It is a requirement of Good Clinical Practice (GCP) and the Research Governance Framework for Health & Social Care 2005, that all research projects have a scientifically sound and ethically valid protocol.

The protocol is the starting point of any high quality research and all research studies must be conducted according to the protocol. A protocol provides written evidence for the necessity and feasibility of a study, as well as giving a detailed plan of investigation.

This document is to be submitted for approval to a Research Ethics Committee.This allows the ethical and peer review processes to validate the scientific and ethical considerations of the study. The guidance detailed below is for Clinical Trials of NonInvestigational Medicinal Products (Non CTIMPs).

Red border or text – Mandatory text – not be changed or removed

Blue border or text – further details to be inserted in line with the comments attached

Yellow border or text – if applicable to this study, further details to be inserted

Purple border or text – further information to be inserted by the statistician

The front page of the Protocol requires the full study title along with the REC Reference number for that protocol.

The protocol must be versioned and dated with the date of finalisation of the version.

(If there are any subsequent changes made to the protocol, both the version number and finalisation date should be updated accordingly.)

TITLE OF THE PROTOCOL:

A peer-support weight action programme to supplement brief advice in general practice

Short title/Acronym: Peer-support weight action programme (SWAP)arch 2012

Sponsor:	Barts and The London NHS Trust/ Barts and The London School of Medicine and Dentistry ***[please delete as appropriate following discussion with the Joint Research Office(JRO) re. Sponsor]***
	Representative of the Sponsor: **Gerry Leonard** **Head of Resources** Joint R&D Office 5 Walden Street London E1 2EF Phone: 020 7882 7260 Email:gerry.leonard@bartsandthelondon.nhs.uk
REC reference:	Insert once known

Include aChief Investigator (CI) Agreement Page where the CI should sign, date and insert the research site address to confirm the version has been approved, is the final version and the study will be conducted as specified in this protocol.

Chief Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version 3, dated 22nd January 2015)**,or any subsequent amendmentswill be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirementsand any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Dr Hayden McRobbie

Chief Investigator Site: **Wolfson Institute of Preventive Medicine**
Barts and The London School of Medicine and Dentistry
Queen Mary University of London

Signature and Date:

Statistician Agreement Page

The clinical study as detailed within this research protocol **(Version 3, dated 22nd January 2015)**,or any subsequent amendmentswill be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirementsand any subsequent amendments of the appropriate regulations.

Statistician Name: Sandra Eldridge

Site: Pragmatic Clinical Trials Unit
Queen Mary University of London

Signature and Date:

Principal Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version 3, dated 22nd January 2015)**,or any subsequent amendmentswill be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirementsand any subsequent amendments of the appropriate regulations.

Principal Investigator Name: Professor Peter Hajek

Principal InvestigatorSite: **Wolfson Institute of Preventive Medicine**
Barts and The London School of
Medicine and Dentistry
Queen Mary University of London

Signature and Date:

STUDY SUMMARY/SYNOPSIS

TITLE	A peer-support weight action programme to supplement brief advice in general practice
SHORT TITLE	Peer-support weight action programme (SWAP)
Protocol Version Number and Date	Version 3 **22nd January 2015**
Methodology	Randomised controlled trial
Study Duration	36 months
Study Centre	**Wolfson Institute of Preventive Medicine (Psychology Section)**
Objectives	(1) Determine if WAP can generate a better sustained weight loss over 12 months in overweight adults than best-practice intervention that is routinely provided by nurses in general practice (2) Determine the cost-effectiveness of the two interventions (3) Determine the effectiveness of the program in participants from deprived communities (4) Define other determinants and predictors of program adherence and outcome (5) Identify factors related to maintenance of the initial weight loss
Number of Subjects/Patients	330
Main Inclusion Criteria	Adults, aged 18 years and older, with a BMI of 30 kg/m2 or over, or BMI of 28 kg/m2 or over with co-morbidities referred from general practice.
Statistical Methodology and Analysis	The primary analysis will compare weight loss between the experimental and control groups, adjusting for baseline weight. We propose to implement a strict ITT analysis as our primary outcome, with participants lost to follow-up included as achieving no weight loss. Baseline variables such as demographic data including socioeconomic indicators, baseline weight and health status, and motivational and cognitive variables including self-efficacy will be introduced into the regression models as covariates. These covariates will be chosen and detailed in a full analysis plan prior to the regression modeling analyses.

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
JRO	Joint Research and Development Office
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

Index

1 Introduction

1.1 Background

Some 42% of men and 32% of women in England are overweight (BMI 25 kg/m2 or over) and some 24% are obese (BMI 30 kg/m^2 or over) [1]. Ill health resulting from obesity is responsible for about 10% of morbidity and mortality in the UK and costs the NHS about 7 billion pounds annually [2]. Obesity is associated with a number of adverse health conditions including cardiovascular disease, Type 2 diabetes, osteoarthritis and a number of cancers. Weight loss has been shown to improve many of these illnesses [3], and reduce all cause mortality [4].

Obesity has links to health inequalities. These have declined over the past few decades, but are still present. E.g. the proportion of women with a raised waist circumference is 37% in the highest income quintile and 51% in the lowest income quintile [1]. Ethnicity is also relevant, e.g. the highest obesity rates are reported in Afro-Caribbean and Irish men [1].

