Department for Health | UNIVERSITY OF BATH

Evaluating the safety and acceptability of a progressive exercise training intervention for Chronic Lymphocytic Leukaemia: a randomised-controlled pilot trial.

Short title: Safety and acceptability of exercise for Chronic Lymphocytic Leukaemia.

IRAS PROJECT ID: 292564

ISRCTN:

TRIAL PROTOCOL: Version two

SPONSOR: University of Bath

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Contents

List of abbreviations

AE	Adverse Event
ANOVA	Repeated Measures Analysis of Variance
BMI	Body Mass Index
CI	Chief Investigator
CLL	Chronic Lymphocytic Leukaemia
CLL16	CLL-specific module.
DEXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
FACIT	Functional Assessment of Chronic Illness Therapy
HR	Heart Rate
HRA	Health Research Authority
IPAQ	International Physical Activity Questionnaire
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
LV	Left Ventricular
METs	Metabolic Equivalents
PARQ	Physical Activity Readiness Questionnaire
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PIC	Participant Identification Centre
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RPE	Rating of Perceived Exertion
RUH	Royal United Hospital
SAE	Serious Adverse Event
VO_{2MAX}	Maximal oxygen uptake
WHO	World Health Organisation

Trial summary

Trial Title	Evaluating the safety and acceptability of a progressive exercise training intervention for Chronic Lymphocytic Leukaemia: a randomised-controlled pilot trial.	
Short title	Safety and acceptability of exercise for Chronic Lymphocytic Leukaemia.	
Clinical Phase	I	
Trial Design	Pilot, single centre, randomised-controlled, phase I trial	
Trial Participants	People diagnosed with Chronic Lymphocytic Leukaemia (CLL) will be invited to participate in this study. These people will be physically inactive and have asymptomatic early-stage CLL monitored without anti-CLL treatment, also known as 'watch and wait' CLL. Participants will be randomly allocated to either an exercise training intervention group, or a usual care control group.	
Planned Sample Size	Exercise training intervention n= 20 Usual care control group n= 20 Total sample size N= 40	
Intervention Duration	16 weeks	
	Objectives	**Outcome Measures**
Primary	Investigate the safety and acceptability of an exercise training intervention, in physically inactive people, with asymptomatic early stage 'watch and wait' CLL.	The following will be assessed for safety and acceptability of exercise: • Safety (incidence and severity of adverse events) • Uptake (proportion of people approached who attend screening, proportion of people who attend screening that are deemed eligible) • Adherence (proportion of exercise sessions prescribed that are actually completed) • Compliance (prescribed vs. actual aerobic exercise performed per exercise session) • Retention (the proportion of participants who complete baseline measures that also complete follow-up measures)

Secondary	Investigate the effect of an exercise training intervention on CLL disease activity, immune markers, overall fitness, health and wellbeing in physically inactive people, with asymptomatic early stage 'watch and wait' CLL.	The following measurements will be collected to assess the effect of an exercise training intervention in participants with 'watch and wait' CLL: • Frequency of CLL cells in peripheral blood measured by flow cytometry • Immune competency (e.g. phenotypic and functional analyses of PBMCs, differential blood count, viral infection history, immunoglobulins, complement proteins) • Basal inflammation (e.g. cytokines) • Metabolic factors and hormone levels (e.g. glucose, insulin, growth factors) • Clonality of tumour cells (e.g., PCR). • Genetic and epigenetic features of tumour and immune cells. • Physical fitness (predicted VO_{2MAX}) • Body composition (height, weight, waist and hip circumference, fat mass, lean mass) • Wellbeing indices (physical activity, stress, fatigue, sleep, quality of life, self-efficacy, Motivation) • Resting blood pressure and heart rate. • Left ventricular (LV) function (volumes; ejection fraction; strain; diastolic function). • Comparison of LV manual measures with artificial intelligence.
Intervention	A home-based, progressive, exercise training intervention, observed by a member of the Research Team via a video communication platform.	
Dose	Two home-based static bike exercise sessions observed by a member of the Research Team via a video communication platform, and one un-supervised walking exercise 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.

