Feasibility of a progressive, walking-based exercise programme for monoclonal gammopathy of undetermined significance and smouldering multiple myeloma: a single-arm pilot trial.

Short title: Feasibility of exercise for asymptomatic monoclonal gammopathies.

IRAS PROJECT ID: 238573

ISRCTN: 65527208

TRIAL PROTOCOL: v3.1 19/DEC/18

SPONSOR: University of Bath

Key trial contacts

Chief investigator	Dr John Campbell	j.campbell@bath.ac.uk	01225 385 495
PhD student	Annabelle Emery	a.r.emery@bath.ac.uk	01225 383 655
Sponsor	University of Bath	pro-vc-research@bath.ac.uk	01225 383 162
Local NHS collaborator	Dr Sally Moore	sallymoore5@nhs.net	01225 824 488
Protocol authors	Dr John Campbell Dr James Turner Dr Sally Moore Annabelle Emery	j.campbell@bath.ac.uk j.e.turner@bath.ac.uk sallymoore5@nhs.net a.r.emery@bath.ac.uk	01225 385 495 01225 383 566 01225 824 488 01225 383 655
Co-investigators	Prof Mark Drayson Prof Dylan Thompson Dr Oliver Peacock Dr James Betts Dr Kate Edwards Dr Fiona Gillison Ms Regitse Lewis Dr Daniel Augustine	m.t.drayson@bham.ac.uk d.thompson@bath.ac.uk o.j.peacock@bath.ac.uk j.betts@bath.ac.uk kate.edwards@sydney.edu.au f.b.gillison@bath.ac.uk regitse.lewis@nhs.net daniel.augustine@nhs.net	01214 144 074 01225 383 177 01225 383 270 01225 383 448 +61 2 9036 7396 01225 384 387 01225 825 596 -
Trial management group	Dr John Campbell Dr Sally Moore Dr James Turner Annabelle Emery Patient representative	j.campbell@bath.ac.uk sallymoore5@nhs.net j.e.turner@bath.ac.uk a.r.emery@bath.ac.uk -	01225 385 495 01225 824 488 01225 383 566 01225 383 655 -

Contents

List of abbreviations

ADL	Activities of daily living
AE	Adverse event
BMI	Body mass index
BMPC	Bone marrow plasma cell
CI	Chief Investigator
CRAB	Calcium, Renal insufficiency, Anaemia, Bone lesions (symptoms of multiple myeloma)
CPET	Cardiopulmonary exercise test
DEXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
FACIT	Functional assessment of chronic illness therapy
FLC	Free light chains
HR	Heart rate
HRA	Health Research Authority
IMWG	International Myeloma Working Group
IPAQ	International physical activity questionnaire
METs	Metabolic equivalents
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
M-protein	Monoclonal protein
NK	Natural killer
PARQ	Physical activity readiness questionnaire
PBMC	Peripheral blood mononuclear cells
PSQI	Pittsburgh sleep quality index
RCT	Randomised controlled trial
REC	Research Ethics Committee
RM	Repetition maximum
RPE	Rating of perceived exertion
SAE	Serious adverse event
SF-36	36-item short form survey
SMM	Smouldering multiple myeloma
VO_{2MAX}	Maximal oxygen uptake
WHO	World Health Organisation

Trial summary

Trial Title	Feasibility of a progressive, walking-based exercise programme for monoclonal gammopathy of undetermined significance and smouldering multiple myeloma: a single-arm pilot trial.	
Short title	Feasibility of exercise for asymptomatic monoclonal gammopathies.	
Clinical Phase	I	
Trial Design	Pilot, single-centre, single-arm, phase I trial	
Trial Participants	People diagnosed with monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM).	
Planned Sample Size	N = 20	
Intervention Duration	16 weeks	
	Objectives	**Outcome Measures**
Primary	Assess the feasibility and safety of an exercise programme for people with MGUS and SMM.	Uptake, adherence, compliance, retention, adverse events.
Secondary	Assess the effect of an exercise programme on disease activity and potential mechanistic markers, and overall fitness and wellbeing in MGUS and SMM.	• Disease activity of MGUS and SMM • Physical fitness • Free-living physical activity • Body composition • Wellbeing indices • Resting blood pressure and heart rate • CRAB indices • Immune competency • Systemic basal inflammation levels • Metabolic factors and hormone levels
Intervention	A progressive, walking-based exercise programme	
Dose	Two supervised exercise sessions and one home-based session per week for 16 weeks.	

Roles of the trial sponsor

The sponsor takes formal responsibility for the initiation, management and financing of the research.

Roles and responsibilities of the trial management group

A trial management group will monitor the progress and review the scientific rigour of the trial. The group will also monitor safety data, trial end points and recommend to the sponsor whether to continue, modify, or stop the trial. Meetings will be held quarterly.

