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Safety and acceptability of exercise for chronic lymphocytic leukaemia

Submission date
21/09/2021

Recruitment status
No longer recruiting

Registration date
23/09/2021

Overall study status
Completed

Last Edited
20/12/2024

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
It is widely thought that regular exercise exerts anti-tumour effects against all cancers. At a population level, it is thought that people who exercise have a lower risk of developing cancer, and among patients who exercise, there is a lower incidence of cancer relapse. Animal studies support this idea, and show that if you give mice different types of cancer, exercise slows cancer growth. Despite these important findings from animal research, it remains unknown in humans whether exercise can work in the same way and slow cancer growth. This problem exists mainly because most people diagnosed with cancer require treatment, so it is not possible to look at the effects of an exercise training program, on its own, against cancer. This study aims to overcome these problems by investigating the effects of exercise in people with chronic lymphocytic leukaemia (CLL) on a 'watch-and-wait' basis until treatment is needed. CLL is a type of blood cancer, and it is the most common adult leukaemia in the UK. Most patients are diagnosed by chance and have no disease symptoms and as such do not need urgent treatment and have no major health problems caused by their cancer. This means researchers can look at how exercise affects their cancer without having to take into account the effects of cancer treatment or cancer-related health problems. In addition, patients with CLL have lots of tumour cells in their blood which means blood samples can be easily taken to see how the cancer is affected by exercise, whereas with other cancers surgery would be needed. Finally, by taking blood samples, the researchers can store cancer cells to study the mechanisms by which exercise helps patients with CLL.
As this type of study has not been done before, the main aim of this pilot study is to see if exercise is safe and acceptable to people with CLL. Another important aim of the study is to see what the exercise program does to cancer cells, to find out whether a larger study is worth pursuing and how large it should be.

Who can participate?
Patients over the age of 18 years living with 'watch-and-wait' chronic lymphocytic leukaemia (CLL)

What does the study involve?
Forty physically inactive patients will be recruited into this study. Twenty will be randomly allocated to a 16-week home-based exercise program and twenty patients will be randomly

allocated to a control group (no exercise). The researchers will determine if the exercise program is safe and acceptable to patients. They will also see what happens to tumour cells, fitness, strength, and body composition, and will also monitor changes to other parts of the lifestyle like diet.

What are the possible benefits and risks of participating?
The benefits of participating are following the study, participants will be given a report of the test results, including blood pressure, body composition (body mass index [BMI], fat, muscle and bone density), diet, physical activity level and fitness level.
The possible risks of participating include discomfort from blood sampling. A trained phlebotomist will take samples, following best practice so these risks are minimized. Participants will be exposed to a small dose of radiation, which is considered safe, from a Dual-Energy X-ray absorptiometry (DEXA) scan. A trained researcher will perform the scan, following best practice to minimise risks. There are complications associated with exercising, however, the risk of these complications will be assessed before participants enter the study and researchers will take all possible measures to minimise this risk. The questionnaires to assess mental health may include uncomfortable questions, and participants will be instructed to contact their GP or health care team if they have any concerns about these. Wearing activity monitors may in some cases result in some minor skin irritation, but this should be minimal and guidance will be included to reduce this risk.

Where is the study run from?
The University of Bath in collaboration with the Royal United Hospital, Bath (UK)

When is the study starting and how long is it expected to run for?
July 2019 to March 2023

Who is funding the study?
World Cancer Research Fund (UK)

Who is the main contact?
1. Dr John Campbell, j.campbell@bath.ac.uk
2. Dr Frankie Brown, F.Brown@bath.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
292564

Central Portfolio Management System (CPMS)
48653

Study information

Scientific Title
Evaluating the safety and acceptability of a progressive exercise training intervention for chronic lymphocytic leukaemia: a randomised-controlled pilot trial

Study objectives
Exercise is safe and feasible for people living with ‘watch and wait’ chronic lymphocytic leukaemia.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 26/04/2021, London - Dulwich Research Ethics Committee (Health Research Authority, 2nd Floor, 2 Redman Place, Stratford, London, E20 1JO, UK; +44 (0)207 104 8241; dulwich.rec@hra.nhs.uk), REC ref: 21/LO/0217

Primary study design
Interventional

Study design
Randomized; Interventional; Design type: Screening, Psychological & Behavioural, Physical, Active Monitoring

