DEUS pilot study

Diet and Exercise in Uterine Cancer Survivors: Student Study

Full Title of the trial	Randomised, Controlled, Pilot Clinical Trial to assess the feasibility of a healthy eating and physical activity program in endometrial cancer survivors
Version and date of the protocol	Version 5.0, 12 October 2015
Sponsor	University College London (UCL)
Active intervention	Eight 90-min weekly group sessions about healthy eating and physical activity focusing on self-monitoring, goal setting, and rewards. The group will be followed-up at three months upon completion of the intervention.
Control group	Usual care
Phase of trial	Phase 2
Trial sites	UCLH, Barts Health

Study Management Group

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1. Summary

Title:	Randomised, Controlled Pilot Clinical Trial to assess the feasibility of a healthy eating and physical activity program in endometrial cancer survivors
Short title:	Diet and Exercise in Uterine Cancer Survivors (DEUS) pilot trial
Intervention:	Shape-Up: A manualised eight-week weekly group intervention about healthy eating and physical activity for cancer survivors.
Phase of trial:	Phase 2
Objectives:	Primary: Assessing the feasibility of the overall trial procedures. Secondary: Obtaining variance estimates for clinical outcome measures to be used in a larger-scale RCT.
Type of trial:	Phase II, individually randomized, controlled, two-site, pilot trial in endometrial cancer survivors
Trial design and methods:	Eligible volunteers will be randomized into either intervention or control group (usual care).
Trial duration per participant:	Approximately six to eight months for each participant.
Estimated total trial duration:	15 months.
Planned trial sites:	University College London Hospitals NHS Foundation Trust and Barts Health NHS Trust
Total number of participants planned:	64 (32 participants per arm)
Main inclusion criteria:	Endometrial cancer survivors who have been diagnosed the previous three years and completed all treatment.
Statistical methodology and analysis:	Sample size was based on the feasibility outcomes that include recruitment, compliance, and retention rates. Analysis for the secondary outcomes will be exploratory, as the study is not powered to detect differences.
Trial registration	To be registered at ClinicalTrials.gov

2 Introduction

2.1 Background

Endometrial cancer is the most common gynaecological cancer in developed countries with more than 75% of the patients surviving for at least five years. In the UK, more than 8000 women are diagnosed each year with endometrial cancer (ONS, 2014).

Low physical activity, poor diet and obesity are risk factors for the development of endometrial cancer (WCRF, 2013). A growing body of evidence suggests that they may be linked with quality of life after cancer treatment (Koutoukidis et al., 2014). While the evidence on the impact of post-diagnosis health behaviours on endometrial cancer survival is scarce, of low quality, and inconsistent (Koutoukidis et al, on preparation), evidence from other cancer sites suggests that similar factors that affect cancer development may also influence survival (Boyle et al., 2013, Richman et al., 2013, Bradshaw et al., 2014, WCRF, 2014). Thus, recommendations for cancer survivors include healthy eating, physical activity, and maintaining a healthy weight (Rock et al., 2012). However, only about 1% of endometrial cancer survivors seem to meet the current fruit and vegetable, physical activity, and non-smoking recommendations; while 57% meets only the non-smoking recommendations, and 22% meet none of the recommendations (von Gruenigen et al., 2011). This is in line with the National Diet and Nutrition Survey data demonstrating an overall low dietary quality in the UK (NDNS, 2014). Therefore, most survivors remain at high-risk for obesity related diseases.

These behaviours exist despite cancer diagnosis being perceived as a "teachable moment" (Demark-Wahnefried et al., 2005). Capitalising the "teachable moment" of cancer, behaviour change interventions in high-risk populations might be more effective than those targeting the general population (McBride et al., 2000, NICE, 2014b). Indeed, cancer survivors want better information after treatment (Armes et al., 2009, Nicolaije et al., 2012) for informed decision-making and for taking control over their lives with confidence. A combination of short consultation times and lack of skills may generate generic responses and limit the ability of the medical team to individually tailor disease prevention guidelines. This is reflected by lack of relevant discussions between the survivors and the health-care professionals in the presence of cardiovascular risk factors, like obesity and hypertension (Weaver et al., 2013). Therefore, feasible and effective interventions are needed to promote implementation of the aforementioned recommendations.

2.2 Rationale

Theory-based behaviour change interventions from the USA suggest that improving diet and physical activity is safe, acceptable, and feasible and can help cancer survivors improve their quality of life (von Gruenigen et al., 2012, Demark-Wahnefried et al., 2012, Mosher et al., 2013). In contrast, there are only limited studies to support these data in the UK to allow generalisability of these results. The available feasibility trials have targeted survivors of other cancer groups and have demonstrated promising results in behaviour change and both psychological and physiological outcomes (Grimmett et al., 2014, Saxton et al., 2014).

These studies support both the feasibility and effectiveness of behavioural interventions in cancer survivors. However, the majority of these interventions were long-term and resource intensive which may render them inappropriate for wide dissemination. Furthermore, these interventions may not be fully applicable to other cancer groups given the in between differences in long-term treatment effects.

Importantly, adherence to the lifestyle intervention strongly correlates with quality of life outcomes in cancer survivors (Winger et al., 2014) and ceasing the intervention reduces the rate of improvement in outcomes (Demark-Wahnefried et al., 2012). We now understand the mechanisms of behaviour change interventions better. Systematic reviews have shown that self-monitoring of behaviour may improve diet and activity outcomes. Other promising techniques included facilitate social comparison, action planning, goal setting, provide information about the consequences, provide feedback on performance, provide rewards, time management, behaviour relapse prevention, use of follow-up prompts, problem solving, and plan social support. (Michie et al., 2009, French et al., 2011). These techniques fit well within the theoretical context of self-regulatory theories, including Control Theory (Carver and Scheier, 1982) and Social Cognitive Theory (Bandura, 2004). Guidelines suggest that individually-tailored strategies, like "self-monitoring of behaviour and progress, stimulus control, goal setting, social support, assertiveness, cognitive restructuring, reinforcement of changes, and relapse prevention" are effective behaviour change components (Cavill and Ells, 2010). NICE guidance suggests addressing "problem solving, goal setting, how to carry out a particular task or activity, planning to provide social support or make changes to the social environment, self-monitoring of weight and behaviours that can affect weight, and feedback on performance" (NICE, 2014b).