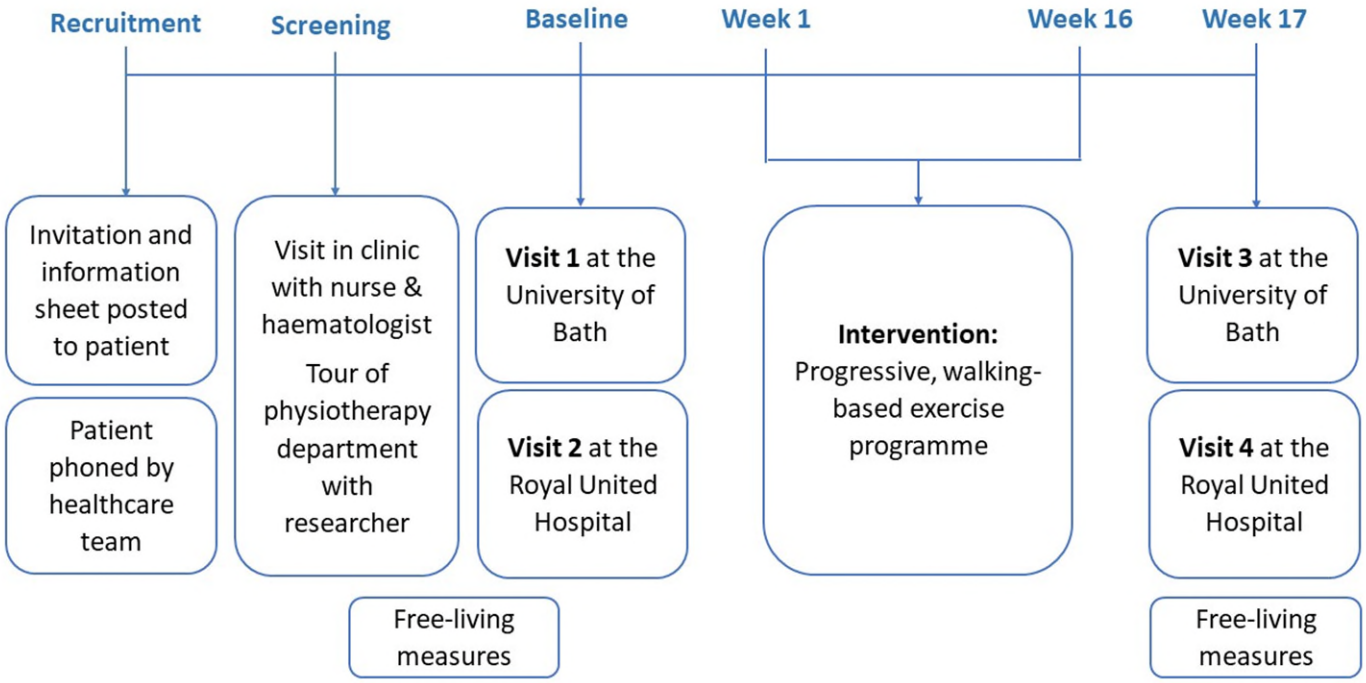
Protocol contributors

Contributor	Expertise
Dr John Campbell	Exercise oncology and immunology
Dr James Turner	Exercise oncology and immunology
Dr Sally Moore	Clinical management of patients with haematological disease
Annabelle Emery	Designing and delivering exercise programmes
Prof Mark Drayson	Haematology, multiple myeloma biomarkers, trial design
Prof Dylan Thompson	Director of Research, Department for Health, University of Bath
Dr Oliver Peacock	Objective assessment of physical activity
Dr James Betts	Human nutrition and metabolism, statistics
Dr Kate Edwards	Exercise training and immune modulation in chronic disease
Dr Fiona Gillison	Implementation of behaviour change in physical activity interventions
Ms Regitse Lewis	Therapies Team Lead for Oncology and Palliative Care Specialist Physiotherapist
Dr Daniel Augustine	Consultant Cardiologist

Key words

Monoclonal gammopathy of undetermined significance; smouldering multiple myeloma; exercise; feasibility; disease activity; health

Trial flow chart



	TRIAL WEEK																	
MEASUREMENT	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Primary outcomes																		
Uptake	X																	
Adherence		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Retention																		X
Secondary outcomes																		
Disease activity	X																	X
Physical fitness	X																	X
Physical activity level	X																	X
Body composition	X																	X
Wellbeing indices	X																	X
CRAB indices	X																	X
Heart rate and blood pressure	X																	X
Mechanistic markers (immune competence, inflammation, hormones and growth factors)	X																	X
Control measures																		
Dietary intake	X																	X
General health status	X																	X

Overview of trial period and measurements. Primary outcomes are recorded throughout the trial period (uptake, adherence, compliance, retention, adverse events). Secondary outcomes and control measures are taken before and after the 16-week trial period.

Background and summary

Multiple myeloma (MM) is an incurable cancer of plasma cells – a type of white blood cell residing in the bone marrow. MM is the second most common haematological malignancy (Li et al., 2016), accounting for 2% of new cancer cases and 2% of cancer-related deaths in the UK each year (CRUK, 2014). MM is characterised by bone marrow plasma cells (BMPC) which produce a monoclonal [M]-protein – identical antibodies produced by one plasma cell clone. Patients also present with end organ damage (CRAB symptoms; elevated calcium, renal insufficiency, anaemia and bone lesions) as a result of plasma cell invasion of bone tissue and infiltration into organs, and blood hyperviscosity due to high circulating M-protein concentration (Kyle and Rajkumar, 2009).

MM has two pre-cursor conditions: (i) monoclonal gammopathy of undetermined significance (MGUS) and (ii) smouldering multiple myeloma (SMM). MGUS and SMM reflect the early stages of MM, presenting with BMPC and M-protein, but without end organ damage. MGUS is the earliest manifestation which is present in >4% of adults aged >50 years (Kyle et al., 2006; Dispenzieri et al., 2010) and, overall, carries a 1% risk of progression to MM per year (Kyle et al., 2002). MGUS can be broadly stratified into four risk cohorts, where progression risk in low-risk vs. high-risk cohorts is 5% and 58%, respectively at 20 years (Rajkumar et al., 2005). SMM reflects more severe disease and carries a 50% risk of progression at 5 years (Kyle et al., 2007). A 'watchful waiting' disease management approach is advocated for MGUS and SMM until symptoms of end organ damage arise (i.e. MM). This approach involves regular measurement of M-protein concentration with increasing frequency with more severe disease (e.g. for low-risk MGUS monitoring is only performed when MM symptoms arise; intermediate-high risk MGUS is typically monitored every 6 months for the first year, then annually; SMM is monitored every 2-3 months initially, decreasing to every 4-6 months and then 6-12 months if clinically stable (Korde, Kristinsson and Landgren, 2011)). The purpose of disease monitoring is to identify transformation to MM and commence active treatment, typically via chemotherapy and stem-cell transplantation (Ludwig et al., 2014). International guidelines do not currently recommend active treatment for MGUS or SMM (Kyle et al., 2010) due to the toxicity and cost consequences of anti-cancer drugs where the risk of disease progression is uncertain (Rajkumar et al., 2005), and uncertainty regarding the efficacy of therapy against all plasma cell clones (Campbell et al., 2017). However, risk stratification models highlight people with SMM and higher-risk MGUS as those who may benefit most from interventions to delay progression to symptomatic MM.

Physical activity may be an effective way to manage disease burden in SMM and MGUS. Epidemiological evidence from over 1.44 million people identified a lower risk of 20 different types of cancer in those with the highest vs. lowest leisure-time physical activity, including a ~20% lower risk of MM (Moore et al., 2016). Data from the National Health and Nutrition Examination Survey indicates that leading a physically active lifestyle does not preclude the advent of MGUS, as a high proportion of people with MGUS in the United States reportedly lead a physically active lifestyle and participation rates appear to be in line with population norms (NHANES, 1999-2017). Instead, we hypothesise that after the initiation of MGUS, exercise and the associated physiological responses that arise from regular participation may suppress MGUS and delay progression to MM. Evidence from animal studies suggest that exercise may be a powerful means of ameliorating tumour growth, as it has been shown that regular exercise can suppress a wide range of transplantable, genetic and chemically-induced tumours in mice (Pedersen et al., 2016; Ashcraft et al., 2016). In humans, evidence in support of this anti-tumour hypothesis has been demonstrated in a case study which showed that an exercise programme reversed BMPC accumulation and decreased M-protein levels in a patient with SMM (Boullosa et al., 2013). Furthermore, the concept of physical activity reducing the risk of cancer is supported by reduced recurrence in more common and heavily researched cancers of the breast (Holmes et al., 2005), colon (Meyerhardt et al., 2006) and prostate (Kenfield et al., 2011). Further investigation into the role of exercise in early blood cancers is thus warranted, given the potential anti-tumour benefits that may be attained, and the lack of current treatment options available to people with SMM and MGUS.