An increasing number of people are in need of interventions to help them to lose weight. General Practitioners are encouraged to measure BMI and monitor patients with a BMI of 30 kg/m2 or greater. Such patients are expected to be recommended healthy eating and physical activity, and to receive drug therapy and/or a referral to practice nurse or dietician, if indicated.

1.2 Current Situation

The menu of evidence-based interventions currently available for people unable to lose weight on their own is relatively limited. Current pharmacological treatments have modest effects which can be beneficial, but are likely to be lost once the medication is stopped [5]. Surgical interventions are more successful but are currently expensive and unsuitable for large-scale use [6,7]. Dietary interventions on their own have only uncertain effects [8] and brief routine interventions within primary care have generally reported disappointing results [9].

More intensive behavioural interventions generate a small but sustainable weight loss [10], which can engender significant and clinically worthwhile long-term health benefits [11]. Such interventions however are normally limited to commercial or research context. Weight management in overweight individuals who seek help normally requires changes to their habitual lifestyle which are difficult to implement and maintain without specialist input, structure and support [12,13]. The NICE guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children recommends multi-component interventions as the treatment of choice. These interventions should include "behaviour change strategies to increase people's physical activity levels or decrease inactivity, improve eating behaviour and the quality of the person's diet and reduce energy intake" [14]. Where the recommendation is translated into brief advice by

GPs accompanied by referrals to practice nurses, the results can be disappointing [15].

There are several factors responsible for effective multi-session and multi-component interventions remaining relatively exclusive. Intensive weight management programmes can make considerable demands on staff expertise and budgets, and they also face the challenge of participant retention. The programmes usually include, as one of their core active ingredients, assignment and monitoring of tasks. These are difficult to implement for most participants, and the participant drop-out is usually large [16].
In the field of health behaviour modification, group approaches can dramatically reduce the costs of treatments and increase their reach [17]. They may also have a potential to improve participant retention. Social support has been associated with positive change in a number of areas, including weight management [18]. Some potentially useful pointers can be derived from the field of smoking cessation, which shares a number of key features with weight management. Interaction-oriented groups have been shown to improve attendance and participant retention [19], mutual linking of individual tasks improved treatment compliance and short-term outcome [20], and on a national scale group treatments seem to be yielding results superior to individual treatment [21]. Current group weight management programmes have usually a strongly didactic focus with limited efforts to utilise social support and to link the progress of individual participants with each other. It is likely that the mutual-support-oriented group approach, which has proved useful in smoking cessation, can be used here as well.

Similar to smoking cessation, primary care has a key role to play in helping overweight and obese people to achieve a healthy weight. GPs have been incentivised via the Quality and Outcomes Framework to keep a register of all adults enrolled in their practice with a BMI over 30. There is also a clinical care pathway for the management of overweight and obesity to help guide GPs [22]. The pathway includes referral to specialist centres. One of the barriers to intervening with people who are overweight and obese is the lack of referral options. The NHS currently does not offer evidence-based weight management treatment for people who need help losing weight akin to e.g. stop-smoking services, which are available across the country. As discussed above, patients are usually managed by general practice teams. Some training for practice nurses is available, e.g. Counterweight Programme. This reported some results from a randomised trial funded by manufacturers of orlistat [23,24] but it did not publish the results from the control group, or make clear what proportion of successful clients lost weight due to medications, and so its efficacy is difficult to appraise. The Healthy Weight Healthy Lives strategy document and NICE guidelines support local commissioning of weight management programs [14,25]. Several types of such programs are currently being commissioned by PCTs, but their efficacy is generally not known. There is a need for evidence-based public-domain weight management programs that are effective and cost effective, readily accessible, and attractive for patients from diverse ethnic and socio-economic backgrounds.

1.3 Experimental Intervention

The weight action programme(WAP) is a multi-modal health behaviour modification intervention developed at the Wolfson Institute of Preventive Medicine via extensive client feedback and piloting with underprivileged groups since 2002. The programme is a multi-component service that aims to provide participants with tools to lose weight and maintain a long-term healthy lifestyle. The contents include the standard elements of cognitive behavioural interventions, dietary advice, self-monitoring,

information on healthy cooking and eating and caloric content of food, cue management, provision of opportunities for exercise and close monitoring of exercise levels, and a range of concrete and verifiable tasks agreed individually with each participant. Participants are asked to wear a pedometer in order to record daily number of steps at baseline. Throughout the course, individual pedometer step targets are gradually increased until an optimal sustainable level is reached.

An innovative feature of the programme consists of the use of group-oriented interventions aiming to increase participant retention, involvement and adherence to weekly tasks. This also makes the programme more cost-effective. The focus of the WAP course is to help participants to maintain a healthy lifestyle after the programme finishes.

The programme was initially implemented within NHS Tower Hamlets, and then modified to include participant feedback, to make it suitable for community use in deprived inner city areas and to include the latest guidance and evidence on the management of overweight and obesity in adults and children including the NICE 2006 guidance.

The programme has been developed to cater specifically for underprivileged groups including ethnic minorities. Where information is imparted, it is mostly in pictorial and easily understandable format.