2.3 Preliminary work

The intervention is based on the Shape-Up eight-week weight management programme developed by the charity Weight Concern. This programme is based on "Social Cognitive Theory" (Bandura, 2004) and "Control Theory" (Carver and Scheier, 1982). A version of this program has been favourably evaluated in terms of acceptability, physical, and psychological outcomes (Rapoport et al., 2000). The focus of the programme lies on self-control, self-efficacy, and relapse prevention. Behavioural techniques will include self-monitoring of behaviour with the use of food and physical activity diaries, behavioural goal setting, action planning, graded tasks, problem solving, self-reward, and review of behavioural goals. It will also provide information about health consequences and emotional consequences, pros and cons, behavioural practice, habit formation, reducing exposure to cues for the behaviour, behaviour substitution, associative learning, distraction, social support (unspecified), demonstration of behaviour (for resistance exercises), instructions on how to perform the behaviour (for resistance exercises), and reframing (Michie et al., 2013). A version of Shape Up for the general population is currently used in North Essex. It shows positive results in adoption of health behaviours and successful modest weight loss; with 96% of 422 respondents recommending it as a weight management programme. It is also being run in the borough of Camden – part of the population pool for the current intervention – as part of the local Joint strategic needs assessment (Camden, 2013).

We will tailor this programme (Shape-Up for Cancer Survivors) to help endometrial cancer survivors improve their diet, activity pattern, and, manage their weight. To do so, we have run focus groups and individual interviews with endometrial cancer survivors to explore their attitudes, barriers, and facilitators for diet and physical activity. They provided information about the accompanying motivational text. Furthermore, they were presented with the original Shape-Up and gave structured feedback on the context and format of the booklet. Secondly, an expert panel will convene to inform the tailoring of the manual. Thirdly, the new manual will be produced and endometrial cancer survivors will give feedback on it. Their feedback together with feedback from the pilot trial will inform the production of the manual for the larger trial.

2.3.1 Qualitative data

Focus groups (n=5 and n=3) and individual telephone interviews (n=8) with endometrial cancer survivors discussed topics about attitudes, barriers of, and facilitators for healthy eating and physical activity and acceptability, ideal timing, and delivery of lifestyle

interventions. Results were analysed using thematic analysis and were then applied in the COM-B model. This is a systematic framework for characterising behaviour change interventions proposing that behaviour (B) is shaped by interactions with physical and psychological capability (C), environmental and social opportunity (O), and reflective and automatic motivation (M). It demonstrates acceptable reliability in characterising obesity-targeted interventions (Michie et al., 2011). By using this framework, we aimed to consider the whole picture of potential diet and activity determinants and effectively choose the most promising of them to target in the intervention.

Most survivors reported changes towards a healthier lifestyle after treatment. Results suggested that survivors were motivated towards healthier choices by reflecting on health consequences and enjoying engaging in these activities. Treatment bowel effects shaped the capability of consuming specific foods, like chilli and high-fibre foods and of engaging in some exercises. Both physical and social opportunities influenced healthier eating and activity. We also presented the Shape-Up manual to them. Their overall feedback was positive, and they provided us with rich and thoughtful comments and suggestions according to their needs and preferences.

2.3.2 Expert panel

An expert panel including a nutrition research student, a specialist dietitian, a health psychologist, two academic nurses working with cancer survivors and a dietitian from Weight Concern will comment on the proposed changes of Shape-Up based on the feedback of the qualitative work and the current nutrition and physical activity recommendations for cancer survivors. This will aid further refinement of the booklet.

2.3.3 Production of the new booklet

Based on the above, the current booklet will be produced by the end of February 2014, about a month before the commencement of the first intervention group. While the currently used version is focusing on weight loss, the new version will primarily be focused on healthy eating and physical activity. A stronger focus on resistance, flexibility, and balance exercises will be added. Furthermore, specific recommendations about radiotherapy and chemotherapy treatment effects will be added to the booklet. It will also include a short section on sleep hygiene (HMS, 2007) given indications of disturbed sleep patterns in cancer survivors (Rock et al., 2012). Endometrial cancer survivors who will participate in the steering group of the trial will then review the booklet. Their feedback together with the

feedback from the participants in the trial will be used to finalise the content and format of the manual.

2.4 Aim

The aim of this pilot study is to assess the feasibility of a manualised healthy eating and physical activity programme in endometrial cancer survivors post active treatment.

The main research question is: "Is it feasible to design a randomised controlled trial that will assess if the Shape-Up programme is more effective than usual care in improving the health-related quality of life of endometrial cancer survivors?".

2.5 Study objectives

2.5.1 Primary research objective

The primary research objective is to assess the feasibility of the overall trial procedures.

2.5.2 Secondary research objectives

Secondary research objectives will include:

1. To obtain variance estimates for clinical outcome measures to be used in the large-scale RCT. These will inform primary outcome and measure of the larger trial and, subsequently, the sample size calculation.
2. To assess willingness of the clinical staff to recruit participants
3. To assess willingness of eligible participants to be randomised
4. To examine potential adverse effects of the intervention
5. To perform a basic economic analysis with the aim to inform the larger trial
6. To assess reasons for loss to follow up.
7. To access the overall acceptability of the intervention

2.6 Study Design

The DEUS pilot trial is an eight-week, two-arm, individually randomised, controlled pilot trial comparing the use of the Shape-Up programme to usual care. According to MRC guidance for complex interventions (Craig et al., 2008), this is a Phase 2 feasibility study. Randomisation will be performed with minimisation using a 1:1 allocation.

3 Methods: Participants, interventions, and outcomes

3.1 Study setting

Participants will be recruited from the outpatient clinics of two major academic hospitals in London; University College London Hospitals NHS Foundation Trust, and Barts Health NHS Foundation Trust. We chose those hospitals based on their statistics for endometrial cancer patients from the National Cancer Registration Service. The intervention program will be delivered in the University College Hospital Macmillan Cancer Centre, located in central London. All assessments will take place at the Institute for Sports, Exercise, and Health, University College London.

3.2 Selection of Subjects

3.2.1 Inclusion criteria

1. Women aged >18 years (no upper age limit)
2. Women diagnosed with endometrial cancer (C54.1) within the previous 36 months
3. Women who are able to understand spoken and written English

3.2.2 Exclusion criteria

1. Women with stage IVB (metastatic) endometrial cancer (any metastasis beyond the pelvis)
2. Women on active anti-cancer, and/or palliative treatment
3. Women with second primary cancer
4. Women who lack mental capacity to decide to take part in the study and to participate in it (upon clinical team's judgement in accordance with the Mental Capacity Act 2005 Code of Practice 2007)
5. Women with severe depression (upon consultant's judgement based on the DSM-IV criteria)
6. Women unavailable for longitudinal follow-up assessments
7. Women who participated in a professionally delivered weight loss or exercise program during the previous 6 months
8. Women with a WHO performance score 3-4 (Oken et al., 1982)

These criteria comply with all but the disability category in the NICE Equality Impact Assessment for lifestyle weight management services (NICE, 2014b).

