Research Protocol for IRAS application - LJMU sponsored research

FULL/LONG TITLE OF THE STUDY:
A high-PRotein Mediterranean diet and resistance Exercise for cardiac rehabilitation: a pilot randomised controlled trial

SHORT STUDY TITLE/ACRONYM

The PRiME Study

RESEARCH REFERENCE NUMBERS

IRAS Number	256927
Sponsor reference number	
ClinicalTrials.gov number	
REC reference number	

This protocol has regard for the HRA guidance

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to adhere to the signed LJMU's Sponsorship CI declaration.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: Date: 30/09/2019

Name: (please print): Fatima Perez de Heredia

SPONSOR STATEMENT:

Where LJMU takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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KEY STUDY CONTACTS

Chief Investigator:	Dr Fatima Perez de Heredia Benedicte, 01512312003 F.PerezDeHerediaBenedicte@ljmu.ac.uk
Investigators:	Richard Kirwan, 07565427663, r.p.kirwan@2018.ljmu.ac.uk Dr Ian Davies, 0151 231 5290, I.G.Davies@ljmu.ac.uk Dr Tom Butler, 01244 511660, t.butler@chester.ac.uk (University of Chester) Prof Gregory Lip, gregory.lip@liverpool.ac.uk (University of Liverpool) Prof Dick Thijssen, 0151 904 6246, D.Thijssen@ljmu.ac.uk (Liverpool John Moores University) Dr Joseph Mills, 0151 600 1991, joseph.mills@lhch.nhs.uk (Medical Director for Advanced Life Support, Liverpool Heart & Chest Hospital NHS Trust)
Sponsor:	Liverpool John Moores University
Funder:	Liverpool Clinical Commissioning Group Research Capability Funding has been approved. 0151 296 7000, enquiries@liverpoolccg.nhs.uk
Chief Investigator Signature:	

There are no potential conflicts of interest.

TRAINING / CPD

Name of investigator (add new row if required)	Date completed LJMU REC training	Date completed LJMU research integrity training	Date completed research governance training	Date completed HTA training (or NA)	Date completed other training (add new column if required)
Dr Fatima Perez de Heredia				15/11/2017, to be refreshed before starting sample collection	
Dr Ian Davies					
Dr Tom Butler					
Prof Gregory Lip					
Prof Dick Thijssen					
Dr Joseph Mills					
Richard Kirwan	08/10/2018			01/11/2018, to be refreshed before starting sample collection	

STUDY SUMMARY

Study Title	A high-PRotein Mediterranean diet and resistance Exercise for cardiac rehabilitation: a pilot randomised controlled trial	
Internal ref. no. / short title	PRiME	
Proposed start date	January 2020	
Proposed end date	January 2021	
Countries in which the study will take place	England	
Lead NHS trust & R&D contact	Liverpool Heart & Chest Hospital, Research & Innovation Team (Michael Noorzadeh), 01516001158, michael.noorzadeh@lhch.nhs.uk	
Study Design	2x2 Factorial Randomized Controlled Diet & Exercise Intervention	
Study Participants	Participants in phase-3 & 4 cardiac rehabilitation	
Planned Sample Size	Cross-sectional analysis n=240 Intervention n = 60 (4 groups of 10-15 individuals)	
Planned Study Period	12 months (3 months for each patient but 7 months allowed for staggered recruitment)	
	Objectives	**Outcome Measures**
Primary	Determination of the feasibility of the intervention and its applicability in a fully powered RCT	Standard deviation of the key secondary outcome measures, willingness of participants to be randomised, number of eligible participants within the CR population, follow-up rates, response rates to questionnaires, acceptability of nutritional and exercise protocols, adherence/compliance rates, time and finances needed to implement the intervention..
Secondary	Reduction in the sarcopenic obesity index Improvement in cardiometabolic risk markers	Body composition measured by DXA and anthropometry. Changes in cardiometabolic risk markers (e.g. lipid profile, fasting glucose, HbA1c).

FUNDING AND SUPPORT IN KIND

Please provide details of how the study is being funded, both internally and externally.

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
LCCG RCF	£ 27,166

ROLE OF STUDY SPONSOR AND FUNDER

The research will be carried out by researchers from LJMU (the study sponsor), in collaboration with Liverpool Heart and Chest Hospital (both institutional members of the Liverpool Centre for Cardiovascular Science). Funding comes from LJMU and the LCCG RCF. The researchers are not receiving any payments other than their usual salaries.

Any support in the form of food products to be used in the intervention will be obtained under the explicit agreement that the supplying organization will have absolutely no role in study design, conduct, data analysis and interpretation or manuscript writing. The final decision regarding any of these aspects of the study will remain with the research team.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS AND INDIVIDUALS

Trial Oversight Committee (TOC): it will consist of the academic investigators, Liverpool Heart and Chest clinical leads, and Community centre leads. The TOC will supervise the study in its entirety.

Trial Steering Group (TSG): it will consist of patients engaging with cardiac rehabilitation (CR) (phase 3, patient group), the principal investigator, co-investigators, and staff employed on the trial. The TSG will be responsible for reviewing the protocol design and ethical considerations, such as participant information, and valuable feedback on patient 'friendliness' and acceptability will be documented and fed back to the TOC. Any changes made will be reported and documented.