The WAP has been evaluated in two pilot studies of 162 overweight adults (mean BMI of 35 kg/m2) from multi-ethnic areas of high deprivation [26]. The average weight loss was 2.8kg at end of treatment and 4.5kg at 3-month follow-up (with 24% participants attending follow-up losing 5% or more of their body weight). Limited promotion via GP practices and local adverts generated a large volume of interest. The client retention was at least as good as in comparable programs conducted in research settings with more traditional clients (59% completed the 6-week treatment) and the program received very high approval ratings. Clients also demonstrated significant improvements in knowledge of healthy eating, and in their exercise levels as measured by pedometer monitoring. Clients considered the group support essential in helping them to stick to their tasks and to lose weight [26]. In its current form, WAP also includes information on orlistat as per Tower Hamlets Obesity Care Pathway.

We propose to evaluate the long-term efficacy of a community-based weight management intervention (WAP) compared to what is currently the most common approach in primary care, i.e. a routine intervention delivered by practice nurses.

1.4 Rationale and Risks/Benefits

The benefits to the participant are the chance to try a safe treatment that could enhance the likelihood of achieving and maintaining a beneficial weight loss. We do not anticipate any harm to participants from receiving either the experimental or control interventions.

Social support has been associated with positive change in a number of areas, including weight management [18]. Group approaches can also dramatically reduce the cost of treatments and increase their reach [17]. The proposed project will build on previous pilot work that showed that the group-based WAP program is attractive to people from deprived communities and different ethnic backgrounds seeking help with weight management, and that it generates good short-term results. The trial will

evaluate whether the gains are sustained in the long term, and whether the program can improve on what is already being achieved with interventions practiced routinely in primary care. The project has a considerable potential to make a practicable and economical contribution to options available to people, especially those from underprivileged groups, who seek help with their weight problem.

2 Trial Objectives and Design

2.1 Trial Objectives

The proposed study will determine whether a promising group-based weight management program (Weight Action Programme; WAP) targeting underprivileged groups has a long-term effect that is over and above the effect of a 'best practice' weight management intervention that is provided in primary care by practice nurses.

Primary Objective
Determine if WAP can generate a better sustained weight loss over 12 months in overweight adults than best-practice intervention that is routinely provided by nurses in general practice.

Secondary Objective

a) Determine the cost-effectiveness (in terms of costs of interventions and QALYs derived from the EQ-5D) of the two interventions
b) Determine the effectiveness of the program in participants from deprived communities
c) Define other determinants and predictors of program adherence and outcome
d) Identify factors related to maintenance of the initial weight loss

Primary Endpoint
The primary endpoint is change in weight at 12 months post-randomisation.

Secondary Endpoint
Secondary endpoints are change in BMI, waist circumference, systolic blood pressure, diastolic blood pressure, proportion of participants losing at least 5% and 10% of baseline body weight, and changes in questionnaires for food craving, food knowledge, eating habits, and physical activity levels. All outcomes will be measured at 6 and 12 months. We will also assess the quality of life (measured using the EQ-5D questionnaire), and cost-effectiveness.

2.2 Trial Design

Randomised controlled trial (RCT)

2.3 Study Scheme Diagram

See figure 1 on the following page.