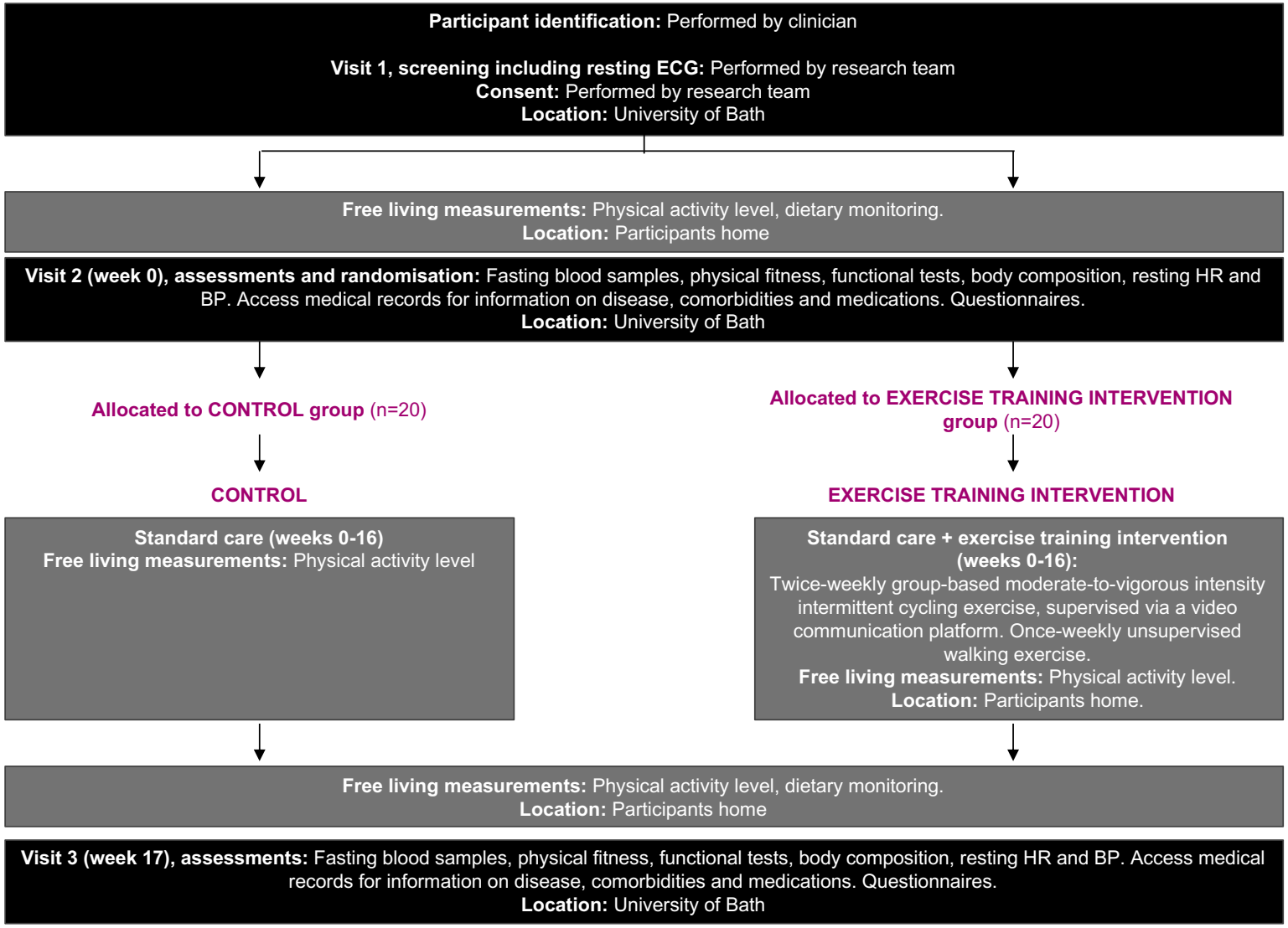
Roles and responsibilities of the trial management group

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.

Key words

Chronic lymphocytic leukaemia; exercise training; B cells; health; feasibility; T cells

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																		
Blood tumour cell frequency	X																	X
Immune competency	X																	X
Basal inflammation	X																	X
Metabolic factors and hormone levels	X																	X
Clonality of tumour cells	X																	X
Genetic and epigenetic features of tumour and immune cells	X																	X
Body composition	X																	X
Wellbeing indices	X																	X
Heart rate and blood pressure	X																	X
Physical fitness	X																	X
Control measures																		
Dietary intake	X																	X
Physical activity level	X		X				X				X				X			X
General health status	X																	X

Background and Summary

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia in the UK with an estimated annual incidence of 7.6 per 100,000 people (Smith et al., 2018).

CLL is characterised by the clonal proliferation and accumulation of mature B cells within the blood, bone marrow, lymph nodes and spleen (Hallek et al., 2018a). The most common presentation of CLL is the incidental discovery of a B cell lymphocytosis, of at least 5000 B cells per μL of peripheral blood, sustained for at least 3 months (Hallek et al., 2018a). Diagnosis is subsequently confirmed by evaluating the blood smear, B cell clonality and immunophenotype.

CLL is considered incurable but treatable and the majority of recently diagnosed patients present with asymptomatic, early stage disease (Hallek et al., 2018b). In such cases the current gold standard approach is clinical observation without therapy – defined as 'watch and wait' – patients are monitored without anti-CLL treatment, until there is evidence of progressive or symptomatic disease, summarised and defined as 'active disease' (Hallek et al., 2018a). Patients with asymptomatic, early stage CLL, monitored via 'watch and wait', will be referred to as patients with 'watch and wait' CLL, throughout this protocol. Patients with 'watch and wait' CLL are reviewed at least twice within the first year from diagnosis to assess the rate of disease progression, for those with stable disease, monitoring is then extended to an annual check (Oscier et al., 2012). The purpose of disease monitoring is to identify progression to 'active disease' and commence active treatment, typically via chemoimmunotherapy, depending on the patient's clinical stage and symptoms. Current guidelines do not recommended treatment in 'watch and wait' CLL, clinical trials investigating early therapeutic intervention have not observed an improved clinical outcome in patients with CLL when compared to 'watch and wait' (Herling et al., 2020, Dighiero et al., 1998, Hoechstetter et al., 2017, Hallek et al., 2018a). Therefore, the evidence gained from clinical trials suggests that there is no clinical benefit of exposing patients with asymptomatic, early stage disease to the toxicity of anti-CLL treatment before there are signs of progression to 'active disease'. Moreover, the majority of patients with 'watch and wait' CLL experience an indolent disease course with neither compromising morbidity nor an elevated risk of premature death caused by the CLL (Binet et al., 1981). Therefore, people with 'watch and wait' CLL may benefit from non-toxic interventions that delay the progression to 'active disease'.