Liverpool Heart & Chest Hospital, Service Users Research Endeavour (SURE) group: This is a Patient & Public Involvement Group whose membership comprises former or existing patients, carers or members of the public. The SURE group works alongside LHCH Trust's Research Committee to appraise, monitor and complement research projects from a service user's point of view, from the quality and clarity of the documentation to the feasibility of a patients' involvement in a study.

Liverpool Heart & Chest Hospital, Research & Innovation Team: to improve the quality, relevance, and focus of research and to ensure all the study follows the guidelines set for research by the Department of Health.

PROTOCOL CONTRIBUTORS

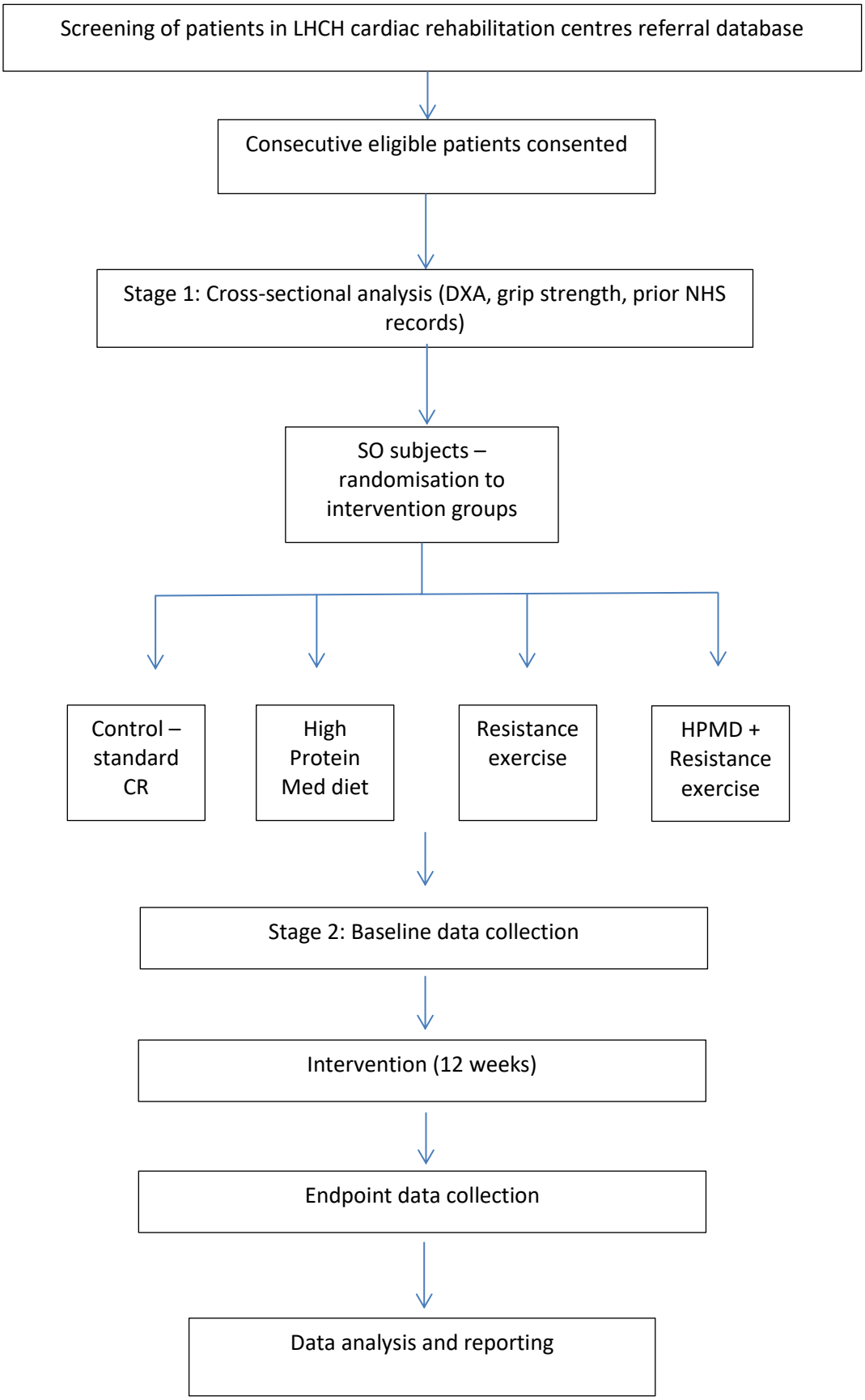
The study proposal was reviewed and approved by LJMU's Research Committee.

Details of the study were finalised by collaboration of the supervisory team, and the specific methodology was further developed with the participation of the PhD student. The research methods to be used are validated and established techniques commonly used in clinical research.

The research team have already met with the Service Users Research Endeavour (SURE) group of the Liverpool Heart and Chest Hospital and with the Research and Innovation Committee of the LHCH. Feedback was received during both meetings, and the study was approved by the SURE Group and the R&I Committee.

We will continue the work with specific focus groups of patients in CR. The PPI groups will participate and feed back on the different aspects of the research.