3.3 Interventions

3.3.1 Active intervention

A nutrition researcher (DAK), trained by Weight Concern, who has clinical experience with cancer survivors, will facilitate the Shape-Up sessions following the standardised and scripted Shape-Up protocol. An extra trained provider will attend the intervention meetings to aid with facilitation (i.e. to help in an unexpected emergency and to monitor the timing) but will not participate in the discussion. S/he will deliver the intervention in case of unpredictable circumstances. In addition to usual care, cancer survivors in the intervention group will be assigned to groups of eight to ten. The allocation to groups will be on a first-come first-served basis to avoid delays in delivering the intervention in randomised participants, which may increase dropout rates. These groups will meet every week for eight weeks and each session will last approximately 90 minutes.

The currently used Shape-Up is a manualised healthy lifestyle programme developed by psychologists and dietitians that helps service users to learn new behaviours and manage their weight (Weight_Concern, 2013). The intervention is under the tier 2 weight management services (DH, 2013) and in line with NICE guidance on lifestyle weight management services (NICE, 2014b) and individual approaches in behaviour change (NICE, 2014a). The tailored version's major focus is on strategies for improving healthy eating and physical activity and its minor focus is weight management. Furthermore, it has specific information about management of treatment effects after treatment. Behavioural approach techniques are following those of the original Shape-Up. The course is structured as follows:

- Session 1: Preparing to Shape-Up
- Session 2: Keeping to a regular eating pattern
- Session 3: Physical activity
- Session 4: Eating a balanced diet
- Session 5: Keep an eye on food serving sizes
- Session 6: External triggers
- Session 7: Internal triggers
- Session 8: Food labels and the Shape-Up Change plan

The format of the intervention is self-help and peer education. Importantly, participants need to work at home between sessions about achieving the goals they decided during the week. Each week, participants will be asked to read part of the Shape-Up Guide in preparation for the following week's session. Week by week, new concepts will be introduced to help group members make lifestyle changes that will eventually lead to improved wellbeing. Each session will take roughly the following form:

- A brief review of the previous week's session, and how everyone got on during the week
- A volunteer-led discussion: A volunteer introduces a topic for the session and the group discusses
- The new topic
- Break
- Introduction of another topic, by the facilitator
- Round-up, and preparation for the next session:
  - choosing a volunteer to run part of the next week's session
  - giving out tasks for the coming week
  - each person mentions one thing that they felt they have personally obtained from this session and/or their goal(s) for next week.

Participants should set their first SMART goal (Specific, Measureable, Attainable, Relevant, Time-bound) for regular eating after the second session, and the first SMART goal for physical activity after the third session. After each of the subsequent sections, participants should set at least one eating and one activity SMART goal. At the fifth session, each participant has to bring in a weighed portion of a particular food. At the end of each session, participants will be asked if they envisage any circumstances to prevent them from participating in the next session. Those who will miss sessions will receive standardized e-mails or mail with the content of the session so that they can keep up with the program. Participants in the intervention group will be asked not to discuss the intervention with fellow patients in an attempt to minimize contamination and avoid leakage of intervention details between patients in the study arms.

3.3.2 Control group

Participants in the control group will be offered usual care until the three-month follow-up. Quantifying usual care is challenging, but our preliminary qualitative study suggested that 14/15 survivors did not received any unsolicited advice about healthy eating

and physical activity from their health care professionals after treatment. Some survivors prompted them for potential advice but many did not receive satisfactory advice. Some of them were referred to Macmillan resources about healthy lifestyle (unpublished data).

During the course of their participation in the trial, we will contact the participants only for the assessments. After the completion of the 24-week follow-up, we will have a five-minute discussion with the control arm participants. We will use the following statement:

> "Eating well and being active following cancer treatment is important for your overall health and well-being. The effects of diet, excessive weight, and physical activity on womb cancer survival and recurrence are not clear, but we do know that these factors influence heart disease. Normal weight, healthy eating, and physical activity are linked with higher ability to do everyday tasks (like lifting a box from the floor), and higher quality of life in womb cancer survivors. Being physically active and eating healthy foods together with no smoking can add both years in your life and life in your years."

The statement focuses on information about health consequences targeting reflective motivation, because this emerged from the qualitative data as the most important reason to follow a healthy lifestyle. We will give them the WCRF ""Healthy living after cancer" booklet; a brief self-help manual. By providing only this information, we aimed to match the currently offered usual care as accurately as possible but also meet ethical standards.

3.4 Outcome measures

3.4.1 Primary outcome measures

The primary outcome measures for the pilot trial are:

1. The recruitment rate
2. The adherence (attendance of the sessions)
3. The retention rate (complete follow-up)

The main criterion to judge the pilot study successful and a large-scale RCT feasible using the recruitment measure was recruiting (consenting) 30% of the eligible participants (32 participants per 110 estimated to be eligible in each centre during the 6 month recruitment). This target seemed reasonable based on our previous experience and similar rates indicated in the literature (Daley et al., 2007, Korde et al., 2009).

3.4.2 Secondary outcome measures

1. Clinical outcomes to be used in the large RCT:
    I. Health-related quality of life
    II. Diet quality
    III. Physical activity
    IV. Hand-grip strength
    V. Weight
    VI. Body composition
    VII. Shape-Up evaluation questionnaire
    VIII. Health care services use

The primary measure to be used in the large-scale RCT is projected to be a change in global quality of life as measured by the EORTC Quality of Life Questionnaire Core 30. However, the choice of measure will be finalised after taking into account the results of the feasibility study.

2. Willingness of clinical staff to recruit participants will be assessed with a short one-to-one interview with the clinicians at the beginning of the third month of recruitment
3. The number and type of potential adverse effects of the intervention will be recorded during the intervention and at the follow-up interview (e.g. gastro-intestinal complaints from a change in diet)
4. Costs relevant to recruitment, screening, implementation and follow-up will be calculated. We will also measure retrospectively health care resource use and cost them at national rates
5. Reasons for none participation and loss to follow up will be tracked for each participant lost and merged in similar categories
6. At 8 and 24 weeks follow-up, a purposive sample (30%) of participants in each arm will be qualitative interviewed to assess their participation in trials, the acceptability of the intervention and the materials, their overall experience of the program, including potential facilitators or barriers to adherence. All participants who may dropout will also be approached for an interview. These data will help with the refinement of the intervention.