Exercise may also be an effective way to improve global health in MGUS and SMM. Indeed, structured exercise programmes has been found to improve a wide range of health outcomes in people with haematological cancers (e.g. MM, Hodgkin lymphoma, non-Hodgkin lymphoma). People with haematological cancers who perform structured exercise show improvements in quality of life, fatigue, strength (Groeneveldt et al., 2013; Persoon et al., 2017; Furzer et al., 2016; Joske et al., 2013) and cardiorespiratory fitness (Persoon et al., 2017; Furzer et al., 2016; Joske et al., 2013). High adherence was reported in these trials (85%: (Joske et al., 2013); 87%: (Groeneveldt et al., 2013); 91%:

(Furzer et al., 2016); 86%: (Persoon et al., 2017)) with no adverse events related to trial participation. Given that exercise is safe in these most advanced diseases, exercise is likely safe in MGUS and SMM, but this is yet to be evaluated. Accordingly, this study aims to confirm the feasibility and safety of exercise, as well as preliminarily explore the effects of exercise on disease activity, fitness and wellbeing outcomes, with a view to evaluating these outcome measures in a future, larger randomised-controlled trial.

In addition to establishing the benefits of exercise in MGUS and SMM, this study provides a unique methodological model to investigate the effects of exercise on neoplastic activity in humans. Given the relatively non-invasive and inexpensive measures of disease activity used in MGUS and SMM (e.g. M-protein, free light chains) which enable real-time monitoring of tumour flux, and the absence of confounding therapies (e.g. chemotherapy) that are typical of other cancer diagnoses, MGUS and SMM provide a unique model to prospectively assess the short-term effects of exercise on tumour activity *in vivo*, and in doing so conduct mechanistic investigations to discover how regular exercise averts tumour growth in humans. A number of anti-tumour mechanisms of exercise have been proposed, including immune function, inflammation and metabolic hormones (McTiernan, 2008), which will be explored as secondary outcome measures in our study herein.

In summary, the present pilot study aims to assess the feasibility and safety of an exercise programme in MGUS and SMM, and to provide preliminary data on disease activity, fitness and wellbeing outcomes for sample size calculations in a larger randomised controlled trial (RCT). Additionally, as part of this pilot study, a PhD project will investigate the potential mechanisms involved in possible changes in disease activity. Pilot data will allow a future larger randomised-controlled trial to be designed optimally and to be adequately powered to assess the effect of exercise on disease activity, mechanisms and global fitness and wellbeing outcomes in MGUS and SMM. The unique clinical model proposed herein is anticipated to improve our wider understanding of how physical activity is linked to reduced cancer risk.

Aims and outcomes

The present trial will investigate the feasibility and safety of a 16-week progressive, walking-based exercise programme for MGUS and SMM.

Primary objectives and outcomes, measured throughout the trial period:

- Uptake (proportion of people approached who attend screening, proportion of people who attend screening that are deemed eligible)
- Adherence (proportion of supervised and home-based exercise sessions prescribed that are actually completed)
- Compliance (prescribed vs. actual aerobic exercise completed per supervised/home-based session)
- Retention (the proportion of participants who complete baselines measures that also complete follow-up measures)
- Safety (incidence and severity of adverse events)

Secondary objectives and outcomes, measured pre- and post-trial period:

- Disease activity of MGUS and SMM (M-protein, serum free light chains, beta-2 microglobulin)
- Physical fitness (VO_{2MAX}, balance, flexibility, strength)
- Free-living physical activity (e.g. duration, intensity, frequency, energy expenditure) and sedentary time (also measured during 8-month follow-up)
- Body composition (height, weight, waist and hip circumference, fat mass, lean mass, sagittal abdominal diameter)
- Wellbeing indices (frailty, fatigue, sleep, quality of life)
- CRAB indices (e.g. calcium; renal function [creatinine, estimated glomerular filtration rate; eGFR]; anaemia [full blood count, haemoglobin]; bone health [bone mineral density, bone mineral content, bone turnover biomarkers])
- Resting blood pressure and heart rate

- Immune competency (e.g. phenotypic and functional analyses of peripheral blood mononuclear cells (PBMCs), serum and salivary immunoglobulins, differential blood count, infection history)
- Systemic basal inflammation levels (e.g. cytokines)
- Metabolic factors and hormone levels (e.g. glucose, insulin, growth factors)

Trial design

The trial is a pilot, single-centre, single-arm, phase I trial to evaluate the feasibility and safety of a progressive, walking-based exercise programme for MGUS and SMM. The intervention is a progressive, individually-prescribed, walking-based exercise programme for 16 weeks alongside usual care.

Participant eligibility criteria

The following inclusion criteria define people who are eligible for the trial:

- A diagnosis of:

  SMM. Defined by IMWG criteria as absence of MM defining events or amyloidosis, AND either: (i) serum monoclonal protein (IgG or IgA) >30g/L OR urinary monoclonal protein >500mg per 24h, AND/OR (ii) clonal bone marrow plasma cells 10-60%. People with SMM, given their higher risk of progressing to MM, will initially be prioritised for enrollment into the trial, followed by people with MGUS, described next.

  OR

  MGUS. Defined by IMWG criteria as absence of end-organ damage attributable to the plasma cell proliferative disorder (such as hypercalcaemia, renal insufficiency, anaemia, and bone lesions [CRAB]), or amyloidosis AND BMPC <10%* AND serum M-protein <30 g/L. *Bone marrow may not be sampled in people with low-risk MGUS where there are no clinical features concerning myeloma (Rajkumar et al., 2014).

  People with MGUS who present with disease progression risk factors will be prioritised for enrolment into the trial, risk factors are: non-IgG subtype, serum M protein ≥15 g/L, and abnormal serum free light chain ratio outside normal range [0.26-1.65]. Those with three risk factors will be prioritised first, followed by two risk factors, then one risk factor, and then zero risk factors.

- Age >18 years

Sub-groups will be excluded due to safety risks:

- World Health Organisation (WHO) performance status >1
- Pregnancy
- Deemed unsafe to exercise according to the Physical Activity Readiness Questionnaire (PARQ)
- Any comorbidity that is likely to progress or be exacerbated over the course of the trial period
- Cognitive impairment deemed a risk by the healthcare team for participation in the trial (e.g. diagnosis of neurodegenerative disease)
- Unable to understand explanations and/or provide informed consent
- Any condition and/or behaviour that would pose undue personal risk or introduce bias into the trial

Trial procedures

Recruitment

The Royal United Hospital Bath maintains an active database of people who are routinely monitored for MGUS and SMM, diagnosed by International Myeloma Working Group (IMWG) criteria (Rajkumar et al., 2014). Suitable candidates will be posted an invitation letter and participant information sheet, and will receive a follow up telephone call 5-7 days later from a member of the healthcare team to discuss the trial and gauge interest in participating.

Those who are interested will be asked preliminary screening questions with the aim of minimising the number of unnecessary visits for people who will be deemed ineligible at a later stage. People will then be invited to attend a screening visit in the outpatient haematology clinic (zone A12, Royal United Hospital Bath).

As part of routine care, people with MGUS and SMM are regularly contacted by the healthcare team via telephone and post (e.g. to update on clinic appointments, to discuss results from regular disease monitoring tests, and to make contact about relevant patient events such as Myeloma UK meetings). Therefore, this recruitment method is deemed suitable by the healthcare team as it is familiar and reflects usual communication practice. Consent to use personal data (e.g. address / telephone number / medical history / age) is not being collected prior to screening as only members of the healthcare team will access this information, and at this stage this information is being used solely to identify people who are potentially eligible to participate and to advertise the trial.

