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Effect of a combined programme of dietary restriction and physical activity on the physical function and body composition of obese middle-aged and older adults with knee OA (DRPA): protocol for a feasibility study

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ABSTRACT

Introduction Knee osteoarthritis (OA) is the most common chronic illness among older adults. Up to the submission date of this protocol, there are no published UK studies reporting the efficacy of a combined intervention programme of physical activity and dietary restriction on the musculoskeletal function of obese older adults with knee OA in spite of the clinical recommendation for exercise and diet for people with knee OA. The aim of this study is to assess the feasibility and acceptability of a combined dietary restriction and physical activity intervention programme and collect preliminary data.

Method and analysis This single-arm intervention study is scheduled to begin in September 2017 and conclude in November 2018. It will take place at the Royal Orthopaedic Hospital (ROH), Birmingham and the School of Sport, Exercise and Rehabilitation Sciences (SportExR), University of Birmingham. Participants will receive a physiotherapy usual care programme for knee OA for 1 month, after which they will continue to exercise in their local gym/leisure facility for 3 months. Participants will also follow dietary restriction throughout the 4-month intervention. Mixed analysis techniques will be used to analyse the quantitative and qualitative outcome measures.

Ethics and dissemination It is approved by ROH R&D Foundation Trust and the Health Research Authority. The Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high-quality peer-reviewed journals.

Trial registration number ISRCTN12906938.

Strengths and limitations of this study

- Mixed-methods data collection to provide detailed information about the combined programme.
- Collaboration with secondary healthcare providers to conduct the study.
- Measurement of outcomes across several domains including biomarkers for knee osteoarthritis to inform the selection of the appropriate outcome measures for a future study.
- Due to limited resources, this will be a single-centre feasibility study.

INTRODUCTION

Knee osteoarthritis (OA) is a major public health problem worldwide and a common condition in older adults due to high incidence and prevalence rates.[1 2] Approximately 3.64% of the global population is affected by knee OA.[3] In 2010, 4.71 million people aged ≥45 years sought treatment for knee OA in England.[4] The impact of knee OA includes pain, decline in physical function, reduced quality of life (QOL) and increased disability.[5]

In addition to advancing age, obesity is also a known risk factor for developing OA and causing disability.[6–10] Obesity increases the negative impact of the disease and patients with arthritis may need surgical intervention to reduce body weight and thereby relieve pain.[7]

In overweight and obese adults, knee OA management should focus mainly on weight reduction.[11 12] The evidence supports a calorie-restricted diet in adults but the optimal method(s) for weight reduction are still varied in terms of intervention length. Introducing a low-calorie diet is challenging in older adults with knee OA because of the need to maintain the appropriate intake of the important nutrients. For example, maintenance of the recommended daily calcium intake is essential for women who may be at risk of osteoporosis.[13] For overweight and obese patients with knee OA, previous studies

have indicated that the ultimate goal of weight loss should be at least 10% of body weight, in order to provide significant pain reduction.[14 15] Recently, a systematic review (SR) recommended that total body weight should be reduced by at least 5% over a period of 20 weeks in this population to experience symptoms improvement.[15]

The European League Against Rheumatism and the Osteoarthritis Research Society International (OARSI) guidelines recommend exercise as a core intervention for knee OA management.[16 17] Patients with mild to moderate knee OA have been shown to benefit from muscle strengthening and aerobic exercises with respect to decreasing pain and improving mobility.[18] In the UK, usual care is considered as the first line of knee OA treatment in clinical practice[19] and its main foci are exercise and advice.[20 21] Exercise intervention may include different types of exercise, for example, strengthening exercise (weight bearing and non-weight bearing), range of motion (ROM) and stretching exercise. Advice may concentrate on the importance of exercise and provide patients with information about pain relief strategies, for instance, analgesics and home heat therapy.[20 21] However, the most effective way of delivering exercise to optimise patient outcome is still unclear, particularly in older people with knee OA.[21] The published literature reports that both aerobic walking and quadriceps strengthening exercises have a positive effect on participants with knee OA and, overall, there is no superiority of one approach over the other.[22]

Combining weight loss and exercise regimens is recommended for older adult patients with knee OA.[23–26] A recent SR investigated the effectiveness of combining physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese older adults with knee OA.[27] Only one pilot study[23] and two trials, the Arthritis, Diet, and Activity Promotion Trial[24] and the Intensive Diet and Exercise for Arthritis[25] were identified. The reviewers concluded that there was unclear quality of evidence for the benefit of combining interventions.[27] To date of developing this protocol, there are no published UK studies reporting efficacy of a combined intervention programme for older adults. As a consequence, there is a need to develop a study incorporating a mixed methods approach to investigate the acceptability, feasibility as well as the efficacy of a combined intervention programme in older adults with knee OA.

