate look up list to link trial IDs with patient details.
- Prior to statistical analysis, all data in Participant Trial Files will be entered to secure databases that will be anonymous.
- Patients who use the FHL study website will need to provide an e mail address to use the web site. They will be informed that this will not be passed to a third party. They will be assured that their diet and physical activity records and on line questionnaires are secure as the website has a SSL (Secure Sockets Layer) encryption certificate.
- Patient tracking log for screened and consented patients, patient trial notes will be stored securely in the recruiting centres for 10 years in accordance with the ICH GCP guidelines and their local trust policies. Computers used to collate the data will have access restrictions via user names, passwords and the use of encrypted digital files and storage media.
- Source data from MFT and copies of source data from the recruiting sites, the trial master file and trial database will be stored by Wythenshawe Hospital, Manchester University NHS Foundation Trust in a secure fashion for 10 years in accordance with the ICH GCP.

20. Insurance / indemnity

The Sponsor is an NHS organisation, so the NHS indemnity scheme will apply.

MFT will be liable for clinical negligence and other negligent harm to participants taking part in the study and covered by the duty of care owed to them by the site concerned.

The recruiting sites will be loaned Alere point of care testing machines for the duration of the study. Staff will have been trained for the appropriate care and maintenance of these machines.

21. Trial Conduct

21.1 Protocol Amendments

Any changes in research activity will be reviewed and approved by the CI and submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to enrolment into an amended protocol according to SOP 16.

Deviations from the protocol may be taken by an investigator without prior approval from the Sponsor or regulatory bodies in order to eliminate an immediate hazard to a patient. The rationale must be submitted to appropriate regulatory bodies as soon as possible after the deviation and documented in the patient note and CRFs.

21.2 Protocol Deviations

The Regulations and guidance state that no deviation must be made from an approved trial protocol, unless it is an urgent safety measure taken to protect a patient from immediate harm. The research team are encouraged to contact the CI if a potential protocol deviation has occurred (or if an event has occurred and it is unclear whether it should be classified as a deviation) and the CI will advise the site what information and actions are required.

There is a legal requirement to report serious breaches of GCP or the trial protocol to REC within a defined timeframe. If a major deviation meets the criteria for a serious breach, it is notified immediately to the Sponsor and reported to the REC within 7 days of confirmation.

22. Peer review

The trial has had high quality peer review by the funding body Prevent Breast Cancer, i.e. 3 independent expert reviewers. Prevent Breast Cancer awards grants in open competition and is an NIHR partner.

23. Publication

The data from the trial will be owned by the sponsor MFT. Trial results will be written as a final report for the funding body and disseminated at national / international scientific conferences and peer reviewed scientific papers and a number of web sites which for example may include Prevent Breast Cancer, the Manchester Breast Centre, Manchester Biomedical Research Centre Cancer Prevention and Early Detection, University of Manchester Women's Cancer. Outputs from the trial will be written up jointly by the Chief Investigator and all co-applicants. Trial outputs will need to acknowledge the source of funding from Prevent Breast Cancer. Participants in the trial will be informed that copies of the final report will be available to them on request and would be anticipated within 4 months of the final patient completing their 12 month assessments. The protocol will be publically available on the ISRCTN register.