Exercise may be an effective way to manage disease burden in people with 'watch and wait' cancer. Epidemiological evidence, from adults in the general population, prior to a cancer diagnosis, indicates that cohorts with higher levels of physical activity have lower rates of cancer incidence (Moore et al., 2016). Furthermore, following a diagnosis, both epidemiological and randomised controlled trial evidence suggests that exercise reduces the relative risk of cancer mortality and cancer recurrence. The strongest evidence for a reduction in the relative risk of cancer mortality and recurrence has been observed in the most common and highly studied cancers of the breast, colorectal and prostate (Cormie et al., 2017, Friedenreich et al., 2016). Mechanistically, 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 reduce tumour mass in a wide range of genetic, transplant and chemically-induced tumour models in mice (Pedersen et al., 2016, Ashcraft et al., 2016, Rundqvist et al., 2020). Together, this evidence from epidemiology studies, clinical trials and preclinical animal models raises the question of whether exercise can be used as an intervention to manage disease activity in people with 'watch and wait' CLL, and delay the progression to 'active disease'. However, before studies investigate time to disease progression in CLL, the safety and acceptability of exercise training in people with 'watch and wait' CLL must be established.

Exercise training may also be an effective way to improve fitness, overall health and wellbeing in for people with 'watch and wait' CLL. It is well established that exercise training reduces the risk of cardiometabolic disorders such as hypertension (Herrod et al., 2018) and dyslipidaemia (Kelley et al., 2005). The evidence of the effects of exercise on these variables in people with haematological cancers is limited, but it is anticipated that the universal cardiometabolic and muscle-mass benefits of exercise are translatable to CLL. As a proxy indicator of cardiometabolic health, it has been shown that cardiorespiratory fitness is modifiable by exercise training in people with haematological cancers. In 122 (including 14 CLL) participants with a haematological malignancy receiving chemotherapy (Courneya et al., 2009), objectively measured cardiorespiratory fitness improved by 4mL/kg/min of O_2 in an exercise training group compared to a decrease of 2mL/kg/min of O_2 in a usual care group. Patient-rated physical functioning, quality of life, fatigue, depression, and happiness scores were also improved in the exercise group (Courneya et al., 2009). A growing body of evidence indicates that quality of life (QoL) is enhanced in people with haematological cancers who are engaged in exercise training, the most pronounced impact is the observation of a positive effect on fatigue and depression (Knips et al., 2019). Given that exercise training is safe in these people with haematological cancers, some of which were on active treatment (Courneya et al., 2009) at the time of the observations, exercise training is likely safe, acceptable and effective for improving a wide range of health and wellbeing related outcomes in people with 'watch and wait' CLL, but it is yet to be evaluated.

In addition to establishing the benefits of exercise training in people with 'watch and wait' CLL, this study provides a unique methodological model to investigate the effects of exercise on neoplastic activity in humans. Given that CLL tumour cells are highly abundant in peripheral blood (>5000 cells/ul) and thus easily and relatively non-invasively accessible, and the absence of confounding therapies (e.g. anti-cancer therapy), that are typical of other cancer diagnoses, people with 'watch and wait' CLL provide a unique model to prospectively assess the short-term effects of exercise training on tumour cell mass and 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, adipose tissue and metabolic hormones (McTiernan, 2008), which will be explored as secondary outcome measures in our study herein.

Accordingly, this study aims to confirm the safety and acceptability of an exercise programme in people with 'watch and wait' CLL, as well as preliminarily explore the effects of exercise training (pre-intervention to post-intervention) on tumour cell mass (CLL tumour cell frequency) in peripheral blood. The aforementioned data will be used as preliminary data for a power calculation, for a future larger randomised control trial. Additionally, this study will enable preliminary assessment of changes (pre-intervention to post-intervention) to a wide range of health outcomes in people with 'watch and wait' CLL, including cardiorespiratory fitness, strength, body composition, free-living physical activity levels, and wellbeing and physical function indices. Finally, this study will enable preliminary assessment of the changes (pre-intervention to post-intervention) to the potential anti-tumour mechanisms of exercise including immune function, inflammation, adipose tissue and metabolic hormones.

The hypotheses of this pilot study are as follows:

- Exercise will be safe and acceptable in people with 'watch and wait' CLL.
- Exercise will reduce the frequency of CLL tumour cells in the peripheral blood of people with 'watch and wait' CLL.
- Exercise will improve the cardiorespiratory fitness and the health and wellbeing of people with 'watch and wait' CLL.

Aims and outcomes

The present trial will investigate the safety and acceptability of a 16-week home-based, progressive, exercise training intervention.

Primary objective:

1. Investigate the safety and acceptability of an exercise training intervention, in physically inactive people, with 'watch and wait' CLL.