Screening

Telephone screening questions were developed by the researcher and haematologist with the aim of reducing the number of unnecessary face-to-face screening visits. The criteria checked during telephone screening are simple self-report questions:

- WHO performance status
- Pregnancy
- PARQ (a brief questionnaire that is standard to complete in exercise settings, e.g. when joining a gym. It covers aspects of medical status that are used to determine a person's safety to exercise. People who give positive responses (answering 'yes') will require clearance to participate from the haematologist during face-to-face screening).

Exclusion criteria that require the clinical judgement of the haematologist will only be addressed in face-to-face screening visits:

- Any comorbidity that is likely to progress or be exacerbated over the course of the trial period
- Cognitive impairment deemed a risk by the healthcare team for participation in the trial (e.g. diagnosis of neurodegenerative disease)
- Unable to understand explanations and/or provide informed consent
- Any condition and/or behaviour that would pose undue personal risk or introduce bias into the trial

Disease activity history, comorbidities and concomitant medications will be accessed from medical records by the researcher for reporting of eligibility after informed consent has been obtained.

Pre-screening procedures for the cardiopulmonary exercise test (Visit 2, page 14) will be performed at the screening visit. This includes resting electrocardiogram (ECG) and blood pressure. The ECG will be reviewed by Dr Daniel Augustine (Consultant Cardiologist, Royal United Hospital Bath) to identify risks that preclude cardiopulmonary exercise testing and ensure timely referral of participants for further assessment and intervention as needed. Anonymised ECG traces will be sent to Dr Daniel Augustine via NHS mail.

Consent

Written informed consent will be taken during the screening visit once patient eligibility has been confirmed and any questions about the trial have been answered. The haematologist will take informed consent.

People who elect not to participate during the initial telephone call, 5-7 days after receiving the recruitment material, will be asked during their next routine clinic appointment if they are willing to provide written informed consent to share their demographic data. This will be reported cross-sectionally at one time point to characterise people that decide not to take part for the primary trial outcomes, and will inform future design (e.g. recruitment strategies) of a larger RCT in this patient group.

Trial assessments

The trial comprises four measurement visits; two baseline visits (1 & 2) prior to the 16-week trial period, and two follow-up visits (3 & 4) following the 16-week trial period. Visits 1 & 3 take place in the Disability in Sport and Health

laboratory at the University of Bath, and Visits 2 & 4 take place in the Cancer Research Suite at the Royal United Hospital Bath. Measurements will also be taken throughout the 16-week trial period to address the primary outcomes.

Free-living measures

The participant will be given resources and equipment (i.e. an instruction pack), food diary, activity monitor and a sterile urine sample tube) for these measures at the screening visit after informed consent has been obtained. This allows measures to be completed prior to Visit 1 which will be scheduled a minimum of 9 days after screening.

Dietary composition: Participants will be provided with a 3-day food diary and instructions that explain how best to record everything they eat (e.g. portion size, cooking method, brand) for two weekdays and one weekend day. The records will be analysed using Nutritics software with the primary aim of characterising any changes to dietary intake between measurement points.

Physical activity: Participants will be given a BodyMedia Sensewear armband to wear for 9 days (to capture 7 full days) for measurement of free-living physical activity. The monitor is worn on the upper arm and records acceleration and skin temperature continuously. No identifiable data is collected by the BodyMedia Sensewear. Participants will be provided with instructions on how to use the monitor which emphasise the importance of wearing the monitor continuously aside from during waterborne activities e.g. showering/swimming. Data from complete days (>80% wear time) will be reported to examine any change in physical activity level between measurement points. The BodyMedia Sensewear will be loaned to the participant for the duration of measurement only. The devices are covered by the University of Bath insurance policy.

Urine sample: On the morning of Visit 1, participants will be asked to collect a mid-stream sample of their first-void urination in a universal, sterile sample tube for later analysis.

Visit 1

Participants will attend the University of Bath for a 1.5-hour measurement visit scheduled between 06:00 and 11:00 on a weekday. Participants will be asked to arrive fasted and having avoided caffeine since 22:00 the night before, and having avoided strenuous exercise and alcohol for 24 hours. A parking permit for the University will be given to participants at the screening visit. A sugary snack will be available for participants to consume following the visit.

Questionnaires

General health status: Incidence of recent infections, smoking status, alcohol intake (AUDIT-C), menopausal status (females only), stress (Perceived Stress Scale) and demographic information will be self-reported by the participant.

Quality of life: Health-related quality of life (QoL) will be assessed using the 36-item short form survey (SF-36) which includes eight domains: physical functioning; bodily pain; role limitations due to physical health problems; role limitations due to personal or emotional problems; emotional wellbeing; social functioning; energy/fatigue; general health perceptions and is validated for use with older adults. Overall QoL will be assessed using the Satisfaction with Life Scale: a 5-item questionnaire scored using a 7-point Likert scale that is validated for use in older adults.

Frailty: The International Myeloma Working Group (IMWG) frailty score is a validated questionnaire assessing aspects of frailty including comorbidities, basic activities of daily living (ADL) and instrumental ADL. The score is interpreted as fit (score = 0), intermediate-fitness (score = 1) or frail (score ≥2). Increased frailty is associated with mortality and treatment toxicity in people with MM (Palumbo, Bringhen and Mateos, 2016). Reducing frailty prior to MM diagnosis (i.e. in people with MGUS and SMM) may delay a deterioration in frailty further along the disease continuum and therefore improve treatment outcomes and prognosis. The determinants of the frailty score are potentially responsive to exercise training, e.g. functional capacity and comorbid cardiovascular diseases.

Sleep quality: The Pittsburgh sleep quality index (PSQI) is validated to assess sleep quality and pattern in older adults. It is a 19-item questionnaire scored using a 0-3 Likert scale, with a total score >5 indicating poor sleep quality.

Fatigue: The functional assessment of chronic illness therapy (FACIT) fatigue scale is validated to assess fatigue in older adults. It is a 13-item scale scored using a 0-4 Likert scale, with a total score <30 indicating severe fatigue.

Physical activity: The international physical activity questionnaire (IPAQ) short-form is validated to assess moderate and vigorous intensity physical activity and sedentary time. Participants will be asked whether their responses are representative of the past year, e.g. whether their physical activity level has been stable or whether they can pin-point a distinct change (taking up a new exercise behaviour). This will be plotted against their past 1-year disease activity.

Resting measurements

Blood pressure: Measured following 25 minutes of rest. An automated sphygmomanometer will be applied to the left arm. Systolic and diastolic pressure (mmHg) and pulse (bpm) will be measured three times in a seated position with 1 minute between each measurement.

Resting blood sample: Venous blood will be drawn from the antecubital vein by a trained phlebotomist (Vein Train course, University of Surrey, December 2015. Signed off as competent by University of Bath October 2017) after resting for 25 minutes. A total of 50 mL of blood will be drawn for later analysis; 15 mL in serum vacutainers (2 x 7.5 mL), 10 mL in EDTA vacutainers (2 x 5 mL), and 25 mL in a heparin-treated syringe (2 IU liquid heparin [1 IU/µL] per 1 mL blood).