STUDY FLOW CHART



ABBREVIATIONS

CI	Chief Investigator
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
LJMU REG	LJMU Research Ethics and Governance
LHCH	Liverpool Heart & Chest Hospital
NHS	National Health Service
NRES	National Research Ethics Service
PIS	Participant/ Patient Information Sheet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
CVD	Cardiovascular disease
CHD	Coronary Heart Disease
CR	Cardiac Rehabilitation
CM	Cardiometabolic
SO	Sarcopenic Obesity
MPS	Muscle Protein Synthesis
LBM	Lean Body Mass
DXA	Dual-energy X-ray absorptiometry
HPMD	High Protein Mediterranean DIet
BACPR	British Association for Cardiac Prevention & Rehabilitation

1 BACKGROUND

Cardiovascular disease (CVD) in the UK is behind 1 in 4 deaths/year (>150,000 people), with coronary heart disease (CHD) being the most common type [1]. In addition to the loss of life, the economic cost of CVD is considerable; in 2015 healthcare for CVD alone in the UK amounted to £10.9 billion with a further £7.7 billion lost from the economy due to productivity loses [2].

Mortality figures due to CHD have been reduced recently, in part due to increased provision of cardiac rehabilitation (CR), a therapeutic approach based on exercise training to improve cardiac function, plus advice regarding smoking cessation, dietary changes and weight loss [3].

2 RATIONALE

Most of the evidence on the benefit of CR examines the links between exercise and CV morbidity and mortality [4]; however, there is considerable evidence showing improvements in markers of cardiovascular risk through different dietary strategies [5]. Of particular relevance, results from studies on both the primary

and secondary prevention of CVD suggest Mediterranean diet-based approaches are the most adequate to treat these patients [6-13].

Obesity, and in particular, visceral adiposity, is associated with cardiometabolic (CM) risk markers (e.g., high cholesterol and triglycerides levels, HbA1c, etc.) [14-16], however, an "obesity paradox" appears to exist in the cardiac population, where increased mortality has been linked to low body mass index (BMI) [17, 18]. However, low lean body mass (LBM) is the likely driver of this phenomenon due to sarcopenia, a progressive loss of LBM associated with aging [19]. Patients with a combination of low LBM and abdominal distribution of body fat, known as sarcopenic obesity (SO), are at greater risk of CVD, exacerbated in CR [20-23]. Thus, increasing relative LBM content, rather than simply promoting weight loss, may be an appropriate target in CR patients.

One particular barrier to maintaining or accruing LBM is the presence of anabolic resistance in older adults, which can result in a reduced muscle protein synthetic (MPS) response to both exercise and the ingestion of currently recommended intakes of protein [24]. Protein intakes above currently recommended levels (1.0-1.5 g/kg/BW) [25] combined with sufficiently intense resistance training [26] can overcome this anabolic resistance and positively influence muscle mass, ultimately leading to greater improvement in body composition, when accompanied by a reduction in total body fat mass [27].

3 RESEARCH QUESTION

We aim to determine the prevalence of sarcopenic obesity in a CR population and how this body composition relates to markers of cardiometabolic health. As there is no consensus definition of SO, multiple definitions, along with their relationship with CM risk markers, will be investigated.

We aim to investigate to what extent a high-protein Mediterranean-style diet and resistance exercise, alone and in combination, can augment LBM. Furthermore, we will ascertain whether the above interventions improve markers of cardiometabolic health.

Therefore, we will conduct a feasibility study with embedded pilot to obtain preliminary data on the practical and clinical considerations and cost-effectiveness of the proposed interventions, in preparation for an appropriately powered randomised controlled trial for increasing lean mass and improving cardiometabolic risk markers in patients with SO.

4 OBJECTIVES AND OUTCOME MEASURES

Quantitative research

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To investigate to what extent a high-protein Mediterranean-style diet and resistance exercise, alone and in combination, can augment LBM and muscle strength	Increases in LBM will be measured using DXA and anthropometry. Increases in strength will be measured with grip strength dynamometer	To be performed within 1 week prior to and within 1 week after completion of the 12 week intervention
Secondary Objectives To ascertain whether the above intervention improves markers of cardiometabolic health.	Cardiometabolic risk markers (blood glucose, lipid profile etc) will be measured using blood samples along with measurements of blood pressure	Blood pressure will be measured in the cross-sectional stage, and before

		and after the intervention Blood will be drawn 1 week prior to and 1 week after completion of the 12 week intervention

Qualitative research

Aim/Research Questions	**Objectives**
Primary To determine the feasibility, practical and clinical considerations and cost-effectiveness of the proposed interventions, in preparation for an appropriately powered randomised controlled trial for increasing lean mass and improving cardiometabolic risk markers in patients with SO.	Participants will be asked to provide feedback on: - recruitment, - tasting of high-protein foods, - recipes, appeal of the meals, how they fit with the Merseyside culture, - involvement and support of other members of the family (especially those in charge of purchasing and cooking food), - familiarity session(s) with resistance training, exploring ability to perform exercises and personalising the training system, - preferences to undertake resistance exercise (e.g. in a supervised or unsupervised setting), - preferred follow-up frequency and method (e.g. face to face, phone, etc.), - issues with dietary and exercise adherence, Participants will also: - help shape the protocol and ensure the project is participant-friendly and sensitive by assisting with ethical considerations, - discuss research findings and help with lay dissemination.

5 STUDY DESIGN AND METHODS OF DATA COLLECTION AND DATA ANALYSIS

A single-centre, cross-sectional analysis of the prevalence of SO in CR patients followed by a single-centre, 2x2 factorial, randomised, open label controlled trial.