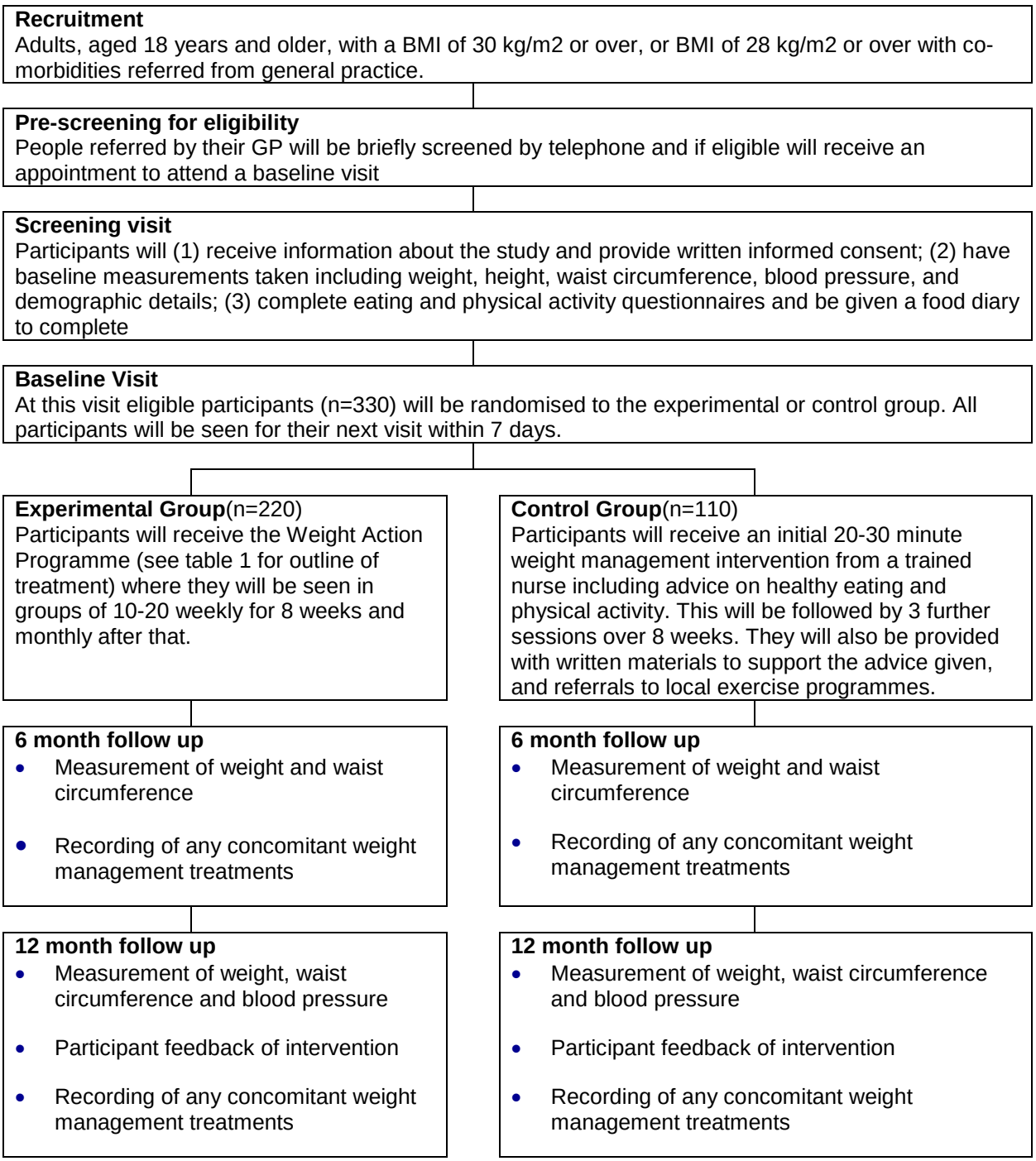
3 Subject Selection

3.1 Number of Subjects and Subject Selection

Participants (adults, 18 years and older, who want to lose weight and have a BMI of 30 kg/m2 or more, or 28 kg/m2 or more with co-morbidities) will be recruited from GP practices. They will receive routine advice to lose weight from their GP and will be referred to the study center. Referral will be via various methods including: (1) a simple fax referral form similar to those that were used in the pilot work (study center staff will then proactively contact potential participants); (2) telephone referral; (3) providing potential participants with the study contact details via 'tear off' pads, mail-shots to patients with BMI of 30 or more (see details below), and in-practice promotional materials; (4) patients contacting the study center via 'Word-of-mouth'; (5) if necessary, recruitment will be boosted by local advertising

We will also identify potential participants via a computerized search of GP records (e.g. people with a inclusion BMI)and generation of GP letters informing them of the option of participating in this project. This would be done by routine practice staff.

Figure 1: Study Scheme Diagram



3.2 Inclusion Criteria

The inclusion criteria are:

- Age 18 years and older
- Wants to lose weight
- Have a BMI of 30 kg/m2 or over, or BMI of 28 kg/m2 or over with co-morbidities

3.3 Exclusion Criteria

The exclusion criteria are:

- Inability to read/write/understand English
- BMI over 45
- Lost more than 5% of their body weight in the previous 6 months
- Women who are pregnant
- Clients taking psychiatric medications (these medications can have a significant effect on weight and psychiatric illness also makes follow-up and adherence to long-term programs difficult)
- Clients who are not registered with a GP
- Currently involved in a research project
- Clients who cannot speak or understand English

We are not excluding any other co-morbidities to ensure the study addresses NHS needs and the results are generalisable. Clients who cannot exercise will not be excluded as WAP program is multimodal and does not rely solely on exercise.

3.4 Criteria for Premature Withdrawal

Clients will only be withdrawn prematurely if they no longer wish to participate.

4 Study Procedures

4.1 Informed Consent Procedures

We will provide detailed trial information and allow sufficient time (at least 24 hours) for people to consider whether they would like to participate in the trial. We will also provide a participant information sheet with details of the study.

All participants will provide written informed consent at the baseline session, prior to randomisation to the study arms.

Written informed consent will be obtained by an appropriately GCP trained person delegated by the Investigator as documented in the site delegation log, prior to any participation/study specific procedures.

4.2 Screening Procedures

Participants who meet the inclusion criteria over the phone (see above) will attend a screening visit. At this initial assessment session participants will have the study explained to them and will provide written informed consent (week -1). Eligibility will be checked and weight, height and BMI will be recorded. If eligible, participants will be invited to attend the following week in order to be randomised. At this session (week 0) participants will complete baseline visit questionnaires, have baseline

measures recorded and then be randomized to the experimental (WAP) or the control group (weight loss intervention from a trained nurse). The first session of WAP and the control intervention will be provided in the following 7-days (see figure 1).

4.3 Randomisation Procedures

Participants who are eligible and consent to take part will be randomly allocated to the experimental or control interventions, in the ratio 2:1 (intervention:control).To preserve allocation concealment, the participants will be allocated in random permuted blocks of size 18, 21, 24 using the allocation ration 2:1 in each block. The randomisation will be conducted by Sheffield Clinical Trials Unit, University of Sheffield. The health professional randomising the patient will access the randomisation programme remotely when the patient is with them, entering their ID number into the programme. No other information will be entered as there are no stratification factors. The allocation will immediately be provided by the programme.