Saliva: Participants will be asked to salivate into a sterile sample tube for 3 minutes. This is adequate time to provide a 1-2 mL sample for later analysis.

Anthropometrics: Body mass will be measured using digital scales and height using a stadiometer. Body mass index (BMI) will be calculated by dividing body mass (kg) by height (m) squared. Waist circumference (cm) will be measured at the narrowest point between the lowest rib and iliac crest, and hip circumference (cm) will be measured at the widest point of the gluteal using a tape measure.

Body composition: The participant will be positioned supine in a dual-energy x-ray absorptiometry (DEXA) scanner with their extremities within limits indicated and not touching their torso if possible. Fat mass (kg), lean mass (kg), body fat percentage (%) and bone mineral density (g/cm^2) will be measured. Fat mass index will be calculated by dividing fat mass (kg) by height (m) squared.

Visit 2

Participants will attend a 1-hour measurement visit at the Cancer Research Suite, Royal United Hospital, scheduled on a weekday. Participants will be reimbursed to cover the cost of parking (Benefits of participating, page 20).

Physical capacity

A functional fitness test battery has been validated in older adults to assess aspects of fitness that closely relate to the performance of activities of daily living (Rikli and Jones, 1999).

Balance: 8ft up-and-go test performance will be reported as the time (s) taken to get up from a sitting position (on a chair with a straight back and no arms), walk 8ft (2.44m) and return to a sitting position.

Strength: Upper-body strength will be reported as the average of three repetitions of a maximal grip strength test (kg) on each hand. Performance in a 30s chair stand test will be reported as the time (s) to complete five repetitions (strength) and the total number of repetitions completed (strength endurance) from a chair with a straight back and no arms.

Flexibility: Upper-body flexibility will be reported for left and right arms as the average distance (cm) between extended middle fingers in a back scratch test performed three times. Lower-body flexibility will be reported for left and right legs as the average distance (cm) between extended middle finger and the tip of the same-side toes in a chair sit-and-reach test performed three times.

Cardiorespiratory fitness

Maximal oxygen uptake (VO_{2MAX}) will be determined using a progressive incline cardiopulmonary exercise test (CPET) to volitional fatigue on a treadmill. Blood pressure and 12-lead electrocardiogram (ECG) will be recorded at rest. Treadmill speed will be kept constant, and after a 5-minute warm up at 0%, the gradient will increase by 3% every 3 minutes until fatigue (Thompson et al., 2010). Breath-by-breath gas exchange, ECG, blood pressure and oxygen saturation will be monitored continuously. A rating of perceived exertion (RPE) will be recorded at the end of each stage. A maximal effort will be verified by meeting two of four criteria: 1) heart rate (HR) within 10 bpm of age-

predicted maximum [220 – age (years)], respiratory exchange ratio ≥1.00, RPE ≥19 or an increment in VO_2 ≤5 mL.kg^{-1}.min^{-1} in response to increased gradient.

Participants unable to comply with the exercise test, for example due to a health problem raised during the exercise test (e.g. abnormal ECG or blood pressure response) or serious discomfort exercising, will discontinue involvement in the study on safety grounds. Abnormal test results will be referred to a cardiologist who will provide follow-up care and advice on the participants continued involvement in the trial. The decision on whether to repeat baseline measures will be discussed with the trial management group; e.g. if follow-up care results in a considerable delay, there may be a need to repeat baseline measures prior to commencing further trial activities.

Trial period measurements

Participants will complete a Session Record Card in each supervised session. Home-exercise will be monitored using a Home Exercise Diary which will be reviewed each week. Participants will also be provided with a fitness tracker (Polar A370 wrist-worn device) for the duration of the trial period to record all training sessions. Data from the tracker will be downloaded by the researcher once a week, and the tracker will be returned after Visit 4.

The primary outcome of feasibility refers to the overall viability of the exercise intervention (e.g. how well can we recruit, can we keep participants engaged, are participants able to achieve the exercise intensities required) and the safety (e.g. do adverse events occur and are they unexpected and related to the trial treatment):

Uptake: Proportion of people approached who attend screening (recruitment rate) and the proportion of people who attend screening that are deemed eligible (screen-pass rate). Demographic characteristics will be compared across those who a recruited and those who decline to participate.

Adherence: Number of supervised and home-exercise sessions completed measured using a Session Record Card, Home Exercise Diary and Polar A370.

Compliance: Prescribed vs. actual aerobic exercise completed in each supervised session will be measured using the Polar A370 and chest strap HR monitor. Compliance to home-based aerobic exercise will be measured using the Polar A370.

Retention: Proportion of participants who complete baselines measures (i.e. Visit 1 and 2) that also complete follow-up measures (i.e. Visit 3 and 4).

Safety: Incidence and severity of adverse events (Table 1). [Recording and reporting of SAEs will follow University of Bath policy – The chief investigator (CI) should report any SAE to the sponsor within 24 hours. A written SAE report (health research authority [HRA] form) should be made by the lead researcher and sent to the CI who will assess the seriousness, causality and expectedness. Where the SAE is related and unexpected, the CI will notify the research ethics committee (REC) within 15 days of receiving the report. AEs and SAEs will be discussed by the trial management group.]

Table 1. Definitions of adverse events

Term	**Definition**
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that product.
Serious Adverse Event (SAE)	A serious adverse event in the context of this trial is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

	NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Follow-up measurements

Free-living measurements will be repeated post trial-period (week 17). Resources and equipment (i.e. an instruction pack, food diary, activity monitor and a sterile urine sample tube) to complete these measures will be given to participants in their final exercise session.

After the trial period, participants will repeat baseline visits. Measurements conducted during Visit 3 will replicate Visit 1, and measurements conducted during Visit 4 will replicate Visit 2, as described above.

Participants will answer a physical activity questionnaire (IPAQ short-form) via telephone interview at time-points which coincide with routine disease monitoring during the 8 months following visit 4.

Withdrawal criteria

Participants may be withdrawn from the trial if there is a change in their eligibility e.g. disease progression to symptomatic multiple myeloma. During visit 2, contraindications and limitations to exercise may be identified during the CPET (Ats and Accp, 2003) which will result in participants being withdrawn on safety grounds. All withdrawals will be discussed with the haematologist and reported in primary outcomes (retention).

Storage of clinical samples

Samples will be collected and processed in a laboratory at the University of Bath:

- 15 mL into serum vacutainers, from which serum will be extracted and stored in multiple aliquots at −80^{O}C for later analysis (e.g. disease activity, immune competence, inflammation, hormones and metabolic factors).
- 25 mL into a heparin-treated syringe, from which peripheral blood mononuclear cells (PBMCs) will be isolated by density gradient centrifugation and stored at −140 to −150^{O}C for later analysis (e.g. phenotypic and functional measures of immune competence).
- 10 mL into EDTA vacutainers, from which a small fraction (50 µL) will be used to assess the leukocyte differential/whole blood cell count. This 50 µl of whole blood is destroyed and rendered acellular during measurement. This process will be repeated twice and average values reported. From the remaining 9 mL, plasma will be extracted and stored in multiple aliquots at −80^{O}C for later analysis (e.g. disease activity, immune competence, inflammation, hormones and metabolic factors).
- 1-2 mL of saliva will be centrifuged and split into multiple aliquots and stored at −80^{O}C for later analysis (e.g. disease activity, inflammation and immune competence).
- 15 mL of urine will be centrifuged and split into multiple aliquots and stored at −20^{O}C for later analysis (e.g. disease activity, inflammation and immune competence).