5.1 RANDOMISATION AND BLINDING

All participants will be assigned to their group by computer randomisation by the PhD student. Due to the nature of the intervention, blinding will not be possible.

5.2 BASELINE ASSESSMENTS

STAGE 1: Screening and focus group
To be carried out at LJMU Byrom St campus (L3 3AF) by the PhD student. The visit is expected to last 30 minutes and will entail:
i) Assessing body composition. This will be done in three different ways.

- Firstly, we will measure participant height using a stadiometer and waist circumference using a tape measure.
- Secondly, we will use a bioelectrical impedance analysis scale to measure lean body mass, total body fat mass and visceral fat mass.
- Thirdly, we will perform a DXA (Dual-energy X-ray Absorptiometry) scan for 15-20 minutes which allows us to create an image of the distribution of lean body mass and fat mass.

ii) Taking blood pressure

- Following standard protocol, participants will be asked to sit for 5 minutes before we take blood pressure; we will measure it three times to ensure an accurate reading.

iii) Grip strength test

- Will be tested using a device that one squeezes as hard as possible (grip strength dynamometer). We will do this three times to ensure an accurate reading.

(iv) Mediterranean Diet Score

- Participants will fill in a brief 13-question questionnaire regarding the frequency of their intake of certain foods

Participants will also be invited to attend a focus group to share views and opinions about food habits and preferences, and about physical activity. This will be carried out at participants community CR centre and will take 15-20 minutes

5.3 INTERVENTIONS (IF APPLICABLE)

Based on the results from the first visit, approximately 60 patients with lower proportions of muscle mass to fat mass will be asked to take part in the diet and exercise intervention, which will last 12 weeks. Participants at this stage will be allocated to one of four groups: 1) standard CR; 2) CR plus personalised advice to follow a high-protein, healthier diet; 3) CR plus resistance exercise; 4) CR plus diet and resistance exercise.

Personalised dietary advice: if allocated to groups 2 or 4, we will ask participants to make changes to their diet to adapt it to a high-protein, Mediterranean-style diet. Research shows that Mediterranean-style diets can reduce cardiovascular risk, and although there are different versions of this type of diet, they all have in common:

- eating more fruit and vegetables,
- reducing commercial pastries, and replacing refined carbohydrate foods (white bread, white rice, white pasta) by wholegrains (wholegrain bread, rice and pasta),
- replacing butter and margarine by olive oil as the main culinary fat,
- reducing fatty meat and replacing by lean meat, fish, and legumes (peas, beans, lentils), and by high-protein, low fat foods, such as low-fat dairy (participants will be provided with 2 high-protein yoghurts to eat each day).

Participants will receive personalised guidance to help follow the new diet in the form of sessions at their community CR centre along with guide books and recipe guides. The goal is to make small, easy changes to their current eating habits, so the diet will be easy to follow. All foods included will be affordable and easy to find in local supermarkets (shopping guides will be provided), and we will provide suggestions and recipes to prepare food.
If allocated to groups 1 or 3, participants will be asked to follow the diet recommendations given during phase 3 of CR.

Resistance exercise: if allocated to groups 3 or 4, participants will be asked to perform resistance exercise. This involves weights or weight machines aimed at building muscle strength. Participants will be shown how to do the exercises by qualified instructors (BACPR cardiac rehabilitation certified) in the community centre where they carry out their current phase 3 cardiac rehabilitation. All exercises have been deemed safe for cardiac rehabilitation patients and an instructor will be available at all exercise sessions should they need assistance. Participants will be required to attend 3 sessions per week and each session is expected to last approximately 45 minutes.

If allocated to groups 1 or 2, participants will be asked to continue with the standard, aerobic-style exercise (treadmills, rowing machines, elliptical trainers) they have used in phase 3 of CR. This will also require 3 sessions per week.

5.4 SUBSEQUENT VISITS

ALL stage 2 participants will have to attend two more appointments at LJMU. The second visit will be just before beginning the intervention, and the third immediately after completing the intervention. Visits are expected to last 45-60 minutes and will entail:
i) Measures of body composition, blood pressure and grip strength, as described above.

ii) A venous blood sample

- We will take about 8 teaspoons of blood. Particpants will need to fast for at least 12 hours prior to your appointment (although water is encouraged), as otherwise this may affect the result of the test.

iii) Focus Groups

- At the final visit we will also ask about participant experiences with the diet and/or exercise regime allocated to them, and to check whether they have experienced any so-called adverse events over the study.

iv) Food diaries (prior to lab appointments)

- Prior to second and third lab visits, participants will given a template of a four-day food diary, which they will need to complete the week before their lab appointment (on three working days plus one weekend or festive day, non-consecutive whenever possible), and bring with them on the morning of the visit. Participants will be contacted the day before to remind them of their appointment and what they must bring.

(v) Mediterranean Diet Score

- Participants will fill in a brief 13-question questionnaire regarding the frequency of their intake of certain foods

5.5 STUDY SETTING

This is a single centre study with all data collection taking place in LJMU, Byrom St. campus. All exercise will be carried out at the participants community CR centre, supervised by trained members of the community CR program.