24. Funding

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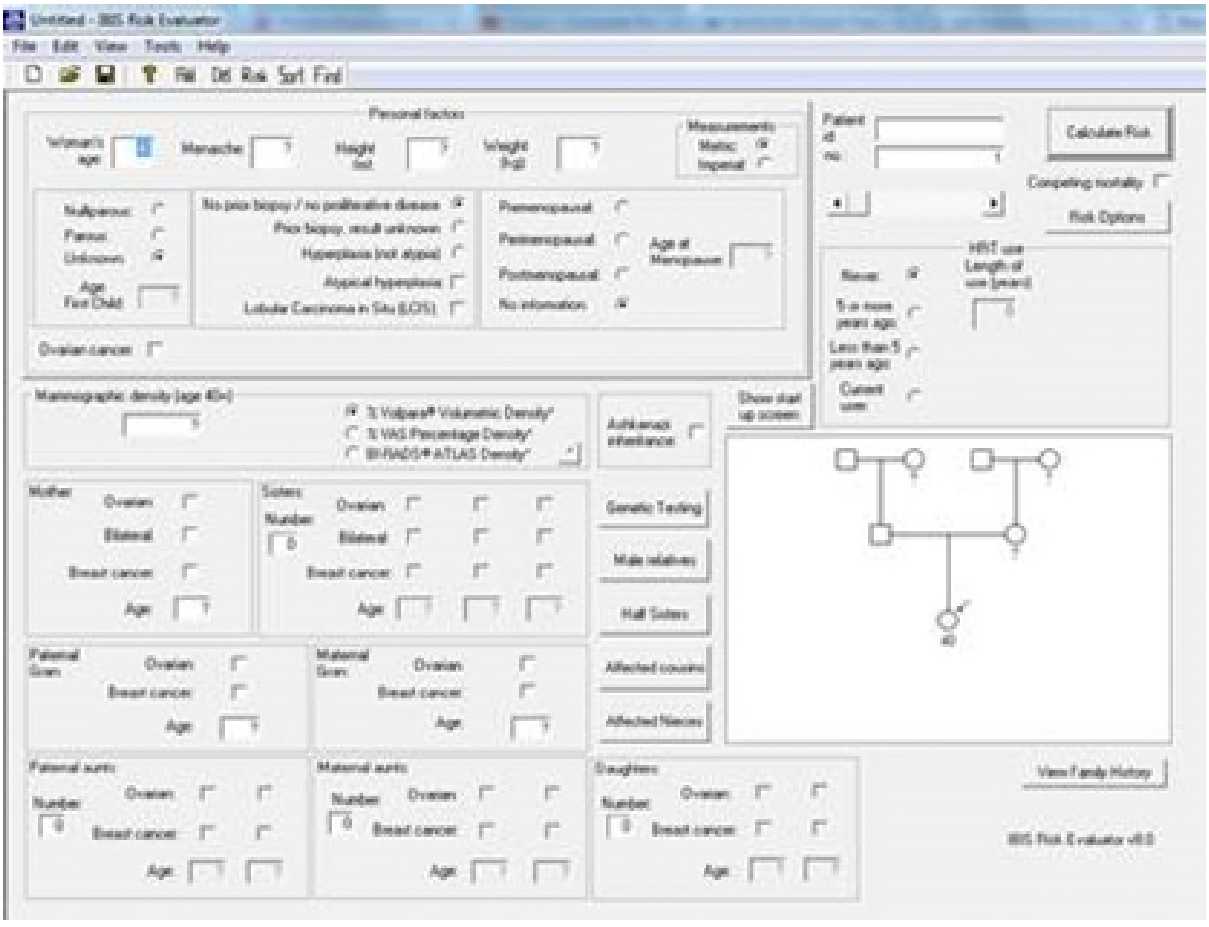
Appendix 1: FHL study Eligibility Screening Questions

Family History Lifestyle Eligibility Questions for website

1. Age: _____(years)
2. Height: _____(metres) **or** _____(feet/inches)
3. Weight: _____(kg) **or** _____(st/lb)
4. Body Mass Index: automatically calculated (kg/m^2)
5. Do you have access to a **phone and the internet**?
6. Can you understand written and spoken English?
7. Have you been seen in a Family History or Genetics clinic and been told you **have an increased risk of breast cancer**?
8. Is anyone in your family already on this research study (**Family History Lifestyle Study**)?
9. Are you **pregnant**, **breast feeding** or **planning pregnancy** in the next 12 months?
10. Have you ever been diagnosed with **cancer**? ****this does not include a diagnosis of non-melanoma skin cancer or precancerous cells on a cervical smear (CIN)****
11. Have you ever been diagnosed with **diabetes?**
12. Have you ever had a **stroke, Transient Ischemic Attack (TIA), angina, heart attack, heart failure, or ventricular or aortic aneurysm?**
13. Are you currently taking medication for raised **cholesterol?**
14. Have you ever been diagnosed with **kidney disease?**
15. Do you currently have a diagnosis of an **eating disorder** (e.g. binge eating or bulimia)?
16. Do you currently have an **alcohol** or **drug dependency**?
17. Have you ever been diagnosed with a **personality disorder** or **bipolar disorder** (formerly known as manic depression) or have you ever tried to **self-harm**?
18. Are you currently taking any of the following medication prescribed for psychosis and schizophrenia: Aripiprazole, Clozapine, Olanzapine, Quetiapine or Risperidone ****Please note, these medicines may have a different brand name. If you're unsure, please check the box the medicine is in****
19. Have you ever had **weight loss surgery** e.g. gastric bypass or sleeve gastrectomy, or do you plan to have this type of surgery in the next 12 months?
20. Are you currently taking any **medication to help you lose weight** e.g. Orlistat, Xenical, Alli?

21. Are you on any **specialist medical diet** to treat conditions such as phenylketonuria, maple syrup urine disease, glycogen storage diseases, urea cycle disorders, advanced kidney disease or advanced liver disease?
22. Are you willing to follow a **healthy diet and physical activity programme to lose** weight?
23. Do you consent to us **informing your GP of your results** (e.g. blood pressure, cholesterol) during the study?

Appendix2: Online Tyrer Cuzick breast cancer risk assessment model http://www.ems-trials.org/riskevaluator/



Appendix 3 : Adverse Event Decision Making and Procedure