Outcome measures, collected throughout the trial period:

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

Secondary objective:

1. Investigate the effect of an exercise training intervention on CLL disease activity, immune markers, overall fitness, health and wellbeing in physically inactive people, with 'watch and wait' CLL.

Outcome measures, collected pre- and post-trial period:

- Frequency of CLL cells in peripheral blood measured by flow cytometry
- Immune competency (e.g. phenotypic and functional analyses of PBMCs, differential blood count, viral infection history, immunoglobulins, complement proteins)
- Basal inflammation (e.g. cytokines)
- Metabolic factors and hormone levels (e.g. glucose, insulin, growth factors)
- Clonality of tumour cells (e.g., PCR).
- Genetic and epigenetic features of tumour and immune cells.
- Cardiorespiratory fitness (predicted, or VO_{2MAX})
- Body strength (measured by 1-rep max resistance exercises)
- Body composition (height, weight, waist and hip circumference, fat mass, lean mass)
- Wellbeing indices (stress, fatigue, sleep, quality of life, frailty, motivation, self-efficacy)
- Free-living physical activity levels via wearable technology (e.g., duration, intensity, frequency, energy expenditure and sedentary time)
- Physical function (e.g., flexibility, sit-to-stand test)
- Resting blood pressure, and heart rate
- Left ventricular (LV) function (volumes; ejection fraction; strain; diastolic function)
- Comparison of LV manual measures with artificial intelligence

Trial design

This is a single-centre, double armed, randomised-controlled, phase I pilot trial, designed to evaluate the safety and acceptability of an incremental, multi-modal, 16-week exercise training intervention. The intervention will be observed by a member of the Research Team via a video communication platform in physically inactive people with 'watch and wait' CLL, compared to standard care, which comprises routine clinical monitoring.

Participant eligibility criteria

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

- Males and females with a working diagnosis of: Chronic lymphocytic leukaemia. Defined by iwCLL guidelines as the presence of 5000 B cells per μL of peripheral blood, sustained for at least 3 months and confirmed by the blood smear, immunophenotype and in some cases genetic features of lymphoid cells (Hallek et al., 2018a).
- Age > 18 years old.
- Asymptomatic early stage disease monitored without anti-CLL treatment.
- Physically inactive (defined by World Health Organisation as 'An insufficient physical activity level to meet present physical activity recommendations'. Current physical activity guidelines for adults are at least 150-300 minutes of moderate-intensity aerobic physical activity, or at least 75-150 minutes of vigorous-intensity aerobic physical activity, or an equivalent combination of both throughout the week (Bull et al., 2020)).
- Access to an appropriate electronic device (e.g. laptop, tablet or smart phone) with an appropriate wireless internet connection (and data allowance if relevant) capable of streaming video.
- All participants will have completed the full appropriate vaccination schedule including seasonal influenza, pneumococcal and COVID-19.

Sub-groups will be excluded due to safety risks:

- World Health Organisation (WHO)/ Eastern Cooperative Oncology Group (ECOG) 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 (e.g. history of syncopal events, significant cardiac or respiratory events)
- 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
- Recent blood counts at levels that are deemed to pose undue risk by the healthcare team.

Trial procedures

Recruitment

Recruitment will be conducted at the Royal United Hospital, Bath with the Great Western Hospital, Swindon and Southmead Hospital, Bristol as Patient Identification Centres (PICs). The Royal United Hospital, the Great western Hospital and Southmead Hospital all maintain an active database of people who are routinely monitored for CLL, diagnosed by iwCLL criteria (Hallek et al., 2018a). Suitable patients who may be eligible to participate will be posted/given an invitation letter with a participant information sheet. Patients identified through the Royal United Hospital will receive a follow up telephone call 7-10 days later from a member of the healthcare team to discuss the trial and gauge interest in participating. Patients identified through the Great Western Hospital, Swindon and Southmead Hospital, Bristol will be invited to volunteer themselves to the researchers after receiving the invitation letter with a participant information sheet.

The study will be advertised to CLL related charities and support groups, and suitable candidates will be invited to volunteer themselves indirectly to the researchers.

Patients who are interested in participating will be asked preliminary screening questions with the aim of minimising the number of unnecessary visits for those who may be deemed ineligible to participate at a later stage. Potentially eligible patients will then be invited to attend a screening visit at the University of Bath.

As part of routine care, people with CLL 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). Therefore, this recruitment method is deemed suitable by the healthcare team as it is familiar to the patient 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 call

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:

- World Health Organisation (WHO) / Eastern Cooperative Oncology Group (ECOG) performance status
- Pregnancy
- Physical Activity Readiness Questionnaire (PARQ) (a brief questionnaire that is standard to complete in exercise settings, e.g. when joining a gym). The questionnaire 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.
- The international physical activity questionnaire (IPAQ) short-form is validated to assess moderate and vigorous intensity physical activity and sedentary time.

Screening visit (Visit 1)

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 research team will take informed consent.

People who elect not to participate during the initial telephone call, 7-10 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 participant group.

Screening measurements: A 12-lead electrocardiogram (ECG) will be recorded at screening to fulfil pre-screening required for cardiopulmonary exercise testing. The ECG trace will be anonymised and shared via NHS mail with a cardiologist at the Royal United Hospital for review.

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.