5.6 STATISTICS AND ANALYSIS

Cross-sectional study: from the results of body composition analysis, the prevalence of SO will be analysed in the sample. Differences in prevalence between genders, and between cardiac conditions (e.g. arrhythmia, myocardial infarction, coronary artery disease etc.) will be assessed by Chi-squared tests. We will use Pearson or Spearman correlations (according to normality) to study the associations between body composition variables, markers of strength and performance, and biomarkers of cardiovascular risk (based on patient data requested from LHCH) and multiple regression to assess the predictive capacity of indicators of sarcopenic obesity and muscle strength on cardiovascular risk.

Pilot study: comparisons between intervention groups for all outcome measures will be performed by means of mixed model ANOVA, to account for inter-subject (differences between treatments) and intra-subject (differences between baseline and endpoint) variability. Since a sample size calculation will not be conducted for this component, interpretation of the results will be largely descriptive and focused on confidence limits around parameter estimates.
Statistical significance will be set at $p<0.05$, and all analyses will be conducted using IBM SPSS Statistics v25 (SPSS Inc., Chicago, IL).

6 PARTICIPANT RECRUITMENT

6.1 STUDY PARTICIPANTS

Participants will be recruited from Liverpool Heart & Chest Hospital Cardiac Rehabilitation unit. Participants in the cross-sectional study will be admissions to phase 3 CR. Participants in the intervention trial will have recently completed phase 3 CR, will have been deemed as cardiac stable, and will be willing to participate in phase 4 CR (Activity for Life). The minimum age restriction for participants will be 40-years

For the cross sectional study, sample size has been estimated as n=240, based on a prevalence of SO of 20% with precision at 5% and confidence at 95%, and using the online calculator at http://sampsize.sourceforge.net/iface/.

The sample size for the feasibility study has been arbitrarily kept small (10-15 participants per intervention group) to allow ease of recruitment and management of participants before development into a fully powered randomised controlled trial.

6.2 INCLUSION CRITERIA

Stage 1:

- Informed consent given
- Referral to cardiac rehabilitation program
- Ability to attend screening at Liverpool John Moores University

Stage 2:

- Informed consent given
- Meeting selected criteria to define sarcopenic obesity (dependent on analysis from stage 1)
- Ability to attend screening at Liverpool John Moores University
- Cardiac function deemed stable after phase 3 cardiac rehabilitation

6.3 EXCLUSION CRITERIA

- Inability to perform resistance exercise (determined by primary care team)
- Renal dysfunction
- Inability/unwillingness to digest/consume dairy products
- Admission to CR due to congenital or drug/alcohol-abuse induced cardiac events
- Pregnancy

6.4 RECRUITMENT TECHNIQUE

Participants will be approached by members of their clinical care team at LHCH, who will invite them to participate and confirm they are willing to be contacted by our research team for more information. Please refer to 6.5 for further details.

6.5 PARTICIPANT IDENTIFICATION

Eligible participants will be recruited from patients recently referred to cardiac rehabilitation (Liverpool Heart & Chest Hospital Cardiac Rehabilitation Unit), which is where we will start our study. In collaboration with the LHCH Cardiac Rehabilitation Uniteligible participants will first be identified by the clinical care team.

Eligible participants will be approached by members of the Knowsley Community Cardiovascular Services team, part of Liverpool Heart & Chest Hospital Cardiac Rehabilitation unit. Participants will be informed of the research and provided with a participation information sheet and asked to reply with their interest after 24 hours. They will then be contacted by the PhD student.

6.6 SCREENING AND ELIGIBILITY ASSESSMENT

The maximum period from screening in stage 1 to the recruitment for the intervention (stage 2) will depend on the participant's progression through CR phase 3. As phase 3 normally last 8 weeks, and assuming a participant has just started CR phase 3 there may be up to 8 weeks from the first (screening) visit to second visit (baseline) measurements.

6.7 INFORMED CONSENT

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.
Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.
The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

6.8 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS FROM STUDY

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up

Should a participant wish to withdraw from the study, their anonymised data will be retained for 10 years. Their data may still be included in the analysis if they withdraw after completing the intervention, and for reasons that do not affect the study outcomes. If the participant wants their data to be removed from the study, they may contact us and request such.

Withdrawn participants may be replaced should sufficient time and resources be available.

The reason for withdrawal by researcher (and by participant, if this information is volunteered) will be recorded in a study file.

7 DATA MANAGEMENT

7.1 ACCESS TO DATA

Direct access will be granted to the research team, authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

7.2 DATA RECORDING AND RECORD KEEPING

The information provided as part of the study will be anonymised. We will use codes to label, trace and identify your samples, records and questionnaires; we will never use any personal data from which participants can be identified, such as name, initials, or date of birth.
Documents that include personal data (such as the consent form, or your contact details) will be stored on password-protected computers and locked filing cabinets at LJMU, accessed only by the research team. They will be destroyed upon completion of the study, unless they would like a copy of the final study results; in that case, we will retain their names, phone numbers and email addresses, so we can contact them later. The results should be available approximately 1 year after the study is completed; participant personal data will be then deleted.
Research data will be stored in databases using the codes as identifiers, never personal data, and they will be kept in password-protected computers only accessed by the research team. Samples will be booked into a database and receive a laboratory code, with only those involved in the research having access. All data and samples will be destroyed after 10 years.
The names of participants will never be published in any communication of results and findings.