The aim of this feasibility study is to assess the feasibility, acceptability and collect preliminary data to inform the design of a definitive trial incorporating a combined intervention programme.

METHODS AND ANALYSIS

Research questions and objectives

This 4-month intervention study aims to answer the central question 'Will the combined intervention programme be feasible and acceptable for the participants and the Royal Orthopaedic Hospital (ROH) physiotherapy staff?'

Additional research questions are formulated:

1. What is the potential for efficacy of the proposed combined intervention programme, as indicated by preliminary data evaluating improvement in outcome measures including: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), body weight, waist circumference (WC), body mass index (BMI), musculoskeletal function including; knee ROM and muscle power, musculoskeletal function including; stair climb and timed up-and-go, pain, QOL and markers of joint remodelling?
2. Are there any associations between changes in body weight, knee pain, BMI and markers of joint remodelling?

Primary objective: Will the combined intervention programme be feasible and acceptable, for the targeted population and the ROH physiotherapy department staff?

Secondary objectives:

1. Assess suitability of main trial measures.
2. Investigate associations between changes in body weight, knee pain, BMI and markers of joint remodelling.

It is hypothesised that the combined programme will be feasible and acceptable either for the targeted population or the ROH physiotherapy department or both. All outcome measures will be assessed for suitability. After 4 months of intervention, it is hypothesised that losing weight will be associated with improvement of knee pain and markers of joint remodelling.

Study design

This is a single-centre feasibility study, consisting of one arm (combined programme of dietary restriction and physical activity) with an embedded qualitative component (focus group for participants and questionnaire for physiotherapy staff).

Study setting

The combined programme intervention and the physiotherapy staff questionnaire will take place within the ROH, Birmingham. Participant assessments and focus group sessions will be conducted at the University of Birmingham (UoB), UK.

Participants

We will recruit 30 older adults (men and women aged ≥45–90 years) with BMI ≥30 kg/m^2. They will have a diagnosis of knee OA (with or without radiographic evidence) and will not be participating in regular exercise more than twice a week. They will be able to understand verbal and written English and be willing to participate and give informed consent for the study. They will be excluded if they have any significant comorbid diseases that would pose a safety threat or impair ability to participate such as coronary artery disease, severe hypertension, peripheral vascular disease, stroke, congestive heart

failure, chronic obstructive pulmonary disease, insulin-dependent diabetes, psychiatric disease, renal disease, liver disease, active cancer other than skin cancer, advanced osteoporosis and anaemia or have had previous acute knee injury (moderate–severe). Additional exclusion criteria are resting systolic blood pressure greater than 200 mm Hg and resting diastolic blood pressure greater than 100 mm Hg, neuromuscular impairments that preclude participating in physical activity, visual, hearing or moderate/severe cognitive impairments as well as unwillingness to modify diet or physical activity patterns or inability to comply with the intervention because of inability to access a gym/local leisure facility, food allergies or reactions to the calorie-restricted diet.

Intervention

The intervention will consist of a single education session, physical activity and dietary restriction components.[28–31]

Educational session

The first physical activity class will be preceded by an educational session lasting for 60 min introduced by a qualified physiotherapist. Information about causes and management of knee OA, importance of exercise and diet and safety considerations will be given as part of physiotherapy usual care for patients with knee OA. Additional information about dietary restriction will be introduced by a clinical dietician in the last 10–15 min of the session. Information in this session is based on the principles of self-management theory,[32–34] self-efficacy theory[35] and the framework of behaviour change[36] and addresses changing lifestyle and coping with pain, stiffness and limited activities of daily living. Participants will have the opportunity to ask any further questions.