4.4 Schedule of Treatment for each visit

Experimental Group: The Weight Action Program (WAP)

WAP is a multi-modal health behavior modification intervention that has been modified and improved through client feedback over the past 5 years. It includes the standard elements of cognitive behavioural interventions, including information on healthy eating and caloric content of food, self-monitoring, cue management, provision of opportunities for exercise and close monitoring of exercise levels. Novel elements include a range of concrete and verifiable tasks agreed individually with each participant, and motivational interventions to ensure adherence to the new lifestyle changes. A range of guidelines for the treatment of obesity report that the best results are achieved with a combination of diet, physical activity and behavioural support. WAP combines all three components.

As in the control intervention, clients will also receive two additional offers in accordance with the local obesity care pathway. Where appropriate, they will be provided with information about orlistat and advised to see their GP if they wish to use it as part of their weight-loss programme.They will receive information about local exercise provision and where 'exercise on prescription' types of interventions are available, they will receive relevant vouchers and referrals.

WAP comprises 8 weekly sessions, followed by monthly follow-up visits lasting up to 1-hour each. The target weight loss is one pound (0.45 kg) per week. Two advisors will be conducting WAP sessions in groups of 10 to 20 participants. Participants will be sent text messages to remind them of the session dates and times.

Clients will not be restricted from using any other weight loss intervention (including pharmacological treatment if their GP believes this is appropriate) during the study. They will, however, be asked to report on the use of such interventions during the study period.

Control Group: Routine intervention as typically provided in primary care

We have chosen to standardise the provision of the nurse intervention to avoid potential bias from considerable variation in the type and standard of help provided across the range of local GP practices. The control intervention will be modelled on

best-practice intervention in primary care, derived from discussions with GPs and Practice Nurses and incorporating national guidelines [14] and NHS materials (e.g. *Raising the issue of weight gain* [27]). We conducted a survey of weight management interventions in a range of general practice surgeries. GPs typically provide brief advice followed by referral to a practice nurse. A minority of practices uses dieticians but in the current climate they tend to be phased out. Practice nurses have sometimes though not always received one-day training in weight management and provide one off sessions or sessions with a degree of follow-up, either optional or scheduled, over two to eight weeks. In about half of the practices the nurses also refer patients to local community-based physical activity programmes. The control intervention will be modelled on the more intensive end of the spectrum, which is still routinely practicable across GP surgeries. Participants will receive weight management intervention from a trained study nurse in 4 sessions delivered over 8 weeks. The initial session will take 20-30 minutes; the follow-up session may be briefer, as per usual practices. The intervention will include advice on (1) **Diet** (e.g. eat at least five portions of a variety of fruit and vegetables each day in place of foods higher in fat and calories; eat breakfast; watch the portion size of meals and snacks, and how often you are eating) and (2) **Activity** (e.g.make enjoyable physical activities part of everyday life; minimise sedentary activities; and build activity into the working day). Clients will receive information about local exercise provision and where 'exercise on prescription' types of interventions are available. They will also receive relevant vouchers and referrals. This advice will be supported with written materials currently used within the NHS including *Why weight matters* and *Your weight your health* [22] and referrals to community physical activity programmes. Where appropriate, clients will also be given information about orlistat and advised to see their GP if they wish to use it as part of their weight-loss programme. The control group will also have their weight monitored at 6 and 12-month follow-up visits. Clients will not be restricted from using any other weight loss intervention (including pharmacological treatment if their GP believes this is appropriate) during the study. They will, however, be asked to report on the use of such interventions during the study period.

Monitoring of intervention fidelity

For the WAP intervention the Chief Investigator (Dr McRobbie) will attend five sessions led by each advisor (two in the early phase of the trial and then quarterly) and formally check the conduct of the session against the counselling protocol to provide feedback to the advisors and record fidelity of the intervention. Dr. McRobbie will also attend five sessions of the control intervention (two in the early phase of the trial and then quarterly) and check the conduct of the session formally against the counselling protocol to provide feedback to the nurse and record fidelity of the intervention.

4.5 Schedule of Assessment

The schedule of assessments is shown in table 2.Since this is a pragmatic trial the use of concomitant treatments will be allowed in both arms. Information on the use of concomitant treatments (including the use of commercial weight loss programmes and pharmacotherapy) will be collected at all follow-up sessions. If the two groups differ in the type or amount of concomitant treatment they access, this will be controlled for in data analysis.

Trial measures

Patient descriptors

At screening (week -1), the study staff will record basic demographic information (age, gender, ethnic group, educational qualification), weight, height, waist circumference, health status, and history of attempts at weight loss.

Primary outcome: Weight at 12 months
The primary outcomes will be change in weight over 12 months from enrollment into the study. A researcher that is blind to treatment allocation will measure weight at 12 months.

Secondary outcomes:
Secondary outcomes will include: change in BMI, waist circumference, proportion of participants losing at least 5% of baseline body weight, changes in healthy eating, changes in physical activity and changes in food craving. All measures at 12 months will be collected by a researcher that is blind to treatment allocation.