Trial assessments

The trial comprises two measurement visits; one visit prior to the 16-week trial period (Visit 2) and one visit following the 16-week trial period (Visit 3). These two measurement visits will take place in the Disability in Sport and Health laboratory at the University of Bath.

Free living measures

The participant will be given resources and equipment (i.e., an instruction pack, food diary and activity monitor) for these measures at Visit 1 after informed consent has been obtained. This allows measures to be completed prior to Visit 2 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. 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 GENEActiv physical activity monitor at six measurement points throughout the study, initially at Visit 1 to enable measures of free living physical activity level to be taken prior to Visit 2 (pre trial period), a further four times during the trial period (weeks 2, 6, 10 and 14), to enable measures of free living physical activity level to be taken throughout, and a final time (post trial period) to enable measures to be taken after the trial (post trial period) has been completed. At each measurement point the participants will be asked to wear the monitor for 9 days (to capture at least 7 full days of wear) for measurement of free-living physical activity. The monitor is worn on the wrist and records acceleration and skin temperature continuously. No identifiable data is collected by the GENEActiv. Participants will be provided with instructions on how to use the monitor and these

instructions emphasise the importance of wearing the monitor continuously, the monitor is waterproof so can be worn 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 GENEActiv physical activity monitor will be loaned to the participant for the duration of measurement only. The devices are covered by the University of Bath insurance policy.

Visit 2 (Week 0)

Participants in both groups will attend the University of Bath, for a 90 minute baseline visit on a weekday morning. Participants will be asked to arrive fasted having eaten their last meal before 22:00 the night before, and having avoided strenuous exercise, caffeine and alcohol for 24 hours. Participants will be provided with reasonable travel expenses, and parking is free of charge. A sugary snack will be available for participants to consume following the visit. A schematic diagram showing the duration and structure of Visit 2 is shown in Table 1.

Table 1: measurement protocol and timing for Visit 2

Time period	Procedure	Description	Duration
0 – 5 min	Meet / greet	Research team meets the patient, explains the study procedures.	5 min
5 – 30 min	Controlled seated resting measurements and questionnaire completion	Resting blood pressure and an echocardiogram will be measured following 20 minutes of rest and questionnaire completion. See below details of questionnaires.	20 min
30 – 35 min	Resting blood sample	Resting blood sample collected from an antecubital vein	5 min
35 - 55 min	Body composition	Body mass and composition via bio-electrical impedance and dual-energy x-ray absorptiometry (DEXA), height, waist, hip.	20 min
55 – 65 min	Physical capacity	Functional fitness test battery. See below details of tests.	10 min
65 – 85 min	Cardiorespiratory fitness	Exercise test.	20 min
85 – 90 min	Debrief	Patient is thanked for participation	5 min

Resting measurements

Blood pressure: 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. Blood pressure measurements will be repeated in a lying position and standing position for evidence of postural hypotension. The resting blood pressure will be used to determine safety to exercise (unsafe if: blood pressure >200/120 mmHg (Ats and Accp, 2003) or participant reports new symptoms).

Resting blood sample: A venous blood sample will be drawn from an antecubital vein by a trained phlebotomist after resting for 25 minutes.

Echocardiogram: An echocardiogram will be performed by a researcher with a national accreditation for echocardiograms. Markers of heart function will be measured, including left and right ventricular strain and diastolic parameters.

Questionnaires

General health status: Incidence of recent infections, smoking status, alcohol intake (AUDIT-C), menstrual cycle phase or menopausal status (females only), stress (Perceived Stress Scale), anxiety and depression (Hospital Anxiety and Depression Scale) and demographic information will be self-reported by the participant.

Health-related Quality of life: Health-related quality of life (QoL) will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and the CLL-specific module EORTC QLQ-CLL16. (EORTC QLQ-C30) 30 items. This scale is commonly used in the literature and very well validated. Includes disease-specific scoring.

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.

Self-efficacy: Self-efficacy will be assessed using a validated questionnaire. It is a 6-item scale using a Likert scale.

Motivation: Motivation will be assessed using a validated questionnaire. It is a 12-15-item scale using a Likert scale.

Body composition

Anthropometrics: Body mass will be measured using digital Tanita 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.

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

Participants in both groups will undergo a baseline lactate threshold test to determine the lactate threshold that will inform the exercise training intervention, and measure the cardiorespiratory fitness level of participants.

Lactate threshold test: Lactate threshold will be determined using a submaximal exercise test to an RPE <17 or 80% predicted HRmax on a Lode cycle ergometer. The test will consist of 3 minutes of rest followed by 3 minutes of unloaded (0W) cycling followed by an incremental phase of exercise with an increase in work load (Watts) of between 5 and 25 watts every 3 minutes (Ats and Accp, 2003). The increment will be adjusted based on age, physical activity level and gender, to achieve the desired RPE or HR within 5-10 stages. A rating of perceived exertion (RPE) and blood lactate, measured using an ear lobe capillary blood sample, will be recorded at the end of each stage. Breath-by-breath gas exchange, heart rate, ECG, blood pressure and blood oxygen saturation will be monitored continuously. The test will be terminated if the participant fails to conform to the exercise test protocol, experiences adverse signs or symptoms, requests to stop, or experiences an emergency situation.