Trial treatment

Participants will complete a progressive, individually-prescribed, walking-based exercise programme including aerobic, resistance and flexibility exercises. The programme will be delivered as two supervised exercise sessions and one home-based session each week.

Aerobic exercise, beginning at a moderate intensity and progressing to vigorous intensity during supervised sessions, is the main component of the exercise programme because it elicits numerous physiological effects that have been hypothetically linked to reduced neoplastic growth:

1) Immune competency: exercise causes a profound intensity-dependent redistribution of immune cells (e.g. natural killer [NK] cells and CD8 T cells) (Campbell et al., 2009), leading to heightened anti-tumour immune surveillance; this process has been found to increase killing of myeloma cells *in vitro* (Bigley et al., 2014). Mobilisation of NK cells is dependent on adrenaline increase during exercise, which is greater at higher exercise intensities (Romijn et al., 1993). In animal studies, the mobilisation of NK cells during exercise has

been shown to reverse tumour growth across five different tumour models, and these anti-tumour effects of exercise are blunted by the beta-blocker propranolol (Pedersen et al., 2016). As such, it is hypothesised that heightened immune surveillance during exercise may, in a form of exercise immunotherapy, lead to reduced neoplastic activity.

2) Basal systemic inflammation levels: systemic inflammation (interleukin [IL]-6; C-reactive protein [CRP]) is reduced following both moderate (Thompson et al., 2010; Stewart et al., 2007; Fedewa et al., 2017) and vigorous (Munk et al., 2011; Stewart et al., 2007) intensity exercise training. Inflammatory cells and cytokines support cell growth, survival and spread (Grivennikov, Greten and Karin, 2010), and medication with anti-inflammatory agents decreases incidence and recurrence of a number of cancers (Rayburn, Ezell and Zhang, 2009). It is hypothesised that the anti-inflammatory effects of regular exercise may also ameliorate neoplastic activity.

3) Metabolic factors and hormone levels: insulin and insulin-like growth factor [IGF]-1 are reduced, and IGF binding protein [IGFBP]-3 is increased with moderate-vigorous intensity aerobic exercise (Francisco Meneses-Echavez et al., 2016). This results in a lower bioavailability of metabolic factors and hormones which are associated with growth and survival of MM cells (Bieghs et al., 2016), and may lead to reduced neoplastic growth.

4) Body composition: visceral adipose tissue is significantly reduced following moderate (Slentz et al., 2005) and vigorous (Irving et al., 2008) intensity aerobic exercise. Body composition change may mediate the mechanistic link between an exercise-induced reduction in systemic inflammation and neoplastic activity, as visceral adipose tissue secretes high quantities of inflammatory cytokines in obese individuals (Fontana et al., 2007) and exercise-induced reductions in inflammation are greater when a reduction in body fat is also measured (Fedewa, Hathaway and Ward-Ritacco, 2017). The resulting reduction in chronic, systemic inflammation as a result of reduced cytokine production by smaller visceral fat stores, may reduce tumour growth, survival and spread (as explained above).

Progressive resistance exercise is incorporated into the supervised exercise sessions in this study to; (i) to support safe progression through the incremental aerobic exercise programme, (ii) to add variety to the exercise classes to maintain participant enjoyment and motivation to attend, (iii) for diverse outcomes for older adults, e.g. reduce falls risk (Buchner et al., 1997).

A home-based session has been included to increase exercise frequency without the additional burden of visits on participant's time and research feasibility. Home-based sessions are also being evaluated for potential use in a future, larger randomised-controlled trial. Walking exercise has been selected as this is an intervention that is accessible to the majority of people with MGUS and SMM.

Supervised exercise sessions

Supervised exercise sessions will be performed in the physiotherapy gym at the Royal United Hospital Bath. Each session lasts approximately 1 hour, and equipment needed for all exercises is available in the physiotherapy gym, including resistance bands and treadmills. A brief screening, including blood pressure measurement and review of health status, will take place before each supervised session to determine safety to exercise (unsafe if: blood pressure >200/120 mmHg (Ats and Accp, 2003) or participant reports new symptoms).

Exercise sessions will be offered at various times throughout the day so the programme is accessible to as many participants as possible, including those with diverse/busy routines (e.g. working / retired). Each exercise class has a maximum capacity of five participants per session. There will be drop-in sessions available for participants who have not been able to attend their scheduled exercise sessions.

Aerobic component

Participants will perform a warm up on the treadmill at a comfortable walking speed and 0% incline ('unloaded walking') for a minimum of 5 minutes. Aerobic training will then commence for 30 minutes. Participants will perform

three sets of 10-minute walking intervals (Table 2). For each interval, the gradient is increased during the 'work phase' to achieve a target HR (8 minutes, 40-80% VO_{2MAX}) followed by 'unloaded walking' (2 minutes). Target HR will be prescribed and monitored using HR data measured during CPET; participants will be given a HR zone that corresponds to the target percentage of VO_{2MAX}. An RPE guide (Borg 6-20 scale) will be used for people who present with a blunted HR response during CPET (e.g. medicated with beta blockers) as their HR response will be too small to differentiate zones that span a 10% change in VO_{2MAX}.

The Polar A370 will be worn with a chest strap HR monitor (Polar H10) during every supervised exercise session to prescribe intensity and record the session. The HR, RPE, speed and gradient will be recorded for each interval.

Table 2. Aerobic exercise prescription

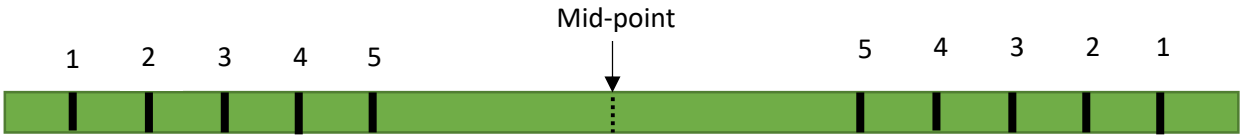
Trial week	Number of intervals	Work duration (minutes)	Work phase intensity (% VO_{2MAX})	Work phase intensity (RPE)	Rest duration (minutes)	Total duration (minutes)
1-2	3	8	40-50	12-13	2	30
3-6	3	8	50-60	13-14	2	30
7-10	3	8	60-70	14-15	2	30
11-16	3	8	70-80	15-16	2	30

The primary outcome of the trial is to assess the safety and feasibility of exercise in people with MGUS and SMM. We anticipate this prescription to be safe, as older adults with heart failure can safely perform interval training up to 95% HR_{MAX} (Wisloff et al., 2007), and people with symptomatic MM – a much more severe form of disease than MGUS and SMM – can safely exercise up to 60% heart rate reserve (Groeneveldt et al., 2013). The programme has been designed to allow gradual adaptation whilst steadily progressing to vigorous intensity over 16 weeks to maximise anti-tumour benefits by stimulating adrenaline-dependent immune cell redistribution (Pedersen et al., 2016). Treadmill walking has been selected because: (i) whole-body exercise elicits a robust array of physiological benefits compared to aerobic exercise of confined muscle groups (e.g. cycling or arm-crank); (ii) weight-bearing exercise improves bone strength (McMillan et al., 2017); and (iii) it is more accessible and can be more readily replicated in the real world, as compared to other exercise modalities.