7.3 SAMPLE HANDLING

Blood samples will be processed and stored according to current UK regulations and rules of good research practice (Human Tissue Act 2004), and will be kept for a maximum of 10 years. Briefly, blood samples will be processed immediately after collection, and the serum will be stored in a secure freezer in the Life Sciences Building at LJMU's Byrom St campus. All samples will be stored pseudo-anonymously; this means that all identifiable information will be removed and replaced by a code to allow the research team to trace the samples and match them with the other measurements (body weight, muscle mass measures, etc.). Once all participants have completed the intervention, samples will be analysed. Once the specified storage period ends, all samples will be disposed of following current UK regulations.

8 SAFETY REPORTING

Adverse Events, Adverse Reactions and Serious Adverse Events will be recorded in the participants documentation as they are brought to the attention of the researchers and if necessary will be reported to the appropriate authority (LJMU REC, LHCH, participants GP etc.) in accordance with LJMU procedures.

9 QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures OF LJMU.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 DECLARATION OF HELSINKI

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki and relevant regulations

10.2 ASSESSMENT AND MANAGEMENT OF RISK

Participants will be scanned by a DXA scanner, which will involve use of small doses of ionising radiation, though this is a minimal amount compared to other medical imaging techniques, such as standard X-ray and CT scans. The DXA scan would be equal to approximately 2 microsieverts (µSv); this is compared to 20 microsieverts for a chest X-ray and 10,000 microsieverts for a CT scan. It is also less than a transcontinental flight (40 µSv) and one day of natural background radiation (8 µSv).

Great care will be taken to ensure vulnerable people (for example, pregnant women) will not be permitted to take part, both during the initial screening and recruitment, and also during the scans where mandatory exclusion criteria are checked before the scan can begin.
The study will limit the involvement of each participant to three scans, and they will be fully informed as to the exposure they will have, should they choose to participate. The radiation exposure is so low that no shielding of the room or of the person conducting the scans is necessary; therefore, the anticipated risk to the participant is negligible.

The participants are being asked to be involved in a study which has a central focus on body weight and composition, which can be a very sensitive subject. As the participants will be willing volunteers for the study, it is expected that only people who are comfortable with this issue will be involved. Additionally, the participants can request for their bio-impedance and anthropometric measurements to be taken by a member of the research team of the same gender. They can also request a chaperone to be present during the procedure. Privacy and confidentially will be ensured when taking measurements, and all data will be anonymised upon collection and storage.

In addition, participants will be reminded that they can withdraw and remove themselves from the situation (and the study) at any time.

For the DXA scans, questionnaires and anthropometric measurements, it is not anticipated that there will be significant inconvenience for those who choose to take part in this project, as their time involvement is minimal at 45 minutes per visit, and we will do our best to accommodate their visit times to their preferences and availability (within the limits of the research requirements).

Participants will be made aware of the requirements of the dietary intervention while seeking consent, and it is expected that those who are comfortable with this dietary change will be involved. The dietary intervention will not use difficult to source ingredients and will be tailored to suit the tastes of the participants. Various recipes and food substitutions will be provided to participants at the beginning of the protocol. The high-protein diet of the protocol would only be potentially detrimental to individuals who have renal deficiency, and therefore this is one of the studies exclusion criteria. Participants will also receive regular contact from the PhD student regarding their adherence.

Participants will be made aware of the requirements of the exercise intervention while seeking consent, and it is expected that those who are comfortable with this change in physical activity will be involved. All participants will have received exercise tolerance tests as part of their NHS cardiac rehabilitation and will be cleared for the exercise protocol. They will also receive instruction from a collaborator suitably trained in exercise for cardiac rehabilitation regarding how to safely complete the exercise protocol.

The involvement of the participants and their data will be kept confidential, with no personal identifying data being present on questionnaires, forms or DXA scans. The unique code that can identify a participant will be kept on a secure system that can only be accessed by the research team. Therefore it is not expected that there will be a significant risk of a confidentiality breach.

Should the participant disclose information indicating a risk of potential harm to themselves or others, the appropriate authority will be contacted (LHCH, patient's GP, police etc,).

10.3 PARTICIPANT CONFIDENTIALITY

The data custodian will be the PhD student. All investigators and study site staff must comply with the requirements of data protection legislation with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Information provided as part of the study will be anonymised. We will use codes to label, trace and identify samples, records and questionnaires; we will never use any personal data from which participants can be identified, such as name, initials, or date of birth.

Documents that include personal data (such as the consent form, or contact details) will be stored on password-protected computers and locked filing cabinets at LJMU, accessed only by the research team. They will be destroyed upon completion of the study, unless participants would like a copy of the final study results; in that case, we will retain their name, phone number and email address, so we can contact them later. Their personal data will then be deleted

Research data will be stored in databases using the codes as identifiers, never personal data, and they will be kept in password-protected computers only accessed by the research team. Samples will be booked into a database and receive a laboratory code, with only those involved in the research having access. All data and samples will be destroyed after 10 years.

The names of participants will never be published in any communication of results and findings.

10.4 EXPENSES AND BENEFITS

Participants will not be reimbursed for travel expenses incurred while participating in the study

Participants in the high protein diet groups will be provided with 2 high-protein yoghurts per day for the duration of the trial.