Physical activity

Participants will receive a physiotherapy usual care programme for knee OA (moderate intensity stretching and strengthening exercise) in the physiotherapy gym under the supervision of a physiotherapy technician for 1 month (60 min per week); it is based on social cognitive theory and group dynamics.[37] Participants will begin with a warm-up exercise for 5 min around the gym including quadriceps, hamstring and gastrocnemius stretches. The group will split into two small groups working across several work stations on ROM, strength, cardio, gait stations for a further 40 min, for example, cycle ergometer, treadmill, leg press, theraband, inner range quads with band gait work using light hand weights. Sit to stand with medicine ball, marching on a trampette, lunges and extension stretches on step, step overs, tandem walking (eyes open–eyes closed), straight leg raising with weights, hamstring curls with weights, bridging, posterior gluteus medius with band, slight hip abduction and through range quads over the edge of a plinth. Group balance work will be carried out towards the end of the session. Cool down will be completed with stretches. All stations will run for approximately 2 min with additional weights and resistance to be added for progression. All participants will receive a home exercise programme as part of their usual care. Home exercise is based on the National Institute of Health and Care Excellence Guidelines for knee OA.[38] The classes are group based as opposed to individualised. The participants will split into two small groups working across several work stations and will spend approximately 2 min at each station. Each participant will exercise according to his/her ability and progression will be tailored accordingly. Personalisation is based around the individual participants hobbies/interests and Activities of Daily Livings (ADLs) with advice being offered accordingly. Participants will monitor their own symptom levels and modify intensity accordingly and work within their own defined tolerance levels. After 1 month, participants will continue to exercise in their local gyms/leisure facilities for a further 3 months. The study team will assist participants with application for a free (or discounted through funding by the study) gym pass via the Birmingham Be Active scheme. Participants will be provided with a programme of recommended exercises to continue in this setting. The participants will be contacted weekly by telephone to encourage adherence. The first 4 weeks will be the adoption stage where the participants will be educated and supported to change their behaviours and the remaining 12 weeks of the study will be for maintenance.[35]

Dietary restriction

Participants will complete a 3-day food diary and then follow dietary restriction throughout the 4 months of the intervention, aiming for a decrease of 300–500 kcal/day or 500–1000 kcal/day as appropriate to initial BMI. The diet will be planned and modified (if required) by a clinical dietician. Participants will monitor themselves by completing a daily log.

Outcome measures

Qualitative component (feasibility objective)

Feasibility of the combined intervention programme will be measured using a post intervention focus group for participants and a questionnaire for the involved physiotherapy staff. The feasibility outcomes will be based on the categories reported in Bowden *et al*,[39] and listed in table 1.

Focus group

Three focus groups will be conducted at the end of the intervention to explore the participants' knowledge, experience and views about the combined intervention programme.[39–43] The focus group will be audiotaped then analysed. A focus group will be conducted for each group (n=10) at the UoB. The chief investigator (CI) (ASA) will lead the discussion by outlining the purpose of the session and discussing consent and confidentiality. Participants' engagement will be encouraged by asking introductory questions about their previous treatment options for knee OA. An example of the participants' focus group

Table 1 Feasibility measurement categories

Categories	For participants	For physiotherapy staff
1. Efficacy	Do they report benefit?	Do they notice improvement?
2. Adherence	Using sheet for recording their gym sessions	Record participant attendance
3. Adaption	Does the intervention need adaption, for example, time or procedure?	Does the intervention require adaptation?
4. Acceptability	► Satisfaction with programme and outcomes ► Perceived appropriateness ► Expressed interest	► Satisfaction with participants' outcomes ► Intent to use again ► Fit within hospital culture ► Perceived positive or negative effects on their time, gym availability
5. Implementation and practicality	Degree of execution, success or failure of execution ► Positive/negative effects on target participants ► Ability of participants to carry out intervention activities and cost	Amount, type of resources needed to implement ► Factors affecting implementation ease or difficulty, efficiency, speed or quality of implementation
6. Integration and expansion	Do they recommend expanding the intervention to other hospitals?	► Does it fit with the hospital goals and physiotherapy department goals? ► Is cost suitable to organisation wishing to include it? ► Could it be applied in the future and how? ► Any positive or negative effects on the ROH or the department?