Process measures
The process measures will include attendance throughout the programme, duration of involvement in the programme (time to drop-out), compliance with individualised tasks including pedometer results, results of knowledge tests, participant feedback on components of treatment at 2, 6 and 12 months (e.g. weekly tasks, new information, group discussion, buddy system), and use of concomitant treatments at 2, 6 and 12 months. Some of these process measures will only be available in the intervention group. Cognitive and procedural variables including ratings of hunger will be collected at treatment sessions. We plan to recruit a larger number of participants in the intervention group than the control group. Nevertheless, the study is not powered to detect significant relationships between all process measures and outcome and so our analysis will be largely hypothesis generating, focusing on the description of relationships between these measures and outcome. For example, calculating mean outcome (and confidence intervals) for those who do and do not improve their exercise levels, relevant knowledge, attend pre-specified number of sessions, use concomitant weight management treatments, etc.

Economic measures
Patients will complete a service use questionnaire to record their use of NHS resources including hospital and primary care services. Costs of attending health care will also be collected. The EQ-5D will be used as a measure of health outcome, with responses converted to QALYs using the area under the curve method. The EQ-5D is a standardised instrument that is applicable to a wide range of health conditions and treatments.

Table 1 – Content of WAP									
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 - 52**
Content	**Preparation**	**WAP Treatment**							**Follow up**
	Assessment Information Measurements (e.g. baseline weight, baseline pedometer steps)	Personalised dietary advice "5 A Day" task Self-monitoring (food diaries and task cards) Information on healthy eating and caloric content of food Calorie tasks and monitoring Information about orlistat and GP prescribing where appropriate Cue management Provision of opportunities for structured exercise Close monitoring and personalised targets to increase exercise levels (from the initial target of 3 x 30 mins moderate intensity exercise per week upwards to 5 x 30 mins per week [28]) Referral to local exercise provision Range of other concrete and verifiable tasks agreed individually with each participant "Buddying" session – increasing support for individuals in the group Coping strategies Boosting motivation Increasing self efficacy								Scheduled weigh-in every month Offered optional weekly weigh ins Maintenance sessions of structured physical activity (increasing target to 5 x 60 mins per week [28])

Table 2: Assessment schedule

Time	W-1	W0	W1	W2	W3	W4	W5	W6	W7	W8	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Informed consent	X																			
Demographics	X																			
Weight loss history	X																			
Height	X																			
Weight*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference		X								X				X						X
Blood pressure		X								X				X						X
Randomisation		X																		
Co-morbidities	X																			
Concurrent medications	X													X						X
Pedometer use**			X	X	X	X	X	X	X	X										
International Physical Activity Questionnaire [29]	X									X				X						X
Food diary use**			X	X	X	X	X	X	X	X				X						X
Weekly tasks (e.g. increase fruit and vegetable intake, increase exercise, monitoring television and computer use)**				X	X	X	X	X	X	X										
Food knowledge assessment	X			X**					X**	X**				X						X
Food craving inventory [30]		X	X			X				X				X						X
Three Factor Eating Questionnaire [31]		X								X				X						X
EQ-5D		X												X						X
Use of health services questionnaire		X												X						X
Participant feedback										X				X						X
Adverse events			X	X	X	X	X	X	X	X	X**	X**	X**	X	X**	X**	X**	X**	X**	X

W=week, M=month

*Weight will only be measured at months 3,4,5 and 7, 8, 9, 10, and 11 in the intervention group **Intervention group only

4.6 End of Study Definition

The study will finish when the last recruited participant has completed their 12-monthfollow-up visit.

4.7 Subject Withdrawal

Subjects will only be withdrawn if they withdraw their consent to participate.However data already collected will be used in the final analyses.

4.8 Data Collection and Follow up for Withdrawn Subjects

All data will be collected on paper CRFs and then entered into the study database. Participants who wish to withdraw from the study will be asked if they would consent for follow-up at 6 and 12 months.

5 Pharmacovigilance

There are no investigational medicinal products used in this study. However participants may be taking medicines, including weight loss medicines, prescribed by their GP.

Participants will be asked to report any adverse events since their last contact with study staff.

5.1 General Definitions

6.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities.

6.1.2Serious Adverse Event (SAE)

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered medically significant by the Investigator

5.2 Investigators Assessment

6.2.1 Seriousness

The Chief/Principal Investigator responsible for the care of the patient, or in his absence an authorised medic within the research team, is responsible for assessing whether the event is serious according to the definitions given in section 6.1.

6.2.2 Causality

The Investigator must assess the causality of all serious adverse events in relation to the trial treatment according to the definition given

6.2.3 Expectedness

The investigator must assess the expectedness of all SAEs according to the definition given. If the SAE is unexpected and related, then it needs immediate reporting.

6.2.4 Severity

The Investigator must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

5.3 Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

5.4 Notification and Reporting of Serious Adverse Events

6.4.1 Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe. For further guidance on this matter, please refer to Appendix 2

5.5 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of theCI toinform the sponsor and Main Research Ethics Committee (via telephone) of this event **immediately**.

The CI has an obligation to inform both the Main Ethics Committee**in writing within 3 days**, in the form of a substantial amendment.The sponsor (Joint Research and Development Office [JRO])must be sent a copy of the correspondence with regards to this matter. For further guidance on this matter, please refer to Appendix 2

5.6 Annual Safety Reporting

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the sponsor. Please see appendix 2 for further information.

5.7 Overview of the Safety Reporting Process/Pharmacoviligance responsibilities

There will be no pharmacovigilance monitoring for this trial however adverse events, if any, will be recorded at each visit and reported as per the sponsor's requirements outlined in section 6.6.