3.5 Participant Timeline

Figure 1 demonstrates the flow chart of the study. Table 1 shows the assessments at each time point.

Figure 1 Flow-chart

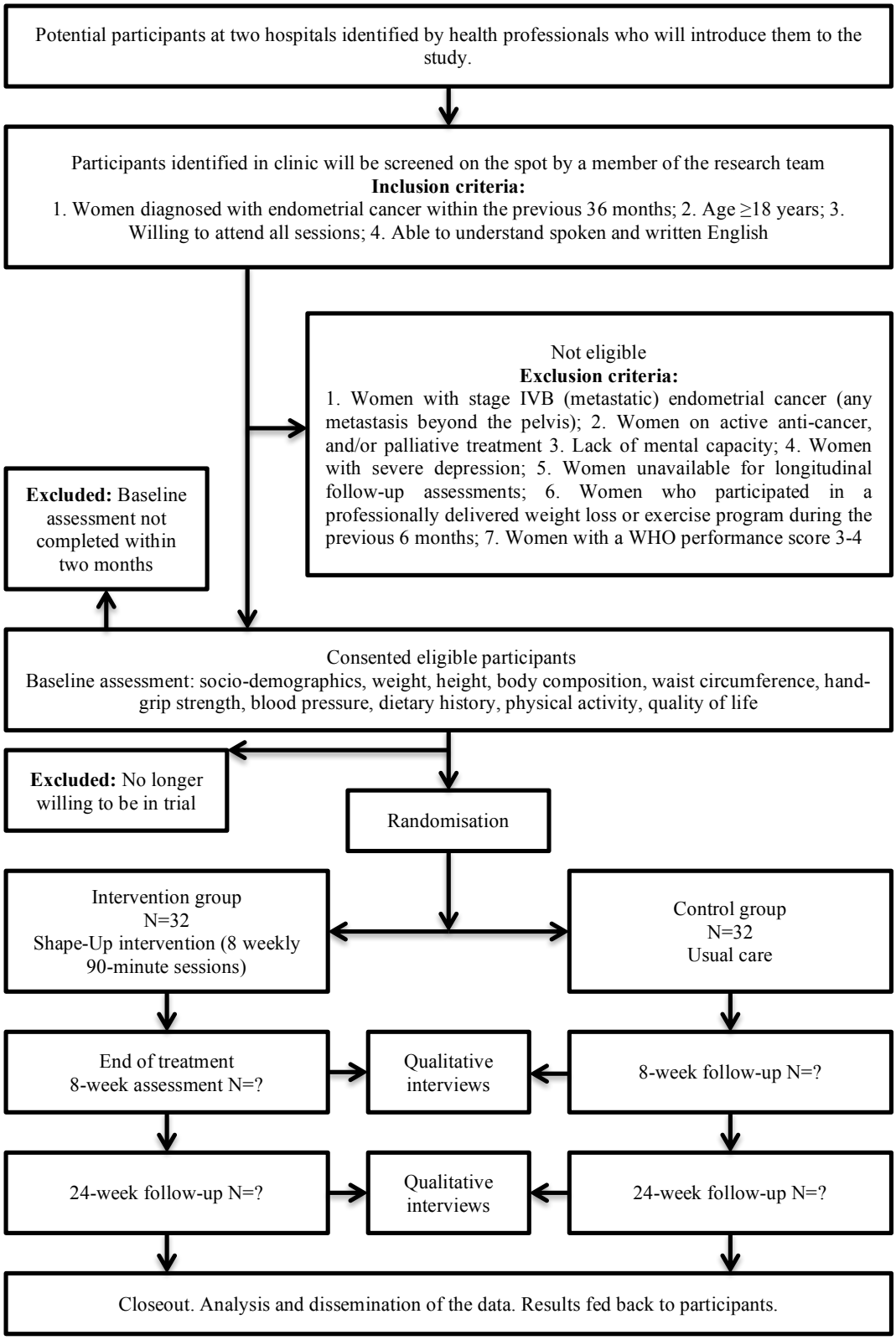

Table 1 Study assessments at specific time points

			Study Period				
	Staff member	Pre-study screening /consent	Baseline	Allocation	Post-allocation		
Time point			Week -3	Week 0	Week 1	Week 8	Week 24
ENROLMENT							
Eligibility screen	Interviewer	X					
Informed consent	Interviewer	X					
Allocation	Study Coordinator			X			
INTERVENTIONS							
Shape-Up	Interviewer						
Usual care	Interviewer						
ASSESSMENTS							
Socio-demographic data	Interviewer		X				
EORTC-QLQ-C30	Interviewer		X			X	X
EORTC-QLQ-EN34	Interviewer		X			X	X
Dietary assessment	Interviewer		X			X	X
Physical activity	Interviewer		X			X	X
Weight	Interviewer		X			X	X
Height	Interviewer		X				
Body composition	Interviewer		X			X	X
Waist circumference	Interviewer		X			X	X
Hand-grip strength	Interviewer		X			X	X
Blood pressure	Interviewer		X			X	X
Shape Up evaluation	Interviewer					X[2]	X[2]
Control group input	Interviewer						X[3]
Qualitative interviews	Interviewer					X	X
Health care resource use	Interviewer						X
EQ5D-3L	Interviewer		X				X
Serious adverse report form	Study Coordinator	As needed throughout the protocol					

[1] Closeout for the control group will be at week 40 after receiving the intervention.

[2] Only the intervention group [3] Only in the control group

3.6 Sample size

Although this is a feasibility study, we have specified a sample size for examining the recruitment rate. Sample size was estimated using the A'Hern's approach for one-stage phase II trials (A'Hern, 2001). Regarding recruitment, a success rate approximately of 30% or more would be desirable, for the trial to be considered feasible. A success rate of 15% or less would be unacceptable. The trial will test the null hypothesis H_0 that recruitment is ≤15% against the alternative hypothesis H_1 that recruitment is ≥30%. With a 5% level of significance and 90% power, 64 participants are needed so that we can estimate whether the percentage of participants with successful recruitment is ≤15% or ≥30%. If we can recruit 15, or more, participants, we can reject the null hypothesis.

A trial of 64 (32 per arm) will be sufficient to test the above hypothesis and allow decisions to proceed to a Phase III trial. This sample size will also allow for rich feedback from the participants to be used for the optimisation of the procedures and the materials in the large study. Lastly, it will allow a certain degree of precision in calculating standard deviations for the secondary outcomes that will be the key design parameters for the main study (Teare et al., 2014).