Resistance component

A whole-body resistance training programme will be performed using elastic resistance band exercises. Elastic resistance bands provide a cheap and simple method of applying resistance. The programme progresses every four weeks targeting increase in muscular strength (Table 3).

Participants will perform two sets of 12-6 repetition maximum (RM) of six large muscle group exercises (reverse fly, chest fly, core twist, squat, calf raise, abduction) in line with resistance training guidance for people with a cancer diagnosis (Galvao et al., 2007). During a familiarisation session, the researcher will identify the colour of resistance band and grip rating that gives 12 RM for each exercise (e.g. level 1-5; diagram below) (Smith et al., 2017). This will be reassessed prior to each structured progression. To ensure continued progression, participants will be instructed to work past the prescribed RM and if they exceed the repetition target then additional resistance will be added prior to the next set/session by increasing grip rating or band colour (Cormie et al., 2013).



During familiarisation, the researcher will demonstrate each exercise and give feedback on a return demonstration performed by the participant. During subsequent sessions, circuit cards will be positioned around the physiotherapy gym to prompt correct technique and the researcher will be on-hand to provide assistance if needed. Participants will be asked to record the number of repetitions they perform, RPE, band colour and grip rating for each set in their session record card.

Table 3. Resistance exercise prescription			
Trial week	**Number of sets**	**Number of exercises**	**RM prescription**
1-2	2	6	15
3-6	2	6	12
7-10	2	6	10
11-16	2	6	8

Home-based exercise

Participants will be asked to complete one 40-minute walk each week at a moderate intensity (RPE 12-14) and daily balance and flexibility exercises (performed on days without a supervised session) which are detailed in the Home Exercise Pack. This increases the weekly aerobic exercise volume to 75-150 minutes at a moderate-vigorous intensity, and increases the frequency of balance and flexibility exercises, in line with WHO guidelines for physical activity in older adults.

Behaviour change

Psychological sources of behaviour are important to consider when introducing a novel behaviour, i.e. an exercise programme, in order to optimise uptake, adherence, compliance and retention. Additionally, developing positive psychological processes in participants should increase the likelihood of continuing exercise after the trial ends for maintenance of any benefits attained. This reflects clinical practice in other exercise-based therapies delivered by the NHS (e.g. cardiac rehabilitation involves ~12 weeks of outpatient exercise classes [phase 3], after which patients transition to independent, ongoing conditioning in the community [phase 4]). In light of this, behaviour change techniques from a standardised taxonomy (Michie et al., 2011) have been included in the trial design (Table 4).

Table 4. Behaviour change considerations	
Behaviour change technique	**Implementation in present trial**
Informational support	• Participants will be given detailed information about the exercise programme in the recruitment material, and will be encouraged to ask questions to ensure they understand the programme and the trial. • At the end of the trial, the researcher will provide participants with information on local exercise referral schemes.
Information on consequences of behaviour	• The recruitment material describes the positive effects of exercise for health, explaining the rationale behind each component of the programme, which will be reinforced by the researcher during face-to-face interactions. • Participants will be given a feedback report highlighting the health benefits attained during the exercise programme.
Feedback on performance	• Participants will be given regular feedback on how well they are meeting the progression targets set out in the exercise programme.
Self-monitoring	• Participants will be given a fitness tracker (Polar A370) to record habitual physical activity and home-based exercise, which will give feedback on their progress.
Instruction on how to perform behaviour	• The researcher will teach the participants how to perform the different exercises outlined in the exercise programme.
Social support	• Group exercise sessions will create a social environment for related peers, with the aim to keep classes at consistent times for each participant to allow relationships to be formed within the group. • The researcher will facilitate grouped home-based exercises by identifying walking routes/meeting points for local participants.

Action planning	• The exercise programme has a highly prescriptive action plan for 16 weeks.

Benefits of participating

Participants will be provided with bespoke feedback on their test results after completing the trial period. This will include physical activity levels, dietary composition, blood pressure, body composition, cardiorespiratory fitness and physical capacity, with reference to population norms and recommended guidelines – and highlighting any changes that occur between baseline and follow-up measures. We will not be providing feedback on data collected from blood samples because most of the measurements are preliminary research parameters and are not diagnostic; routine blood test results will continue as normal and participants will have access to these results as per routine.

Abnormal results from the CPET will be flagged up with the haematologist, who may advise referral to another healthcare professional (e.g. general practitioner or cardiologist) which will be done by letter or email. In this case, 'abnormal' is defined as the presence of a criteria for exercise contraindication or early test termination, as defined in CPET guidelines (Ats and Accp, 2003).

Participants will receive 32 supervised exercise sessions for free, which would typically cost upwards of £320 privately (i.e., £10 per session).

Participants will be given an information sheet upon completing the exercise programme with recommendations on staying active upon completion of this study. This will include a home-exercise programme and resistance bands provided free of charge, and information on local exercise referral schemes.

Participants will be receive a payment of £100.00 in cash at the end of the trial. This amount covers costs associated with travel, calculated based on the number and average distance to travel for trial visits, and parking costs.

Risks of participating

The trial has been designed to reduce risks and burdens as much as possible, with the further aim of reducing potential risks and burdens further by strict adherence to best practice.

The exercise components of the trial (maximal treadmill exercise test and exercise programme sessions) carry a risk of injury and acute complications.

- The acute risks of exercise will be minimised by performing thorough screening at trial entry via medical note review by the haematologist, PARQ, blood pressure checks, and resting and exercise ECG.
- We will also assess risk before each exercise training session by asking participants if they have had any symptoms of health change since their last session, and measuring their blood pressure prior to exercise.
- Exercise training will be personalised to each individual based on their fitness level and ability so as to promote a safe exercise training programme.
- All exercise sessions will be undertaken at the Cancer Research Suite at Bath Royal United Hospital. The Cancer Research Suite is located within the physiotherapy department, and is thus in close proximity to nurses and other care specialists with first aid training. Adjacent to the Cancer Research Suite is an emergency trolley bed, and an emergency telephone for contacting accident and emergency or other care services.

Another consideration is that participants will undergo a body composition assessment by DEXA which uses a very low dose radiation. Participants will be advised that this scan allows the most accurate (i.e. 'gold-standard') measurement of their body composition (e.g. fat, bone mineral density) and it is safe, with each scan eliciting a dose of radiation equivalent to a very short airplane flight (e.g. from London to Paris).

Taking a blood sample via venepuncture brings risks including pain, bleeding, bruising, embolism and infection. These risks are controlled by adherence to best practice. People with MGUS and SMM will be very familiar with the sensations associated with a blood test as this is the primary way their disease is monitored routinely.