ROH, Royal Orthopaedic Hospital.

discussion guide is presented in online supplementary 1. This topic guide will inform exploration of the participants' experiences of the combined intervention. An experienced researcher (ABR, coinvestigator) will be responsible for audiotaping and observing the session, taking notes and overseeing data analyses.

Questionnaire

A mixed questionnaire consisting of open and closed questions has been designed to assess the feasibility of the combined intervention programme.[39 42] The questionnaire consists of 15 items and its design is based on the categories of feasibility (table 1).

Quantitative measures (efficacy objective)

Preliminary data informing potential for efficacy of the combined intervention programme will be collected using:

1. Physical function (WOMAC) scale.
2. Body weight, WC and BMI.
3. Body composition (body impedance analysis).
4. Musculoskeletal function (knee ROM, lower limb muscle power).
5. Physical performance (stair climb, timed up-and-go).
6. Pain intensity (WOMAC pain subscale).
7. QOL (Short Form-36).
8. Blood markers of joint remodelling, including: Adipokines (serum adiponectin and leptin) and for bone turnover; Bone formation (Procollagen I C-Terminal Propeptide (PICP)); Bone (type I collagen) degradation (cross linked C-telopeptide of Type 1 collagen (CTX-1)); Cartilage formation: type IIA collagen N-propeptide (PIIANP), Cartilage (type II collagen) degradation: fragments of cartilage oligomeric matrix protein (COMP) .[44]

These outcome measures were selected based on a previously published SR[27] and OARSI recommendation of performance-based tests to assess physical function of people with knee OA[45] with consideration of the study aims and practical considerations. Physical function WOMAC scale is the planned primary outcome for the definitive study.[46]

Sample size

A formal sample size calculation is not appropriate as one of the study outcomes is to collect data which will inform estimates of SDs for use in a sample size calculation for a future definitive trial. The sample size of 30 participants is based on previous reviews of the literature.[47 48] To ensure a suitably reliable estimate of SDs (to power a future study), sample sizes between 24 and 50 have been recommended.[49 50] This sample size is also recommended by The National Institute for Health Research.[51]

Procedure

Participants will be recruited via the ROH outpatient clinic and the physiotherapy department. Potential participants will be identified by a ROH clinician or senior physiotherapists according to the eligibility criteria. Eligible participants will be provided with a copy of the participant information sheet and a response slip, which will include a telephone number and email address to contact the study team directly and a stamped addressed envelope for those who prefer to respond by post. In

the case of participants who have given blood recently (within the last 3 months), their general practitioners will be conducted by the study team to provide the results. Participants will be invited to attend the School of Sport, Exercise and Rehabilitation Sciences (SportExR), UoB, where the study procedures will be explained in further detail. Participants will be given the opportunity to ask questions and informed consent will be obtained. An approved copy of the participants informed consent form is presented in online supplementary 2. Baseline data will be collected by the study team. Blinded outcome assessment will not be applicable in this study but will be applied in the definitive trial. Participants will be asked to complete a 3-day food diary (weekday and weekend) and to return it by post to a member of the study team (using the stamped addressed envelope provided to them), and a date will be scheduled to begin the exercise classes at ROH. The first class will be preceded by an educational session about knee OA, during which participants will be given the opportunity to ask any further questions. See figure 1 for the DRPA trial flow diagram.[52]

Patient and public involvement

The design of this study has been informed by data gained from several focus groups of older people ≥55 years with knee OA at the Control of Movement and Active Ageing Open Day on 22 June 2016 in the SportExR, UoB.