3.7 Recruitment

Potential participants will be recruited from outpatient clinics at the two hospitals. A member of the clinical team will initially identify potential participants from clinic lists during the weekly pre-clinic meeting. Individual patients will be considered for participation by the member of the clinical team primarily responsible for their care i.e. their consultant or nurse specialist. If during the course of a usual clinic appointment, the clinician believes that the patient is suitable for study participation (i.e. not too ill or distressed) they will ask the patient if they would be interested to hear about the study. Bright colour reminders will be attached at the cover of the patient notes before their appointment to enhance consultants' engagement with recruitment. If the patient is willing to hear about the study, following verbal consent, they will be introduced to the researcher attending the clinic. The researcher will discuss the study, answer any questions the patient might have and provide them with the study information sheet and a consent form that they may take away. During this meeting, the researcher will check that the patient fulfils the eligibility criteria for the study. Congratulation letters will be sent to the two sites for good recruitment each month (Treweek

et al., 2013) and thank you letters to individual clinical staff. Figure 2 shows the planned weekly recruitment rate during the 30 weeks recruitment period.

The clinical teams in the two hospitals will also identify potential participants that have been treated in the two recruitment sites but have been followed up in the local sites or that they have been discussed in the multidisciplinary team meeting but referred for treatment to local hospitals. GP's will be contacted in advance of sending the invitation letter to potential participants to ensure the latter are alive and well. A invitation letter signed by the consultant will be sent to these women together with the participant information sheet and an opt-in form or the barriers to participation survey (Mills et al., 2006). The researcher will contact the women interested, discuss the study, answer any questions they might have and check that they fulfil the eligibility criteria for the study.

The initial plan was to use the same mechanism as the one with the outpatients clinics to identify and approach hospitalised participants being at the end of their treatment to inform them about the study. This was decided by following recommendations for ideal timing for approaching endometrial cancer survivors by those who participated in previous focus groups. However, this extra strategy was not implemented, as the recruitment rate was already acceptable.

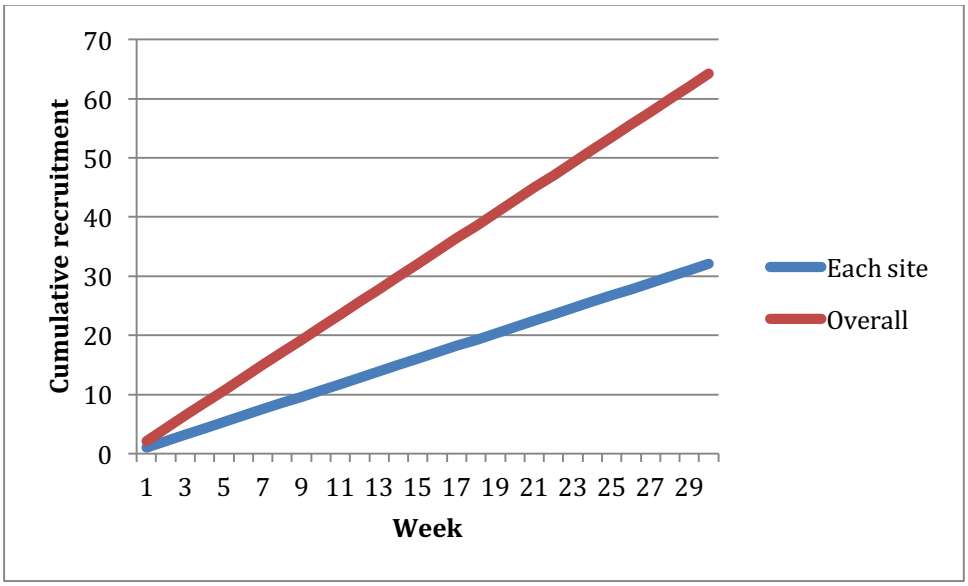

Figure 2 Planned weekly recruitment rate

4 Assignment of interventions

4.1 Sequence generation

Those who will sign the consent forms will be individually randomised with a 1:1 allocation to receive either the Shape-Up intervention or usual care through minimisation. This allocation process is recommended in small trials to ensure balance between groups (Altman and Bland, 2005). The two stratified variables are age (cut-off: 61 years) and obesity (BMI cut-off: 30kg/m^2) being strong prognostic factors of all the clinical outcome measures. The age cut-off was chosen as this is the median age of diagnosis for endometrial cancer (DeSantis et al., 2014) and BMI cut-off is the WHO cut-off to classify obesity.

Initially, the first participant will be randomly allocated a treatment by flipping a coin. For each participant following, the allocated treatment will be determined by RJB based on summing the number of participants in each group with the same characteristics (age and BMI). The subsequent person will be allocated to the group with the smaller total. If totals are the same then the person will be allocated using simple randomisation. A 20% random element will be included in the algorithm (Altman and Bland, 2005).

4.2 Allocation concealment mechanism

The allocation concealment scheme will involve sequentially numbered opaque sealed envelopes that will be kept by the researcher (RJB) who generates the allocation sequence and cannot be physically reached by the rest of the research team. The researcher will maintain no contact with the rest of the group about the allocation concealment until enough participants are allocated in both groups, so that a Shape-Up group can be performed.

4.3 Implementation

The researcher (DAK) who will perform the baseline assessment will feed back to another researcher (RJB) the BMI and the age of the recruited participant in a randomisation form in a sealed opaque envelope. The latter will run the algorithm and allocate the participant. This process will continue until enough participants are allocated in both groups to run a Shape-Up group. For example, week 0 will start after 8 participants are allocated to each group. The three next Shape-Up groups will also run with 8 participants each (total 32). Apart from the researcher who will assign participants (RJB) to the two groups, all research team members will be blinded to group allocation until a Shape-Up group can be run (e.g. the first 16 participants have been randomised). At that point, participants will also be notified in

which group they have been allocated. Thus, randomisation will be conducted without any influence of the research team.

4.4 Blinding

Due to the nature of the intervention, neither participants nor the researchers delivering the intervention can be blinded. The independent trained assessor of the 8-week follow-up will be blinded to treatment allocation. S/he will be provided with the contact details of all participants with no data about their treatment allocation and s/he will request from the participants not to disclose their allocation treatment. The assessor of the 24-week follow-up (DAK) will not be blinded given resource constraints.