The diet and exercise chosen in this study have been shown to have a number of benefits:

- High-protein foods may increase satiety after a meal, reducing hunger.
- This may also lead to a lower calorie intake and consequential potential weight loss.
- This may lead to a loss of fat mass, improving body composition.
- Muscles may grow and become stronger, meaning everyday activities will feel easier.
- Blood sugar levels may improve due to healthier muscles helping with blood sugar control.
- Blood cholesterol and fats may improve, reducing risk of further cardiac events.

10.5 OTHER ETHICAL CONSIDERATIONS

In the unlikely event of finding any abnormalities or anything of clinical significance, the findings will be checked by a clinical specialist. If the specialist feels that the abnormality was medically important, they will discuss the implications with the participant and arrange for further investigations as necessary. Participants will not be informed unless the doctor considers the finding has clear implications for their current or future health. It is important to note that data collected are not carried out for diagnostic purposes, and therefore the data are not a substitute for a clinical appointment. Rather, the data are intended for research purposes only.

10.6 RESEARCH ETHICS COMMITTEE (REC) AND OTHER REGULATORY REVIEW & REPORTS

- Before the start of the study, a favourable opinion will be sought from from the UK Health Departments Research Ethics Service NHS REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements
- Approval will be obtained from LJMU REG (and Co-Sponsors) for any amendments to, or changes of status in the study **prior to** submission to the REC that ethically approved the study and any other regulatory authorities
- All correspondence will be retained.
- The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the HRA for written approval.
- Annual Progress Reports will be submitted to the NHS REC which gave the favourable opinion, the HRA (hra.approval@nhs.net) and the Sponsor (Sponsor@ljmu.ac.uk) on the anniversary of NHS REC Favourable Opinion, and annually thereafter until the End of Study Declaration has been submitted to the NHS REC which gave the favourable opinion, the HRA and the Sponsor
- Upon the completion of the study an End of Study Declaration (within 90 days of the end of the study) and End of Study Report (within 12 months of the end of the study) will be submitted to the NHS REC which gave the favourable opinion and LJMU REG (sponsor@ljmu.ac.uk)

- Annual Progress Reports will be submitted to the NHS REC which gave the favourable opinion and the Sponsor (Sponsor@ljmu.ac.uk) on the anniversary of HRA approval, and annually thereafter until the End of Study Declaration has been submitted to the NHS REC which gave the favourable opinion and the Sponsor.
- Upon the completion of the study an End of Study Declaration (within 90 days of the end of the study) and End of Study Report (within 12 months of the end of the study) will be submitted to the NHS REC which gave the favourable opinion and LJMU REG (sponsor@ljmu.ac.uk)
- Early termination or suspension of the research will be reported to all relevant review bodies and the Sponsor (sponsor@ljmu.ac.uk) within 15 days.

11 SCIENTIFIC REVIEW

The study protocol went through successive stages of scientific review:

1) It was first reviewed and approved for support under the cross-faculty PhD funding scheme. The panel reviewing the proposals was formed by staff from the Faculty of Science, Faculty of Education, Health and Community, and the Institute of Health Research, LJMU.
2) The study was subsequently reviewed and approved by the Service Users Research Endeavour (SURE) Group of the Liverpool Heart and Chest Hospital.
3) Finally, our study protocol was presented at and approved by the Research and Innovation Committee of the Liverpool Heart and Chest Hospital.

All different stages of review were carried out by independent reviewers, both internal (from LJMU) and external (LHCH), meeting the requirements of Level 4 studies.

Level 1 No Peer Review Required – minimal risk (no patient contact)	**Level 2 Review by project supervisor** (student projects with either no or minor patient/participant involvement)	**Level 3 Review by departmental colleague** (Low-risk projects with minimal patient involvement)	**Level 4 External, independent peer review**
Short questionnaire studies for use among hospital staff or GPs.	Human tissue samples [anonymous to investigator]	Human tissue samples [anonymous to investigator]	Clinical trial of an investigational medicinal product

Questionnaires asking patients about the quality of hospital services.	Study administering questionnaires	Study administering questionnaires	Clinical trial of a medical device
Use of data from medical notes by clinician looking after patient.	Qualitative study	Qualitative study	Performance Evaluation of an in vitro diagnostic device
	Study limited to working with data	Study limited to working with data	Other clinical trial or clinical investigation
		Non-intimate examination techniques, e.g. blood pressure measurement.	Research Tissue Bank
			Human tissue (tissue samples and data) [newly obtained, identifiable or obtained from surplus]

12 PATIENT & PUBLIC INVOLVEMENT

The research team initially liaised with Knowsley Community Cardiovascular Service in charge of phase 4 cardiac rehabilitation, to gather information relevant to the current practice and support offered to cardiac rehabilitation patients after leaving the hospital, as well as this population specific characteristics, needs and requirements.

The research team then consulted with the Liverpool Heart & Chest Hospital, Service Users Research Endeavour (SURE) group (see ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS AND INDIVIDUALS on page 7.

The SURE group has already provided advice regarding the participant information documents, and approved the study.

We will continue with specific focus groups of patients in CR. The PPI groups will participate and feed back on the different aspects of the research (see qualitative research in OBJECTIVES AND OUTCOME MEASURES)

All PPI activities will be recorded and evaluated, with aims to present at conferences and publish in appropriate peer reviewed journals.