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic lymphocytic leukaemia

Interventions
STUDY 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 part-supervised via a video communication platform in physically inactive people with CLL, on a 'watch and wait' treatment regimen, compared to standard care, which comprises routine clinical monitoring.
People diagnosed by International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) criteria at the Bath Royal United Hospitals NHS Foundation Trust, Great Western Hospital, Swindon, and Southmead Hospital, Bristol, will be invited to participate. People eligible to participate in this study will be identified by the care team from an existing database of people with CLL. In addition, 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. An invitation letter and participant information sheet will be sent in the post to each eligible patient, followed by a phone call from a member of the care team. People willing to participate and who pass preliminary screening will be invited to visit the University of Bath to undertake an eligibility screening (Visit 1), and to provide informed consent. Following the initial screening visit and after provision of informed consent, participants will undertake measurements Visit 2 and will then be randomly allocated into the treatment arm (exercise programme) or control arm (usual care) by simple 1:1 randomisation using the sealed envelope web programme. Participants in the exercise arm will receive a 16-week home-based progressive, exercise program comprised of twice-weekly exercise sessions supervised via a video communication platform and a once-weekly unsupervised exercise session, designed for them by an exercise and cancer specialist. The 16-week exercise program is designed to promote anti-inflammatory and anti-tumour benefits via vigorous-intensity exercise, whilst other exercises (e.g. resistance bands, stretches) are designed to promote gains in physical activity capacity (e.g. strength, flexibility).
The control group will continue with their usual care (called "watch and wait"). All participants will attend final measurement sessions (Visit 3) at the end of the trial to repeat the measurements that were taken at trial entry.

RECRUITMENT
The Royal United Hospital Bath the Great Western Hospital and Southmead Hospital all maintain an active database of people with CLL, diagnosed by the International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) criteria. People will be identified by a member of the healthcare team from the database as this requires a review of personal data (e.g. medical history, age). People on the database who meet these inclusion criteria will be identified by the care team and will be sent in the post a recruitment letter and a participant information sheet. Approximately 7-10 days later, a member of the care team will phone the patient to invite the patient to

participate in this study. 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.

SCREENING TELEPHONE CALL
During the initial phone call, patients will be asked preliminary screening questions with the aim of reducing the number of unnecessary face-to-face screening visits:
1. WHO performance status
2. Pregnancy
3. Physical activity readiness questionnaire (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 from the haematologist to take part).
4. The international physical activity questionnaire (IPAQ) short-form is validated to assess moderate and vigorous-intensity physical activity and sedentary time.
Patients that fit the inclusion criteria and pass the telephone screening questions will then be invited for Visit 1 at the University of Bath.

SCREENING VISIT (VISIT 1)
Written informed consent will be taken during the screening visit at the University of Bath once patient eligibility has been confirmed and any questions about the trial have been answered. The research team will take informed consent. A 12-lead electrocardiogram (ECG) will be recorded at screening to fulfil pre-screening required for cardiopulmonary exercise testing.

Following the provision of informed written consent, disease activity history, comorbidities and concomitant medications will be accessed from medical records and finally participants will be given a physical activity monitor (to wear for 9 days), and a 3-day food diary to be returned at Visit 1. Participants will be randomly assigned to the exercise or control group.

MEASUREMENTS
The trial includes two measurement visits; one visit prior to the trial period (Visit 2), and one visit following the 16-week trial period (Visit 3). Visits 2 & 3 take place in the Disability in Sport and Health laboratory at the University of Bath. Measurements will also be taken throughout the trial period to address the primary outcomes.

VISIT 2:
Participants will be asked to arrive fasted and having avoided caffeine since 22:00, and having avoided alcohol and strenuous exercise for 24 hours. The visit will take place at the University of Bath for 1.5 hours scheduled between 06:00 and 11:00 on a weekday. The researcher will meet participants in the car park and show them to the laboratory. They will then complete a questionnaires pack. Completing the questionnaires provides ~25 minutes of rest prior to the blood pressure measurement which will be performed three times on the left arm. A blood sample will then be drawn from the antecubital vein. Anthropometric measures (height, weight, waist and hip circumference) will be taken in line with standard procedures prior to the dual-energy x-ray absorptiometry (DEXA) scan. Participants will be positioned on the scanner and asked to lie still as the scanner moves above them. Functional fitness tests will then be carried out, first, dynamic balance will be assessed using the 8ft up-and-go test. Next, upper body strength will be assessed using a handgrip dynamometer, with three measures taken on each side, alternating each time. To measure lower body strength, participants will be asked to perform repeated sit-to-stands as fast as they can for 30 seconds. Upper- and lower-body flexibility will be measured with a back scratch and chair sit-and-reach test, respectively. Cardiorespiratory fitness will be measured using a maximal protocol on a static exercise bike (it

will feel like cycling uphill) with breath-by-breath gas analysis, electrocardiography (ECG), blood pressure and oxygen saturation measured continuously. 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. 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. Participants in the exercise group will be given a fitness tracker watch with a HR strap and a blood pressure monitor and their first exercise session time will be agreed. Participants in the control group will next be seen for Visit 2.