Lactate threshold will be determined by plotting a graph of power in watts (x-axis) against the blood lactate in mM (y-axis). The definition of the blood lactate threshold as the break-point where a curvilinear rise in lactate concentrations is observed when plotted against power will then be used to determine the power at which the lactate threshold occurred. Work rates corresponding to −5%, +5% and +15% of the lactate threshold will be calculated from the lactate – to – work rate relationship. These work rates will then be used as the exercise intensities during the training intervention.

Health and safety: Participants unable to comply with the exercise test, for example due to a health problem raised during the exercise test (e.g. abnormal 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.

Randomisation

Eligible, consenting participants will be randomly allocated (1:1) to an exercise training intervention (ETI) or standard care control (CON) group. Randomisation will be performed using a web-based platform.

Trial period measurements

Participants in the exercise training intervention group will complete a Session Record Card in each observed exercise session. Unsupervised exercise will be monitored using a Home Exercise Diary which will be reviewed each week. Participants will also be provided with a Polar A370 fitness monitor for the duration of the trial period to record all training sessions. Participants will not be required to wear this monitor for the duration of the trial, they will only be required to wear the monitor during the observed and the unsupervised sessions. The Polar A370 fitness monitor is a wrist worn device that measures heart rate continuously using Polar's proprietary 2-LED optical heart rate solution. Participants will be provided with instructions on how to use the Polar A370, participants will be asked to press a button on the face of the fitness monitor, at the start of each observed training session, and at the start of each unsupervised walking session, to record all of the sessions. Data from the monitor will be uploaded by the participant once a week. The Polar A370 fitness monitor will be loaned to the participant for the duration of the trial only. The devices are covered by the University of Bath insurance policy.

The primary outcome of acceptability 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 observed and unsupervised exercise sessions completed, measured using a Session Record Card, Home Exercise Diary and fitness monitor.

Compliance: Prescribed vs. actual aerobic exercise completed in each observed session will be measured using the fitness monitor. Compliance to unsupervised aerobic exercise will be measured using the fitness monitor.

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

Safety: Incidence and severity of adverse events (Table 2). [Recording and reporting of SAEs will follow University of Bath policy – The chief investigator (CI) will report any SAE to the sponsor within 24 hours. A written SAE report (health research authority [HRA] form) will 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 2: Definitions of adverse events

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.

Visit 3 (Week 17)

Free-living measurements will be repeated post trial period (week 17). Resources and equipment (i.e. an instruction pack, food diary and physical activity monitor) to complete these measures will be sent to participants and can be returned during Visit 3.

After the trial period, participants will complete Visit 3, lasting 90-minutes. Measurements conducted during Visit 3 will replicate Visit 2, as described above.

Withdrawal criteria

Participants may be withdrawn from the trial if there is a change in their eligibility e.g. disease progression to 'active disease'. During Visit 2, contraindications and limitations to exercise may be identified during the exercise test (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 at the University of Bath, and then 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. immune competence, inflammation, hormones, compliment proteins and metabolic factors).

- 25 mL into a heparin-treated syringe, from which whole blood will be processed on the day for phenotypic and functional measures of immune competence. In addition, peripheral blood mononuclear cells (PBMCs) and CLL cells 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).

Trial treatment

Exercise training intervention (ETI) arm (for 16 weeks)

The exercise program is designed to elicit all purported anti-tumour mechanisms of exercise via incorporation of regular vigorous intensity exercise, resistance exercises, as well as longer-duration lower intensity exercise. To ensure safety, promote adherence and gains in physical exercise capacity, participants randomised to the exercise intervention will receive a personalised incremental exercise programme based on an initial lactate threshold test, that will generate workload zones (including a target wattage, heart rate and RPE) to ensure participants exercise at predefined intensities throughout the intervention, monitored via fitness monitors that measure continuous heart rate. The programme will be delivered as two home-based, static bike exercise sessions observed by a member of the Research Team via the Microsoft Teams video communication platform and one unsupervised walking exercise session, each week for 16 weeks. At the beginning of each week, during the trial period, participants will be emailed a link to the Microsoft Teams video communication platform. This link will enable participants to attend the training sessions observed by a member of the Research team. Each training session will have a small number of participants, all participants will be given the choice of whether they would like to see other members of the class on the screen at the same time, or not.

Aerobic exercise, beginning at a moderate intensity, (defined as -5% of participants lactate threshold, a rating of perceived exertion of 12-13 and a heart rate of 40-50% of participants VO_{2MAX}) and progressing to vigorous intensity (defined as +15% of participants lactate threshold, a rating of perceived exertion of 15-16 and a heart rate of 70-80% of participants VO_{2MAX}) during observed sessions, is the main component of the exercise programme because it elicits numerous physiological effects that have been hypothetically linked to reduced neoplastic growth (e.g., immune and metabolic changes, and adipose tissue reduction).

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

An unsupervised walking session has been included to increase exercise frequency without the additional burden of an observed session on participant's time. Home-based sessions have been selected to reduce the burden of travel and to reduce the COVID-19 risks for participants.