13 PROTOCOL COMPLIANCE

Protocol adherence will be monitored with weekly phone call with each participant, carried out by the PhD student.
Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.
The Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason. Such occurrences will be detailed in the individual participant study logs

14 INSURANCE

Table 11.1

The research study includes the following:	**Please state YES or NO to at least one.**
treating or preventing disease or diagnosing disease	YES
ascertaining the existence degree of or extent of a physiological condition	YES
assisting with or altering in any way the process of conception	NO
investigating or participating in methods of contraception	NO
inducing anaesthesia	NO
otherwise preventing or interfering with the normal operation of a physiological function	NO
None of the above	NO

Table 11.2

The study is limited to the following activities and will be undertaken in the UK.	**Please state YES or NO**
Questionnaires, interviews, psychological activity including CBT	YES
Venepuncture (withdrawal of blood)	YES
Muscle biopsy	YES
Measurements of physiological processes including scanning	YES
Collections of body secretions by non-invasive methods	YES
Intake of foods or nutrients or variation of diet (other than administration of drugs).	YES

LJMU has Clinical Trials insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management and design of the research by the University and the activities here are included within that coverage.

LJMU's Clinical Trials insurance policies provide an indemnity to our employees and students for their potential liability for harm to participants during the conduct of the research and the activities here are included within that coverage.

15 CONTRACTS AND AGREEMENTS

A standard Non-Commercial Model Agreement (mNCA) will be negotiated with Liverpool Heart & Chest Hospital

A research passport (letter of access) will be applied for, for the PhD student who will undertake the research within the NHS.

16 DEFINITION OF END OF STUDY

The end of study is the date of completion of analysis of samples.

17 END OF STUDY AND ARCHIVING

The end of study is the date of the last visit of the last participant. Relevant consent forms will be obtained for each participant, allowing for the samples to be stored and data to be archived for at least 10 years.

18 ACCESS TO THE FINAL STUDY DATASET

Aim: to describe who will have access to the final dataset
The PhD student, all supervisors and the lead clinician will have access to the full dataset. The study will allow site investigators to access the full dataset if a formal request describing their plans is approved by the

steering group. Any secondary analysis will only be undertaken with the consent of the participants. All patient documentation will reflect the future use of data in research.

19 DISSEMINATION POLICY

- All the data from the study will be own and managed by the research team. Experimental data will be appropriately coded and stored in a database (MS Excel) – all information in this database will be anonymous, and individual data will not be shared, published or disseminated in any way.
- Data will be analysed with appropriate statistical tests (according to the nature and amount of the data within each variable of study). A final report will be produced to inform all parties involved in this study: Liverpool John Moores University, University of Chester, Liverpool Heart and Chest Hospital, Knowsley Community Centre, SURE Patient group, and relevant stakeholders (*e.g.*, funders, NHS). The report will be shared with the partners via email; it will be communicated using social media as well, so that other parties interested can request it.
- Data will be analysed as well for presentation in professional conferences (*e.g.*, European and International Congress on Obesity, European and International Nutrition Conference, British Association for Cardiac Prevention & Rehabilitation Conference etc) and publication in specialised journals (*e.g.*, International Journal of Obesity, American Journal of Clinical Nutrition, European Journal of Clinical Nutrition, Journal of the American College of Cardiology, Circulation, European Heart Journal etc). The research team will be responsible for the authorship and reviewing of the conference proceedings and publications. The fully anonymised dataset will be made public at the request of journals, or as a requirement by the funding bodies (*e.g.*, LJMU repository).
- Current funding from Liverpool John Moores University and the Liverpool Clinical Commissioning Group will be acknowledged in all publications, and so will any additional future funding. These funding bodies do not request publication or reviewing rights. In the event of collaborating with industry sponsors, an agreement will be signed so that the research team retain the rights over data property and publication rights.
- Participants will be informed of the final results of the study – a lay summary will be produced to share the findings with them, and they can receive copy of the final report as well, should they wish. Participants can also request a summary report on their personal results, directly to the PI and/or the PhD student who will be their main contact throughout the study.
- The study protocol will be registered publicly with clinicaltrials.gov

20 AUTHORSHIP ELIGIBILITY GUIDELINES AND ANY INTENDED USE OF PROFESSIONAL WRITERS

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by an LCCG RCF grant and any other grants, should application be successful. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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22 APPENDICES

22.1 APPENDIX 1- REQUIRED DOCUMENTATION

- Research protocol or project proposal
- Letter from statistician
- Summary CV for Chief Investigator (CI)
- Participant information sheet (PIS)
- Participant consent form
- Letters of invitation to participant
- GP information sheets or letters
- Validated questionnaire
- Non-validated questionnaire
- Referee's report or other scientific critique report
- Summary, synopsis or diagram (flowchart) of protocol in non-technical language
- Covering letter on headed paper
- Letter from sponsor
- Letter from funder
- SoECAT
- Non-Commercial Model Agreement
- Evidence of Sponsor insurance or indemnity
- Summary of any applicable exclusions to sponsor insurance
- Summary CV for student
- Summary CV for supervisor (student research)
- MHRA "Notice of No Objection" Letter (Medical Devices) and relevant correspondence

22.2 APPENDIX 3 – AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made