5 Data collection, management, and analysis

5.1.1 Data collection methods

Participants will come for their one-to-one (baseline, week 8, week 24) assessment at the Institute of Sport, Exercise, and Health at University College London, which will last about an hour. Participants will complete the widely used, reliable, and validated European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire and (QLQ-C30) (Aaronson et al., 1993) and Endometrial Cancer Module (QLQ-EN24) (Greimel et al., 2011). Time to completion for the 54 quality of life items should be less than 15 minutes. We will use the Stanford 7-Day Physical Activity Recall (Sallis et al., 1985), a 15-min interview-based tool to assess physical activity by recalling activities the previous seven days, which has shown acceptable reliability and validity (Bonnefoy et al., 2001) and is responsive to change. Thirty randomly selected participants will be invited to wear a reference measure (activPAL, PAL Technologies, Glasgow, Scotland) for seven days before their assessment, so that the validity of the Stanford 7-Day Physical Activity Recall can be estimated in this population.

Dietary intake will be assessed with one 30-minute weekday 24-hour dietary recall (Subar et al., 2012), using a free, self-administered, web based research tool, called ASA24, developed by the National Cancer Institute. ASA24 consists of a website where participants record what they ate and a researcher's website used for data analysis. Using nutrition and statistical software, we can, then, calculate how well their diet fits to recommended healthy eating patterns. We have piloted the dietary assessment with cancer survivors showing high acceptability and feasibility. Diet quality will be calculated by the Alternative Healthy Eating

Index (AHEI) score produced by the 24-hour dietary recall. The AHEI is a score that measures how well diet fits to recommended healthy eating patterns. AHEI was selected because it strongly predicts survival, captures the whole diet, and the intervention targets many dietary behaviours that are reflected in the index (e.g. fruits and vegetables, whole grains, processed meat, salt, etc.) (Chiuve et al., 2012). Similar indices have effectively been used in previous trials (Clutter Snyder et al., 2007). An updated version of the DINE questionnaire (Roe et al., 1994), together with questions about alcohol, fruits, and vegetables will be used to assess the agreement with the 24-hour dietary recall, as it may be used as a potential measure in the large trial. Completion time of the 42 diet questions should be about 15 minutes.

Weight to the nearest 0.1kg and body composition will be assessed using MC980 multi-frequency segmental body composition analyser. This is a simple step on machine, not unlike bathroom weighing scales. Subjects will be barefoot and will hold another pair of electrodes, rather like a pair of handlebars, attached to the base. The electrical impedance between feet and hands will be used to calculate body fat content. This is because the small electrical current generated by the bioelectric impedance analyser can penetrate lean tissue and cells but not fat tissue, depending on the electrical frequency at which the measurements are made. Body composition is automatically calculated from an algorithm developed by the manufacturer.

Using standardised protocols, height will be assessed with a stadiometer to the nearest 0.1cm and handgrip strength using a handgrip dynamometer. Waist circumference will be measured with a measurement tape to the nearest 0.1cm at the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid auxiliary line (WHO, 2008). Blood pressure will be measured using an automated sphygmomanometer with the participant seated comfortably for 5 min before measurement and the arm supported at the level of the heart. All measurements will be taken twice. The final value will be calculated as the mean of the two measurements. Physical measurements should last about 15 minutes in total. Participants will also complete six socio-demographic questions. They will also report their full contact details in separate forms. Overall, the baseline and each subsequent assessment should last about 90 minutes. The final methods were agreed among the researchers after evaluating the relevant literature (NOO, 2011) and available resources. Researchers will be receiving standardised training with all measurements.

At the end of the program, the intervention-arm participants will be given an evaluation form to complete at home and return by post in a business return envelope. This

practice may reduce the social-desirability bias associated with feedback provision. The 18 questions of the evaluation form are based on a previously validated evaluation form (Queensland_Health, 2014) and will form the basis for the structure of the semi-structured interviews. Participants will also complete at all time points the Shape-Up questionnaire; ten items in a 5-likert scale (from "Strongly disagree" to "Strongly agree") that reflect the overall goals of the programme (e.g. I am in control of my food portion sizes, I can set effective eating and activity goals and work towards them). To assess contamination, the control arm will complete at the 24-week follow-up two more questions assessing the input about diet and physical activity they received from external sources.

At the last follow-up, all participants will also complete a 10-min health care resource use 6-item questionnaire (Gordon et al., 2012), asking about their potential appointments with their GP or other health care professional, hospital or other health care services, and medication use since the beginning of the intervention. Quality-of-life adjusted years (QALYs) will be assessed with the validated 6-item EQ5D-3L (Rabin and de Charro, 2001).

After they have taken enough time to decide about their participation, individuals will be asked their reason(s) for none participation with prompts based on a meta-analysis of barriers to participation in clinical trials (Mills et al., 2006). They will be informed that they do not need to disclose this information. The same questions and prompts will be asked to participants who decide to withdraw from the study. Participants may withdraw from the study for any reason at any time. However, we will make every reasonable effort to follow the participants for the entire study period. Participants will be notified at enrolment that, if they choose to opt-out, they will be contacted for feedback that may help in refining the intervention. If a follow-up appointment in the laboratory is not possible after three consecutive contacting attempts, a researcher will try to visit the participants at home for the interview or undertake this by telephone. Participants will not be aware of this option beforehand to maximise the chances for having the physical measurements.

5.1.2 Data management

This study has been registered for Data Protection at UCL Records Office. The Reference Number is: Z6364106/2014/12/14. All participating researchers and NHS staff who will be involved in the study will act to preserve patient confidentiality according to the Data Protection Act 1998 and the NHS Code of Confidentiality. All computers used to collect or store data will be password protected. All original data will be stored in compliance with the Data Protection Act.

All paper and voice records will be transferred to a university computer at UCL and encrypted after being checked for any inconsistencies. The data entry screens will resemble the completed paper forms. The option to select a value from a list of valid codes and a description of each code will be available where appropriate. A second researcher will review records for accuracy. In case that any discrepancies are found, all data will be re-entered. Qualitative data will be transcribed verbatim and checked against the recordings for accuracy. Other relevant files (e.g. addresses where the personalised analysis will be sent after the study) will be transferred to a university computer at UCL and encrypted. The encryption key (i.e. password) will be kept separate to all other study material as described below. These files will only be listened to by the relevant researchers (those directly involved in transcription and analysis of these data). Data will be identifiable by the participant's unique study ID only and any reference to the participant's name will not be included in the transcripts. The code sheet linking the participant's name to their study ID will be kept separate from all other study materials in i) a locked fire−proof filing cabinet in the Department of Women's Cancer in areas with limited access and ii) a password protected electronic file on a UCL server. In accordance with published guidelines, patients' personal details (e.g. name, full address) will not be recorded on any study data collection instruments. Each participant will be allocated a numeric ID as they enter the study, and by which they will be known throughout. This identifier will be recorded on all study documents. All data will be analysed in an anonymous format. All results will be anonymous and reported in such a way that individuals are not identifiable.