Exercise sessions

Exercise sessions will be performed in the participants home and will be observed by a member of the research team via the Microsoft Teams video communication platform. At the beginning of each trial week participants will be emailed the link to attend the observed exercise training sessions. Each session lasts approximately 1 hour, and equipment needed for all exercises will have been delivered to participants homes prior to the first session, including resistance bands, static exercise bikes (Matrix U1) and a blood pressure monitor. A brief screening, including blood pressure measurement and review of health status, will take place before each observed 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 training session will have a small number of participants, all participants will be given the choice of whether they would like to see other members of the class on the screen at the same time, or not. 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 static bike at a comfortable cycling speed with no resistance ('unloaded cycling') for a minimum of 5 minutes. Aerobic training will then commence for 30 minutes. Participants will perform three sets of 10-minute cycling intervals (Table 3). For each interval, the resistance is increased during the 'work phase' to achieve a target work rate in watts (8 minutes, -5% - +15% of lactate threshold) followed by 'unloaded cycling' (2 minutes). Target work rate in watts will be prescribed using work rate data measured during the lactate threshold test; participants will be given a work rate zone in watts that corresponds to the target percentage of lactate threshold work rate.

The Polar A370 fitness monitor will be worn during every observed exercise session to record the session. The HR, RPE, resistance, speed, power output (watts) and average revolutions per minute (RPM) will be recorded for each interval.

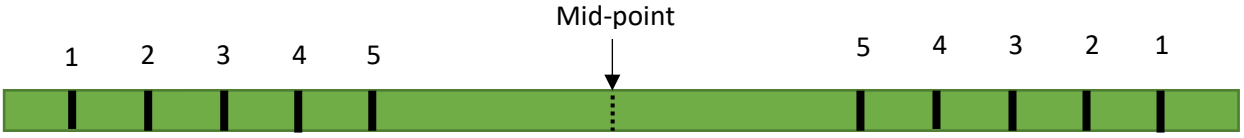
	Table 3. Aerobic exercise prescription						
Trial week	**Number of intervals**	**Work duration (minutes)**	**Work phase intensity (% of LT in watts)**	**Work phase intensity (% VO_{2MAX})**	**Work phase intensity (RPE)**	**Rest duration (minutes)**	**Total duration (minutes)**
1-2	3	8	-5% LT	40-50	12-13	2	30
3-6	3	8	LT	50-60	13-14	2	30
7-10	3	8	+5% LT	60-70	14-15	2	30
11-16	3	8	+15% LT	70-80	15-16	2	30

The primary outcome of the trial is to assess the safety and feasibility of exercise in people with 'watch and wait' CLL. 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). 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).

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 4).

Participants will perform two sets of 15-8 repetition maximum (RM) of six large muscle group exercises (reverse fly, chest fly, tricep extension, 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, 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 4. 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

Unsupervised walking component: Participants will be asked to complete one 45-minute walk each week at a moderate intensity (RPE 12-14) and daily balance and flexibility exercises (performed on days without an observed session) which are detailed in the Home Exercise Pack. The Polar A370 fitness monitor will be worn during every unsupervised walking session to record the session. 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.

Behavioural Support

Behavioural support is important to the successful uptake and maintenance of novel behaviours that require sustained effort and engagement, such the adoption of exercise

programme for people who are currently inactive. Research demonstrates that long-term behaviour change is facilitated by fostering autonomous motivation (i.e., behaviour considered to be personally meaningful and beneficial to a person, rather than behaviour undertaken to please others, or with a lack of understanding as to why), positive self-efficacy (i.e., belief in one's ability to achieve a target being set), and social support. Specific behaviour change techniques linked to these targets, as set out from a standardised taxonomy (Michie et al., 2011), have been included in the trial design (Table 5). To foster participants' self-determined motivation towards the intervention, and towards the exercise within it, the exercise training and implementation of behaviour change techniques will be delivered in an autonomy supportive style (as informed by self-determination theory). This is facilitated through providing a meaningful rationale for compulsory exercise components, offering structure and choice (where appropriate) to tailor advice to ability levels and preferences, and developing a supportive and interested inter-personal relationships between the trainer and participant. Trainers will receive a previously validated 2-hour coaching session on how to deliver autonomy supportive care.

Table 5. Behaviour change considerations

Behaviour change technique	**Implementation in present trial**
Informational support	• Participants will be given detailed information about the exercise training intervention in the recruitment material (what it involves and why), and will be encouraged to ask questions to ensure they understand the exercise training and the trial.
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 (focusing on information rather than praise) on their progress towards the targets set out in the exercise programme.
Self-monitoring	• Participants will be given a Polar A370 fitness monitor to record both the observed and unsupervised sessions, which will allow them to take ownership of monitoring their own 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	• Online 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 encourage participants to identify a peer from their own social network to join them for the unsupervised walking sessions.

Action planning	• The exercise programme has a highly structured, progressive action plan for 16 weeks.

Control arm (CON) (for 16 weeks)

Control participants will not take part in an exercise training intervention, but will be offered exercise advice post-intervention (to minimise contamination of the control group).

Benefits of participating

Participants will be provided with feedback on some of their results within two months of their last visit. This will include blood pressure, body composition, cardiovascular fitness and physical capacity, with reference to the average population and recommended guidelines. Feedback will not be provided on data collected from blood samples because most of the measurements are preliminary research parameters and are not diagnostic.

Abnormal results from the exercise test will be shared and discussed 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 the guidelines (Ats and Accp, 2003).

Participants in the exercise training intervention group will receive 32 observed exercise sessions for free.