6 Statistical Considerations

6.1 Primary Endpoint Efficacy Analysis

The efficacy analysis (change in weight from baseline) will be conducted at 12 months after enrolment into the study.

6.2 Secondary Endpoint Efficacy Analysis

Secondary analyses will also be conducted at 12 month after enrolment into the study. However analyses will also include end of treatment, and 6 month time points.

6.3 Safety Endpoints

There are no safety endpoints for this trial

6.4 Sample Size

A clinically significant effect can be achieved with 3-5 kg weight loss in obese people.[33]
We assumed that WAP would increase weight loss by 2.6kg compared with usual care (WAP 3kg vs. usual care 0.4kg) for participants available for follow-up at one year, and that there would be no difference in weight loss between treatment groups for participants not available for follow-up. Assuming that 50% of participants in both treatment groups were available for follow-up at one year, the difference in weight loss between groups would be 1.3kg (WAP 1.5kg vs. usual care 0.2kg). Assuming a standard deviation of 3 in both treatment groups, and a 5% two-sided significance level, we would require 112 participants in each group to detect this mean difference with 90% power. Our estimate of 50% loss to follow-up is conservative and based on international experience in this field and existing data from similar underprivileged and highly mobile populations and interventions.

To account for potential clustering effects due to group treatment in the intervention arm, assuming a mean cluster size of 18 and an intra-cluster correlation coefficient of 0.05, a total of 208 individuals will be required in the intervention arm. The same power can be achieved with 108 in the control arm and 216 in the intervention arm which we have increased to 110 in the control arm and 220 in the intervention arm to give an allocation ratio between the two arms (2:1) which can be expressed in whole numbers. Thus we require a total of 330 individuals for the entire study.

6.5 Statistical Analysis

The main analysis for each outcome will use intention-to-treat (ITT) principles, meaning that all participants with a recorded outcome will be included in the analysis, and will be analysed according to the treatment group to which they were randomised. P-values will be two sided, and the significance level is set at 5%. The primary outcome (change in weight) will be analysed using a mixed-effects linear regression model, and will include a random intercept for nurse or group. An exchangeable correlation structure for weight at different follow-up time points (e.g. 6 months, 12 months) will be used. This analysis will adjust for baseline weight, age, gender, ethnicity, smoking status, and GP practice.

6.5.1 Change from planned analysis

In version 1.0 of the trial protocol, we specified we would use a baseline-observation-carried-forward approach (BOCF) for dealing with patients with missing weight data during follow-up. This approach assumes that all those who were lost to follow-up returned to their exact baseline weight. Whilst this approach has been commonly used in other randomised controlled trials, it is problematic because it will provide biased estimates of the treatment effect when this assumption is incorrect (i.e. when participants do not return to their exact baseline weight when they fail to show up to their 6 or 12 month appointment) [32]**.** In addition, BOCF will often lead to an inflated type I error (false-positive) rate as it tends to underestimate the standard error for the treatment effect (due to ignoring the within-patient variability in weight when imputing using BOCF [32]**.** This is particularly problematic in the SWAP trial, as it is unlikely that all participants who are lost to follow-up will return to their baseline weight; in many cases, we would expect them to gain weight. Cross-sectional and prospective cohort studies show that individuals gain weight over time, with an average weight gain per year of 0.5kg to 1kg [33].

We will therefore use a mixed-effects linear regression model for the primary analysis. This analysis method provides unbiased estimates of treatment effect and correct type I error rates provided the data is missing-at-random (MAR); that is, that the probability that a participant is lost to follow-up depends on either their previous weight measurements (e.g. their weight at baseline and 6 months if they are lost-to-follow-up at 12 months), and baseline patient characteristics.

This strategy of analysis has been widely recommended in the presence of missing outcome data [32]. We made the decision to change analysis methods before we had any access to the trial data, or ongoing trial results, and therefore there is no risk of bias associated with this decision.

6.6 Economic Analysis

The economic component of the study will involve an incremental cost-effectiveness analysis of WAP over and above routine advice/usual care. The costs of each study arm will be calculated, including the time of health care professionals delivering care, equipment and materials used in the interventions, and overhead costs. Patients will complete a service use questionnaire to record their use of NHS resources including hospital and primary care services. The incremental cost of the WAP intervention over and above routine care will be calculated, and combined with the incremental effectiveness to derive cost-effectiveness measured in QALYs. In order to allow for the skewness typically encountered with cost data, both costs and outcomes will be

bootstrapped and data used to construct cost-effectiveness acceptability curves to show the probability that WAP is a more cost-effective intervention than routine care. A literature review will be conducted to assess the relationship between weight loss outcomes and quality of life, and consequently changes in weight loss outcomes will be transformed into health utilities to estimate the potential quality-adjusted life years (QALY) gains for patients in WAP and usual care to derive an incremental cost per QALY.

7 Data Handling & Record Keeping

7.1 Confidentiality

Confidentiality

Subjects' personal data will remain confidential, and will be handled, processed, stored and destroyed according to the terms of the Data Protection Act 1998.

Participants will be asked to complete the standard WAP questionnaire and the additional questionnaires required for this study. We will not request any medical information about participants from their other doctors (hospital or general practitioner). All information will be kept confidential, just as is normal for people attending the Weight Management Clinic. We will inform participants' GPs, with their consent, of their participation in the study. Copies of all documents sent regarding the current study will be kept in the study master file at 2 Stayner's Road, E1 4AH.