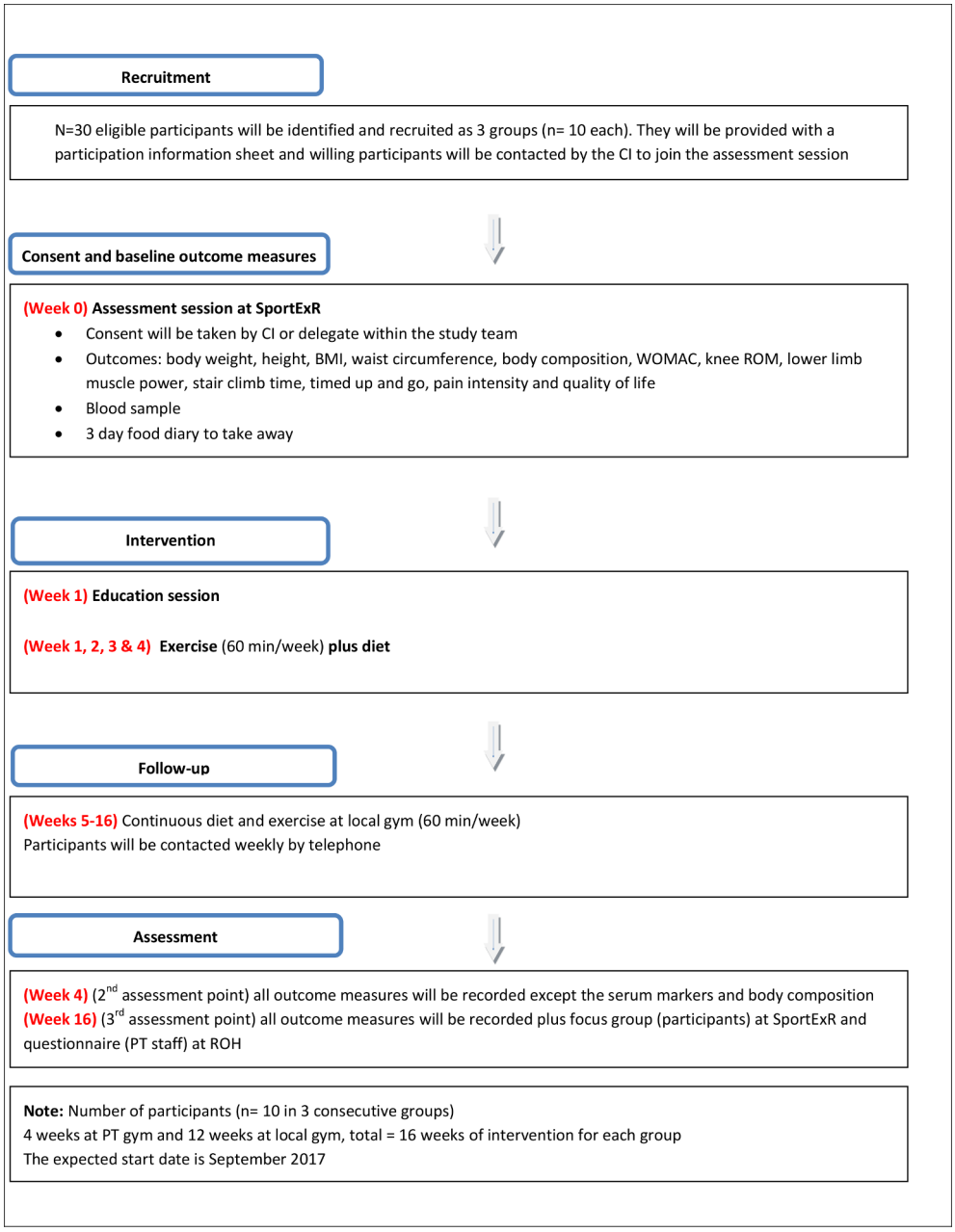

Figure 1 Flowchart of Dietary Restriction and Physical Activity (DRPA) trial flow diagram. BMI, body mass index; CI, chief investigator; PT, physiotherapy; ROM, range of motion; ROH, Royal Orthopaedic Hospital; SportExR, School of Sport, Exercise and Rehabilitation Sciences; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2 Summary of statistical tests

Variable	Form of analysis	How it will be reported	Test
Age (year)	Continuous	M (SD)	Means and SD
Gender	Categorical	Frequency and percentage	Frequency
Height (m)	Continuous	M (SD)	Means and SD
Weight (kg)	Continuous	M (SD)	Repeated measures ANOVA
BMI (kg/m²)	Continuous	M (SD)	Repeated measures ANOVA
WC (m)	Continuous	M (SD)	Repeated measures ANOVA
WOMAC	Continuous	M (SD)	Repeated measures ANOVA
Knee ROM (degree)	Continuous	M (SD)	Repeated measures ANOVA
Lower limb muscle power	Continuous	M (SD)	Repeated measures ANOVA
Physical function (stair climb and timed up-and-go)	Continuous	M (SD)	Repeated measures ANOVA
Pain intensity (WOMAC)	Continuous	M (SD)	Repeated measures ANOVA
Quality of life (SF-36)	Continuous	M (SD)	Repeated measures ANOVA
Body composition	Continuous	M (SD)	Paired t-tests
Markers of joint remodelling	Continuous	M (SD)	Paired t-tests
Associations between changes in body weight, knee pain, BMI and markers of joint remodelling	Continuous	r	Pearson's correlation

ANOVA, analysis of variance; BMI, body mass index; WC, waist circumference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; ROM, range of motion; SF-36, short form-36.