Wearing activity monitors for prolonged periods may, in some cases, result in some minor skin irritation, but this will be minimal and good practice minimises this risk. Participants will be provided with verbal and written information on how to use the activity monitors to minimise this risk.

An important consideration for the research team when designing this study was the amount of time each participant will have to commit to the trial, which includes: 1 hour of screening and consenting, up to 5 hours of measurement visits and, finally, 32 exercise sessions (32 separate one hour visits). The screening visit has been planned to coincide with usual clinic hours at the haematology outpatients, so that people will be accustomed to the timing of this session, the familiarity of the physical environment and the practicalities of attending (e.g. parking, navigation of hospital). Trial measurement visits will be scheduled at a time of day according to the participant's availability. The exercise sessions will be run throughout the day and evenings to allow participants to choose the most suitable time for them to attend. These time considerations were made so that people who want to enrol, but are limited in terms of time availability can participate (e.g. if they have a job).

Statistics and data analysis

Sample size

The aim is to recruit 20 participants. Assuming a recruitment rate of three to four people per month and 15% drop out, we estimate the target can be reached within a suitable time-frame so the findings can be submitted for a PhD thesis (12-15 months).

There is limited information available to enable a formal sample size calculation. This pilot trial will provide preliminary data to determine that a future RCT has promise and is not futile, and to perform a sample size calculation.

Statistical analysis plan

Primary outcome measures do not lend themselves to statistical analysis. Feasibility will be reported as proportions in terms of uptake, adherence, compliance and retention. Safety will be reported as the incidence and severity of adverse events.

Secondary data will be tested for normality (e.g. Shapiro-Wilk) and in the event that some data are not normally distributed, the data will be log transformed. Descriptive statistics will be presented, and longitudinal differences and interaction effects will be identified using repeated-measures T-tests. These data will be used to inform sample size calculations in a future RCT. Incomplete data and missing values will be managed using an intention-to-treat approach with multiple imputation.

The PhD project may utilise correlation analysis to establish whether any change in disease activity is associated to a number of mechanistic markers, and stepwise multiple regression will identify the extent to which a change in the mechanistic markers predict change in disease activity. Subgroup analysis may be performed, e.g. split to high vs. low responders or by presence of mediating variable(s) for further analysis.

Monitoring, audit and inspection

The University of Bath, 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.

Patient safety will be monitored on an ongoing basis by the research and healthcare team. A formal data monitoring committee will not be convened as this is a small single-centre pilot study. Instead, the lead researcher (PhD Student, Annabelle Emery) will present an update on safety at quarterly trial management group meetings, together with the haematologist (Dr Moore), the CI and primary PhD supervisor (Dr Campbell), secondary PhD supervisor (Dr Turner) and patient representative(s).

Ethical and regulatory considerations

Research Ethics Committee (REC) review

Before the start of the trial, approval will be sought from an NHS REC for the trial protocol, informed consent forms, participant information sheet and recruitment letter. Substantial amendments will require review by the NHS REC will not be implemented until the NHS REC grants favourable opinion.

Public and patient involvement

A group of people diagnosed with MGUS and SMM were invited to the University of Bath on the evening of Wednesday 23rd November 2017 to discuss the proposed trial design with the research team. Discussions were held on the following topics, with feedback on each point was incorporated into the trial protocol and other trial documents:

- Proposed recruitment strategies, including invitation letters and follow-up invitation phone calls from the haematology department.
- Wording of trial documents, including the participant information sheet and consent forms.
- Practicalities of participant involvement in the trial, including: total time commitment, time of day preferences for people who are retired and people who are in full-time work, travel to the different research sites (University of Bath and Royal United Hospital), and financial reimbursement for travel.
- All research measurements being taken in this trial, including blood sampling, DEXA (body composition) scans, and the exercise fitness test.
- Design of the exercise programme, including discussions about acceptability of treadmill walking exercise, preferences for class-based exercise sessions rather than private one-to-one exercise sessions.
- Use of fitness trackers (i.e. Polar A370) to monitor participant physical activity levels throughout the trial, which including discussion about patient desire to wear such technology as this is a motivating factor for them to lead a healthier lifestyle.

People with MGUS and SMM will also be involved in the analysis of results via the trial management group, and dissemination of findings through Myeloma UK – for which Dr Moore (haematologist) Chairs meetings of the Myeloma UK South West group.

Regulatory compliance

Procedures for DEXA scanning are compliant with Ionising Radiation (Medical Exposure) Regulations and have been reviewed by a Medical Physics and Clinical Radiation Expert.

Protocol compliance

Prospective, planned deviations to the protocol are not allowed under the UK regulations on research trials. Accidental deviations can happen at any time and should be documented and reported to the CI. Frequently recurring deviations can be classified as a serious breach. Deviations are not anticipated as the research team is relatively small, and each member has been closely involved in the writing of this protocol.

Competing interests

There are no competing interests that will influence design, conduct or reporting of this trial.

Indemnity

The Sponsor (University of Bath) insurance will cover the legal liability for harm to participants arising from the design, management and conducting of this research.

Amendments

Substantial amendments to the documents submitted in the original REC application will be submitted using a valid notice of amendment to REC and to the trial sponsor. Non-substantial amendments will be made throughout the trial as needed. The CI will be responsible for determining whether an amendment is substantial. Substantial amendments will be highlighted in a new version of the document.

Data management and confidentiality

The University of Bath will act as the Data Controller for data generated by this trial.

Identifying data (name, date of birth, contact details and next of kin details) will be kept by the Royal United Hospitals Bath NHS Foundation Trust. This data will be stored in a password-protected Excel spreadsheet on a desktop computer stored in a locked room. This data will be deleted following the final study contact during the eight-month follow up. Signed consent forms will be stored in a locked cupboard and kept for 10 years to evidence the consent process.

Deidentified study data, coded with a unique study ID assigned to each participant, will be kept by the University of Bath. This data will be stored on the University of Bath X Drive which is backed up daily by the Library. The study-specific folder can only be accessed by the research team. Hard copies of trial data will be stored in a locked cupboard at the University of Bath. Study data will be kept for 10 years in line with the University of Bath research data policy (see: http://www.bath.ac.uk/research/data/policy/index.html).

Post-trial care

Participants will be given an information sheet upon completing the exercise programme with recommendations on staying active. This will include a home-exercise programme plus resistance bands, and information on local exercise referral schemes.

The researcher will telephone participants eight months following visit 4 – representing a full year since they entered the study. They will ask questions about current physical activity habits and identify participants who need additional information on how to lead an active lifestyle. Further signposting will be provided as a duty of care.

Access to the final trial dataset

All protocol contributors named in this document will have access to the final trial dataset. Requests for access by other researchers within the Department for Health at the University of Bath will be approved by the trial management group.

Dissemination policy

A trial protocol will be published prior to trial completion. The data arising from this trial will be submitted for publication and presented at conferences and meetings. It will also be reported as part of a PhD thesis. People will be notified of the outcomes of the trial via Myeloma UK South West.

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