Only study staff and representatives of the sponsor or regulatory authorities will have potential access to view study data that could be linked to patient identifiable data

All data on the CRFs and in the database will be pseduonymised and not contain any identifying information.

7.2 Study Documents

- A signed protocol and any subsequent amendments
- Sponsor Self-Monitoring template for the trial team to complete on a regular basis as detailed by the Monitoring section
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethicssubmissions/approvals/correspondence
- CVs of CI and site staff
- Laboratory accreditation letter, certification and normal ranges for all laboratories to be utilised in the study
- Delegation log
- Staff training log
- Site signature log
- Patient identification log
- Screening log
- Enrolment log
- Monitoring visit log

- Protocol training log
- Correspondence relating to the trial
- Communication Plan between the CI/PI and members of the study team
- SAE reporting plan for the study
- Copies of questionnaires

7.3 Registration and Case Report Form

Registration form

Participant demographic and details will be collected using the standard WAP treatment registration form (see screening form v1.0). These will be completed by participants and kept securely and separately from the CRF.

Case report form

The CRF was developed by Profesor Peter Hajek, Katie Myers, Sarah Snuggs and Dr Hayden McRobbie.

The elements of the CRF include:

- Eligibility/exclusion criteria checklist
- Visit details
- Study questionnaires
- AEs page
- End of study form

CRFs will include the following data: participants' demographic and clinical details, weight, height, waist circumference, health status, blood pressure, history of attempts at weight loss and various process measures as detailed in section 4.5. .All CRFs, food diaries, and questionnaires will be pseudonymised and stored separately from patient identifiable data. Pseudonymised and patient identifiable data will be stored securely at 2 Stayner's Road, E1 4AH accessible only to the SWAP study team.

Trial staff will enter all pseudonymised data from case report forms, diaries and questionnaires onto an electronic,MS Access , password protected, bespoke database, with incorporated full audit trail. This database will be stored on a password protected QMUL network. All patient identifiable data will be held on a password protected, bespoke, database with full audit trail and stored on a stand-alone, non-QMUL networked PC stored in the SWAP study offices. The PCTU data manager is the database programmer and data manager for the trial.

Both study staff and participants will complete the CRFs at each visit.

7.4 Record Retention and Archiving

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years. For trials involving BLT Trust patients, undertaken by Trust staff, or sponsored by BLT or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre which is based at 9 Prescot Street. Site files from other sites must be archived at that external site and cannot be stored at the Modern Records Centre.

7.5 Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

7.6 Clinical Governance Issues

8.6.1 Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee must be obtained and subsequently submitted to the JRO to obtain Final R&D approval.

7.7 Quality Control and Quality Assurance

8.7.1 Summary Monitoring Plan

The PCTU will be responsible for monitoring and audit of the study. The PCTU AQA manager will draft a monitoring /audit plan prior to study initiation which will consist of a combination of remote and on-site monitoring. A risk assessment of the study will be conducted by the PCTU QA manager and CI which will inform the frequency of monitoring and audit visits. The PCTU will request that the CI/trial manager completes the "PCTU self-monitoring template" at agreed frequencies as outlined in the monitoring plan and the PCTU QA manager may also carry on-site audit/s. In addition, all copies of completed monitoring reports and audits will be reviewed by the PCTU QA manager who will also follow up any findings. When all corrective/preventative actions have been resolved all reports will be sent to the sponsor and study team for review and filing in the sponsor study file and trial master file.

8.7.2 Audit and Inspection

Auditing: Definition "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.
2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
5. Projects may be randomly selected for audit by an external organisation.

Internal audits will be conducted by a sponsor's representative

7.8 Non-Compliance

(A noted systematic lack of both the CI and the study staff adhering to SOPs/protocol/ICH-GCP, which leads to prolonged collection of deviations, breaches or suspected fraud.)

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the JRO will agree an appropriate action, including an on-site audit.

8 Trial Committees

We will convene a **steering committee** for this trial. The members of this group will be

- Dr Vicky Hobart (Chair, Public Health Consultant)
- Dr Simon Coppack (Consultant physician)
- Dr Clare Grace (Obesity Research Dietitian)
- Professor Luke Vale (Health Economist)
- Dr John Stappleton (Independent Statistician)
- Dr Hayden McRobbie (PI)
- Professor Peter Hajek (Investigator)
- Ms Tania Szendeffy (Lay member and Service User)

The Trial Management Committee (TMC) will comprise the following people

- Dr McRobbie
- Professor Hajek
- Katie Myers
- Sarah Snuggs
- Amanda Douglas (City and Hackney PCT)
- Sandy Smith (PCTU)
- Professor Sandra Eldridge (trial statistician)

Every six months, there will be a full meeting of the team including the members not based in QMUL (4 team meetings will be teleconference). The meeting will be arranged according to the project milestones (please see details below). The team will provide a progress report to the trial steering group and NIHR. The TMC will meet every month.

9 Publication Policy

Study data will be collected and held by the study investigators. Data analyses will be undertaken independently of the study funders.

A paper will be written for publication in a peer-reviewed journal.

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11 Appendices

Appendix 1: Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the	Main REC with a copy to be sent to the

			following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	sponsor