Dissemination

Findings will be presented to members of the public through events held for the purpose of communicating research into ageing, such as the AgeWell event organised for members of the Birmingham 1000 Elders database.

Data analysis plan

Qualitative analysis techniques will be used to address the feasibility objective

The guidelines provided by Kitzinger[40] will be followed to conduct the analysis of data obtained from the focus groups. The phenomenology theoretical orientation[53–55] will use the Krueger[56] and Ritchie and Spencer[57] framework analyses. Open questions from the questionnaire will be analysed similarly.

Quantitative analysis will be used to address the efficacy objective

All data will be entered into a database and analysed using SPSS statistics for Windows, V.21.0. Armonk, New York, USA: IBM Corp. Baseline characteristics will be descriptively summarised using frequencies, means and SD or median and IQRs, depending on the frequency distribution of the data. Baseline characteristics will be compared with postintervention data using SPSS, paired t-tests or repeated measures analysis of variance for interval or normal variables. All statistical tests will be conducted two-sided with an alpha level of 0.05. In addition, closed questions from the questionnaire will be analysed using frequencies and percentages. Details of the selected statistical tests are presented in table 2.

Success criteria will be used to determine the feasibility of the combined intervention programme based on the qualitative and quantitative outcomes.[58–60] The success criteria are presented in table 3.

Data collection, management and monitoring

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Personal addresses, email addresses and telephone numbers will be used to contact participants. Details will previously have been provided by individuals for this purpose, and all details will be kept securely. There will be no electronic storage of personal information, emails will be printed and then deleted. All paper data will be stored securely in a locked drawer. Personal data will be kept for 12 months after the end of the study to allow patient contact for dissemination of results.

Participants will always be identified using only their unique trial identification number on the case report form and correspondence between the participating sites. The investigator will maintain documents in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

Procedure(s) to account for missing or spurious data

Individual data sets will be checked by the CI at regular intervals and any discrepancies highlighted and listed. All missing and ambiguous data will be queried. These will be viewed and discussed by the supervisory team.

Table 3 Success criteria of the combined intervention programme according to the feasibility categories, using the participants and physiotherapy department staff outcomes

Feasibility categories	Participants quantitative outcomes	Participants qualitative outcomes	Physiotherapy questionnaire
	The combined intervention programme will be considered feasible if:	The combined intervention programme will be considered feasible if:	The combined intervention programme will be considered feasible if there is consensus across the PT department staff to support the following points:
1. Efficacy	Significant changes p<0.05 on the planned primary outcome for the definitive study (WOMAC scale) from baseline to 4 months intervention [30]		When they notice any improvement in the participants outcomes and think that the combined intervention programme is better than usual care
2. Adherence	>80% in exercise compliance >80% in dietary compliance[29 30]		Adherence to the classes is similar compared with usual care
3. Adaption		None or just minor changes suggested	The combined programme does not require adaption
4. Acceptability		Participants report (during focus group discussion) that they are satisfied and the intervention programme is fitted with their activities of daily living	They are satisfied with participants outcomes They would support the use of the combined programme The combined intervention programme fits within the hospital culture Delivering the combined intervention programme has not increased their work load
5. Implementation and practicality	<10% missing data in each completed questionnaire (WOMAC and SF-36)[28-31]		They would not need any additional resources to implement the programme There are no factors that may affect the implementation, efficiency, speed or quality of delivery
6. Integration and expansion		Participants recommend the combined intervention programme to other patients	The programme could be applied in future The expansion of the programme would have a positive effect on the PT department and/or ROH The cost of the programme will feasible for ROH and/or other hospital trusts

PT, Physiotherapy; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SF-36, Short Form-36; ROH, Royal Orthopaedic Hospital.