Participants in both groups 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.

There is no financial compensation for visits to the University of Bath, but reasonable travel expenses will be reimbursed, and parking is free of charge.

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 (exercise tests and the exercise 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 ECG.
- Risk will also be assessed before each exercise session by measuring blood pressure and asking participants if they have had any symptoms of health change since their last session.
- Exercise training will be personalised to each individual based on their fitness level and ability so as to promote a safe exercise training programme.

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 brings risks including pain, bleeding, bruising, embolism and infection. These risks are controlled by adherence to best practice. People with CLL will be very familiar with the sensations associated with venous blood sampling as blood samples are collected regularly as part of routine care.

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.

Participants will be given a pack of questionnaires that assess psychological variables (e.g. health anxiety, stress, depression). It is not appropriate for the research team to analyse the questionnaire data making judgments as to whether respondents are depressed for example. As with routine care, any patients that are suspected to be suffering from a condition such as depression by their haematologist, will be referred on to a clinical psychologist specialising in cancer care. However, in the questionnaire pack, it will be explained that should any of these questionnaires give cause for concern, then this should be discussed with their haematologist or local general practitioner.

When designing this study, the amount of time each participant will have to commit was considered. Time commitments include: 1 hour of screening and consenting, up to 3 hours of measurements (fitness, body composition, blood testing and other measurements at Visit 2 and Visit 3) and, finally, 32 exercise sessions (32 different one hour sessions) for those in the exercise group. All visits will be scheduled at a time of day according to the participant's availability. The exercise sessions will be home-based and will be observed by a member of the Research Team via the Microsoft Teams video communication platform, these will 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).

Participants randomly allocated to the control group may be concerned that they are missing out on potential health benefits of being in the exercise group. This will be addressed by offering participants in both groups an information sheet with recommendations on staying active upon completion of this study. This will include a home-exercise programme, resistance bands provided free of charge, and information on local exercise referral schemes.

A final important consideration for the research team when designing this study was the global COVID-19 pandemic. To minimise this risk, the exercise training intervention has been designed to be conducted in participants homes. Appropriate personal protective equipment (PPE) will be worn by the research team during Visit 1, Visit 2 and Visit 3 and the study will adopt the policies that the Trust is following and will begin recruiting when the host institution allows it.

COVID-19 Mitigation Strategies

Given safety and institutional directives with the COVID-19 pandemic in the UK, the research team will adhere to the below policies and procedures:

- Any team member displaying any COVID-19 symptoms (fever (38°C or higher), or sense of having a fever, cough, shortness of breath, muscle aches, sore throat, unexplained loss of taste or smell, diarrhoea, headache) must stay at home and organise for a COVID-19 test by contacting their GP.

- Participants and research team will use hand sanitiser on entry to the University
- The research team will be provided with appropriate PPE (apron, gloves and a face covering/face mask and face shield throughout study participant visits)
- The research team will change gloves and apron between every study participant contact
- The research team will thoroughly wash hands and forearms before and after the session (not just use hand sanitiser)
- All research equipment will be wiped down immediately with disinfectant spray and cloth between study participant sessions
- Where possible staff will be vaccinated, and lateral flow tests will be done.
- Only two members of the research team will enter the participants homes to deliver the exercise equipment, and they will be in the home for no more than 15 minutes.

Statistics and data analysis

Sample size

The aim is to recruit 40 participants. Assuming a recruitment rate of three to four people per month and 20% drop out, we estimate the target can be reached within a suitable time-frame of the funding period (16-18 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. Safety will be reported as the incidence and severity of adverse events. Acceptability will be reported as proportions in terms of uptake, adherence, compliance and retention.

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 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 research team will present an update on safety at quarterly trial management group meetings, together with the haematologist (Dr Moore and/or Dr Murray), the CI (Dr Campbell), 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

Five people diagnosed with CLL attended a meeting with researchers via the virtual communication platform Zoom to discuss the proposed trial design. Discussions were held on the following topics, with feedback on each point 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.
- 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, the idea of using a video communication platform to supervise the intervention.
- All research measurements being taken in this trial, including blood sampling and the exercise fitness test.

People with CLL will also be involved in the analysis of results via the trial management group, and dissemination of findings through CLL related charities and support groups.

Regulatory compliance

Participant's samples will be stored in accordance with the Human Tissue Act 2004. 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.

All data will be collected and stored for 10 years in accordance with the University of Bath Research Data Policy (see: http://www.bath.ac.uk/research/data/policy/index.html). Electronic data will be stored securely with access available only to the research team via password protected University computers and the University of Bath Research storage drive (X:\Health\ResearchProjects\JCampbell). All data and biological samples will be anonymised using a numerical system and the corresponding identity of participants will only be available to the research team. Clinical data that is passed to the academic research team from the clinical team will be anonymised using the same numerical system. Medical records will only be accessed by the patient's healthcare team and will remain on site at the Hospital.

Post-trial care

Participants will be provided with feedback on some of their test results after completing the trial period. This will include blood pressure, body composition, cardiorespiratory fitness and physical capacity, with reference to population norms and recommended guidelines.

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.

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

The data arising from this trial will be submitted for publication and presented at conferences and meetings. People will be notified of the outcomes of the trial via CLL related charities and support groups.

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