5.1.3 Statistical methods

Except the recruitment trial, the study is also examining adherence rate and retention rate (complete follow-up).

Adherence is defined as the proportion of engaged participants attending at least one of the last three sessions of the intervention. Engaged participants are those who have attended at least two sessions of the intervention. Best practice guidance suggests that programmes should be commissioned if at least 60% of participants are likely to adhere (DH, 2013). A success rate approximately of 85% or more would be desirable. That means that 85% or more of the engaged participants in the intervention group will attend at least one of the last three sessions of the intervention. A success rate of 60% or less would be unacceptable. The trial will test the null hypothesis H_0 that adherence is ≤60% against the alternative hypothesis H_1 that adherence is ≥85%. With a 5% level of significance and 90%

power, 27 participants are needed so that we can estimate whether the percentage of participants with successful adherence is ≤60% or ≥85%. If 21, or more, participants have a successful adherence, we can reject the null hypothesis.

Regarding retention (attendance of both follow-up sessions) rate, a success rate approximately of 75% or more would be desirable. A success rate of 60% or less would be unacceptable. The trial will test the null hypothesis H_0 that complete follow-up is ≤60% against the alternative hypothesis H_1 that complete follow-up is ≥75%. With a 5% level of significance and 80% power, 62 participants are needed so that we can estimate whether the percentage of participants with complete follow-up is ≤60% or ≥75%. If 44, or more, participants have a complete follow-up, we can reject the null hypothesis.

Recruitment, adherence, and retention rates will be reported as proportions with 95% CIs. The target lower 95% confidence limit for the following outcomes are:

- Recruitment: 15% or more
- Adherence: 60% or more
- Retention: 60% or more

Continuous variables will be reported by descriptive statistics (non-missing sample size, mean, standard deviation, median, maximum and minimum). Categorical variables will be summarised using frequencies and percentages. Analysis of covariance (ANCOVA) will be used to compare the intervention arm against the control arm in an exploratory way, as the study is not powered to detect differences. All participants will be analysed using the intention-to-treat strategy (Moher et al., 2010). Adjustment for BMI and age will be performed with linear regression in continuous outcomes and logistic regression in binary outcomes. Missing outcome data will be imputed using multiple imputations. Reasons for missing data will be documented and missing data will be quantified. The Statistical Package for Social Sciences (SPSS, Chicago, IL) version 21 will be used for the whole data analysis. Adverse events will be reported descriptively. The level of statistical significance will be set at 5% for the primary outcome measures. We will also calculate intra-class correlation coefficients (ICCs) to measure clustering within groups and k coefficient of variation between groups.

Qualitative data will be analysed using thematic analysis. Two interview transcripts will be independently coded by two researchers (DAK, RB). These lists will be discussed and amended between researchers upon agreement until relevant themes will emerge. DAK will insert the code lists into NVivo software version 10 (QSR International Pty Ltd, 2014).

NVivo version 10 (QSR International Pty Ltd, 2014). Two random transcripts will be recoded by an independent researcher to ensure consistency.

6 Monitoring

6.1 Data monitoring

Given the short length of the intervention, the low risk of harm (see below) and the short follow-up of the intervention, an external Data Monitoring Committee will not be needed. For the above reasons, an interim analysis will not be performed. Nonetheless, the researchers recruiting, implementing, and assessing the intervention will provide a report to the monthly meeting of the research team about study progress, including potential adverse effects, and missing data.

The UCLH/UCL/Royal Free Joint Research Office, on behalf of UCL as Sponsor, will monitor and conduct random audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the Department of Health Research Governance Framework for Health & Social Care (April, 2005), and in accordance with the Sponsor's monitoring and audit policies and procedures.

6.2 Harms

The participants have undergone treatment for endometrial cancer that may include surgery, radiotherapy and chemotherapy. Consequently, they may feel unwell and/or fatigued due to their disease and/or treatment. Participation in each 60-minute assessment and in the 90-min sessions is not expected to increase risk or burden, however, as this may require some time and energy the interview will be conducted in an environment easily accessed by the participants. Participants will have the option to withdraw from the study at any time, without giving a reason and without affecting the quality of the care they receive. The researcher can allow breaks if needed. It is expected that removal of shoes for the body composition measurement could be a minor burden. Some people may find talking about weight and their body composition measurements (e.g. fat content) embarrassing but the session is not anticipated to cause distress. However, the researcher will approach these topics in a sensitive manner. Appointments and groups will be organised at convenient times whenever possible.

Shape-Up is a very low intensity intervention that should be suitable for most people with health conditions, such as diabetes, heart failure, and high blood pressure. Observed changes are unlikely to be associated with unintended or adverse effects (NICE, 2014b). The

proposed modifications to lifestyle i.e. dietary and physical activity changes are in accordance with published guidelines for cancer survivors (Rock et al., 2012). The lifestyle program will generally recommend a diet high in fruits, vegetables, beans and whole grains; foods with high fibre content. It is anticipated that some participants will not be able to tolerate some of those foods due to their radiotherapy and chemotherapy bowel effects. As those foods differ among participants and across the cancer trajectory for each participant, alternative foods will be recommended accordingly. Furthermore, participants will complete a safety pre-activity questionnaire based on the "American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors" before undertaking physical activity (Schmitz et al., 2010). If contra-indications arise, participants will be advised to seek medical advice before engaging in higher levels of physical activity.

It is not anticipated that the assessments, the intervention, or the interviews will cause any distress but if a participant becomes distressed during the study sessions, they can terminate the session whenever they wish. Should the session cause discomfort to the participant, she has the right to take a break, ask questions and terminate her participation. In the unlikely event that the participant becomes distressed, the researcher will follow guidelines provided, as follows:

- Be empathetic, understanding, and non-judgmental in all patient interactions
- If still distressed, offer to contact partner/carer/close other;
- If requested, provide feedback (the content of which will be agreed with the respondent) to the health care professional that is primarily responsible for their care.

All potential adverse effects and unintended effects of the intervention will be reported, as they constitute one of the secondary outcome measures.