Storage and analysis of samples

Two blood samples (10 mL each) will be taken from each participant, one at baseline and one after completing 16 weeks of intervention to analyse the biomarkers of joint remodelling. If the participant has not given blood in the last 3 months, an extra sample will be taken during the first visit (20 mL) for safety testing. Blood samples for storage will be collected, coded and stored in SportExR for 6–12 months. They will be analysed in the Institute of Inflammation and Ageing, UoB under the supervision of a member of the study team. Collection, analysis, storage and destruction of blood samples will be according to local policy and standard operating procedures aligned to the UoB Quality Management System. Any safety bloods (for those participants who may not have had a blood test within the past 3 months) will be taken from SportExR directly to the laboratories of Queen Elizabeth Hospital, Birmingham.

Monitoring and auditing

This study team will allow monitoring of the study, including access to source documents as requested. The UoB Clinical Research Compliance Team will review at intervals agreed with CI.

ETHICS AND DISSEMINATION

This study was approved.

All changes are documented in the trial site file and communicated with the Research Ethics Committee (REC), lead site, sponsor and funder. As stated in the procedure section, eligible participants will be provided with a participant information sheet and their informed consent form will be given at SportExR. Also, the participation information sheet will be given to the physiotherapy staff and their consent will be taken before completing the questionnaire.

The Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high-quality peer-reviewed journals. The CI owns the data arising from the trial and will analyse, tabulate and prepare a final study report with guidance from the supervisory team. The full study report can be accessed 6 months after completing the trial.

DISCUSSION

The feasibility of the combined intervention programme will be assessed based on several areas of focus.[28] It will be considered feasible if the success criteria in table 3 are met.[30 59 60] If the participants suggest major adaption to the study design, for example, cancelling the education session, the programme will be considered as unfeasible.

This feasibility study will answer the central question of whether a combined intervention programme is feasible and acceptable. It is hypothesised that a combined intervention programme of dietary restriction plus usual care for obese older adults with knee OA is feasible and acceptable to the ROH physiotherapists. Participants will experience benefits and the therapists will support the usual care programme plus weight loss in this specific sample. All outcome measures including WOMAC, body weight, WC, BMI, musculoskeletal function (knee ROM and muscle power), musculoskeletal function (stair climb and timed up-and-go), pain, QOL and markers of joint remodelling will show evidence of improvement due to reduction in the participants' body weight, inflammation and pain that which lead to overall improvement in function. It is hypothesised that there will be associations between changes in body weight, knee pain, BMI and markers of joint remodelling.

Participants may find that following designed plans of diet more useful than following general advice. This study has based on several factors to improve compliance with the exercise in the remaining 12 weeks of the intervention such as knowledge, providing facility to local gym and weekly phone call.[61 62] The laboratory test will provide exploratory data for new biomarkers in knee OA. However, the results of this study will add clinical evidence to knee OA management in older adults with obesity and it may inform the provision of usual care of knee OA.

The qualitative component of the study will allow the participants to express their views and impressions about the combined intervention programme and this will inform about the optimal body weight reduction methods and the best way of delivering exercise to achieve better outcomes. Also, the views of physiotherapy staff will be invaluable to confirm whether a combined intervention programme of dietary restriction and usual physiotherapy care is feasible in a hospital setting and could be incorporated into usual care.

Amendment

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor will submit a valid notice of amendment to the REC for consideration.

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Contributors ASA prepared the first draft of the manuscript that has been reviewed and approved by CAG before circulating it to all coauthors. ABR, GB and FP had critically revised the manuscript and provided their input before submission for publication. All the coauthors have been involved in the study design and developing the protocol.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study is approved by the West Midlands-Solihull Research Ethics Committee, REC ref: 17/WM/0122, protocol number ERN_16-1432; RG_17-024, and V.6.0 approved on 10 January 2018 by HRA and the ROH R&D Foundation Trust.

Provenance and peer review Not commissioned; externally peer reviewed.

Author note The protocol was developed by the CI and her supervisor and reviewed by the coinvestigators which include qualified medical staff at ROH. This is a low-risk study which has received peer review from the student supervisors plus independent peer review by ROH R&D Dept and an academic colleague (Dr Leigh Breen, SportExR).

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