6.3 Auditing

The sessions will be audiotaped and the recording will be coded against the Shape-Up Facilitators Manual for assessing intervention delivery and treatment receipt by a researcher experienced in health psychology and behaviour change (Borrelli, 2011). The researcher (DAK) will also audio-record a short debriefing after each session. A member of the research team will randomly perform undisclosed site visits in two assessments and one intervention session to assess protocol fidelity. The Shape-Up evaluation form, which includes a self-assessment of the gained skills and an evaluation of the facilitator, will supplement fidelity assessment. Results will be used to improve protocol fidelity, if needed. Data presented in the

fortnightly meeting of the research team will be reviewed to determine completeness and accuracy. If a problem is identified, the team will assist in resolving the issue.

7 Ethics and dissemination

7.1 Research ethics approval

The study protocol and documents will be reviewed and approved by the relevant sponsor and NHS REC with respect to scientific content and compliance with applicable research and human subjects regulations.

7.2 Protocol amendments

Potential protocol modifications will be formally approved by the REC before being implemented. The amendments will be communicated to the trial registries and outlined at the dissemination of the trial.

7.3 Consent

If a patient were interested to hear about the study, the clinician will introduce the women to the researcher who will explain the study and what participation would involve. After they have had adequate time to consider their participation and ask any questions the researcher will obtain signed informed consent from patients wishing to take part.

Patients treated in the two hospitals who are interested in participating can contact the researcher directly. After the initial contact, the research student will contact their clinical team to assess their eligibility and inform the patients if they do (not) meet the criteria for participating. Patients will be posted or mailed the study information sheet and consent form, whichever more convenient. To take part in the study all participants will need to consent for themselves.

7.4 Confidentiality

All data will be handled according to the Data Protection Act 1998 and the NHS Code of Confidentiality as described in section 7.1.2. Identifiable data will be securely kept for 12 months after the end of the trial.

7.5 Declaration of interests

None declared.

7.6 Access to data

Only the investigators will have access to personal identifiable data. These data will not be disclosed to any other person. Non-identifiable data may be looked at by individuals from University College London, from regulatory authorities or from the NHS Trust, where it is relevant.

7.7 Post-trial care

7.7.1 Archiving

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that she will archive the study master file at UCLH/ for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents for twenty years and in line with all relevant legal and statutory requirements.

7.7.2 Insurance

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Enrolled participants are covered by indemnity for negligent harm through the standard NHS indemnity scheme.

7.7.3 Intellectual Property Rights

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to

effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL. Each participating site agrees to, at the request and expense of UCL, execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

7.8 Dissemination policy

The period between the closeout of the study and the release of the study results will be kept to the minimum possible. An interval of three to four months is expected to be needed before submitting results to relevant journals. Before submission, the research team will review the papers accordingly. The primary papers of the study will report the primary outcome measures of the study. The results will be disseminated regardless of the magnitude or direction of effect. All investigators will be authors of future publications with authorship eligibility to follow international guidelines (International Committee of Medical Journal, 2003). The study results will also be disseminated to the clinical teams in the participating centres, and the participants.

A completely de-identified dataset will be disseminated to a relevant data archive for sharing purposes. The interval for this will be no later than three years after the closeout of the study.

8 Roles and responsibilities

8.1 Trial Management Group

AL and MTK conceived the study. DAK, AL, RB and MTK initiated the study design and RM helped with protocol development and implementation. AL and MTK are the grant holders. MB provided statistical support and DAK is conducting primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

DAK will be responsible for the day to day monitoring and management of the study reporting directly to AL.

AL has overall responsibility for the project, including:

- Managing resources to maximise likelihood of completion within budget and the available time period.
- Ensuring appropriate systems are in place to assure high quality of every aspect of the research; - making best use of the Trial Steering Group which she will chair.
- Oversight of analysis, writing up, reporting and disseminating the results (e.g. designation of appropriate authors for publications and timely outputs).
- Ensuring the research is conducted in accordance with research governance.
- Acting as supervisor to DK.
- Regular meetings with members of the core research team (DAK; RB; TMK; RM).

The two CIs (AL, RM) will oversee the identification of potential participants in each site. RJB, and TMK will provide expert advice during the study and with the analysis and interpretation of the results. Prof. Steve Morris will provide advice regarding the health economic aspects. RJB will be responsible for intervention assignment, and auditing the study including review of the records for accuracy.

8.2 Trial Steering Committee

An external Trial Steering Committee that will meet at regular intervals during the study will oversee the trial. Prof. Allan Hackshaw, Deputy Director of Cancer Research UK & UCL Cancer Trials Centre will be the Chair of the Committee. The committee will also include two other independent members (Dr. Abi Fisher, Dr. Aleksandra Gentry-Maharaj), the two CIs (AL, RM), the trial co-investigators, and a lay representative.

9 Funding

Completion of this project was funded by the UCL Grand Challenges Scheme (D.A.K.), the Department of Women's Cancer at The UCL EGA Institute for Women's Health and NIHR University College London Hospitals Biomedical Research Centre, London, UK. The funders had no role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The study is funded until October 2016.

10 Discussion

In the UK, only few studies have demonstrated the feasibility of the imperative lifestyle behaviour change in cancer survivors. None of them, however, has involved the growing population of endometrial cancer survivors. The results of this feasibility trial will inform a larger lifestyle trial in cancer survivors to test if the program can help survivors to improve their quality of life. The outcome of the pilot study will be translated as (a) feasible study that should be continued without modifications; (b) feasible study with close monitoring that should be continued without modifications; (c) feasible study with modifications in the protocol; or (d) non-feasible study. The study has the potential not only to help cancer survivors improve their well-being but also to help NHS reduce its cost by potential reduction of the use of its services as survivors will lead a healthier lifestyle.

The current intervention is in accordance with all NICE recommendations about weight management programmes but the length of the follow-up and the inclusion of a "weight-in" at each session (NICE, 2014b), given the feasibility nature of the work and the low focus of the intervention on weight itself, respectively. Furthermore, it is in line with the National Cancer Survivorship Initiative, which envisages a sustainable personalised lifestyle support for cancer survivors with them playing an active part on the decision-making in addition to research on patient-reported outcomes (DH, 2010). We hope that Shape-Up for Cancer Survivors will be disseminated nationally as a low-cost, self-help, group program. The manualised format and the facilitator's guide allow for standardised training for facilitators that could be non-health care professionals, accurate replication and evaluation across settings.

11 Appendices

11.1 Informed consent materials

Attached.

11.2 Leaflet for patient notes

Attached.

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