EXERCISE SESSIONS
Those in the exercise group will be delivered a static exercise bike and resistance bands to their homes for their supervised exercise sessions. The programme will be delivered as two home-based, supervised via Microsoft Teams video communication platform, static bike exercise sessions and one unsupervised walking exercise session, each week for 16 weeks. This is a total of 32 supervised sessions. Each session will involve 5-7 participants in an exercise class supervised by an exercise specialist. The exercise classes will include cycling on a static bike, strength exercises (using resistance bands) and stretches for flexibility. All classes will include a warm-up period and a cool-down period. Participants in the exercise group will also be asked to complete one 30-40 minute walk and daily balance and stretching exercises (days without supervised exercise sessions only). In total, the exercise that is being prescribed is designed to meet World Health Organisation physical activity guidelines for older adults and cancer patients of 150 minutes of moderate-intensity exercise per week. The design of these sessions has been informed by patient and public involvement focus group feedback. After 16 weeks, all participants in both the control and exercise groups will have the same measurements taken again (Visit 3).

VISIT 3:
Participants will be asked to arrive fasted and having avoided caffeine since 22:00, and having avoided alcohol and strenuous exercise for 24 hours. The visit will take place at the University of Bath for 1.5-hours scheduled between 06:00 and 11:00 on a weekday. The researcher will meet participants in the car park and show them to the laboratory. They will then complete a questionnaires pack. Completing the questionnaires provides ~25 minutes of rest prior to the blood pressure measurement which will be performed three times on the left arm. A blood sample will then be drawn from the antecubital vein. Anthropometric measures (height, weight, waist and hip circumference) will be taken in line with standard procedures prior to the dual-energy x-ray absorptiometry (DEXA) scan. Participants will be positioned on the scanner and asked to lie still as the scanner moves above them. Functional fitness tests will then be carried out, first, dynamic balance will be assessed using the 8ft up-and-go test. Next, upper body strength will be assessed using a handgrip dynamometer, with three measures taken on each side, alternating each time. To measure lower body strength, participants will be asked to perform repeated sit-to-stands as fast as they can for 30 seconds. Upper- and lower-body flexibility will be measured with a back scratch and chair sit-and-reach test, respectively. Cardiorespiratory fitness will be measured using a maximal protocol on a static exercise bike (it will feel like cycling uphill) with breath-by-breath gas analysis, electrocardiography (ECG), blood pressure and oxygen saturation measured continuously. 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. 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. Participants in both the control and exercise groups will be given a physical activity monitor (to wear for 9 days), and a 3-day food diary to be returned in a pre-paid envelope.

Intervention Type
Behavioural

Primary outcome(s)
1. Safety measured by recording the incidence and severity of adverse events throughout the trial period
2. Uptake measured by recording the proportion of people approached who attend screening and the proportion of people who attend screening who are deemed eligible throughout the trial period
3. Adherence measured by recording the proportion of exercise sessions prescribed that are actually completed throughout the trial period
4. Compliance measured by recording the prescribed vs actual aerobic exercise performed per exercise session throughout the trial period
5. Retention measured by recording the proportion of participants who complete baseline measures that also complete follow-up measures after 16 weeks

Key secondary outcome(s)
1. Frequency of CLL cells in peripheral blood measured by flow cytometry at baseline and after 16 weeks
2. Immune competency measured using phenotypic and functional analyses of PBMCs, differential blood count, viral infection history, immunoglobulins, complement proteins at baseline and after 16 weeks
3. Basal inflammation measured using cytokine analysis by ELISA at baseline and after 16 weeks
4. Metabolic factors and hormone levels measured using the Daytona for glucose, insulin, growth factors at baseline and after 16 weeks
5. Clonality of tumour cells measured by PCR at baseline and after 16 weeks
6. Genetic and epigenetic features of tumour and immune cells measured by PCR at baseline and after 16 weeks
7. Cardiorespiratory fitness measured by a submaximal exercise test at baseline and after 16 weeks
8. Body strength measured by 1-rep max resistance exercises at baseline and after 16 weeks
9. Body composition measured using anthropometrics and a DEXA scan for height, weight, waist and hip circumference, fat mass and lean mass at baseline and after 16 weeks
10. Wellbeing indices including stress, fatigue, sleep, quality of life, frailty, motivation, self-efficacy, social support measured by questionnaire at baseline and after 16 weeks
11. Free-living physical activity levels including, duration, intensity, frequency, energy expenditure and sedentary time is measured via wearable technology at baseline 2, 6, 10, 14 and after 16 weeks
12. Physical function including flexibility, measured using sit-to-stand and 8ft up and go at baseline and after 16 weeks
13. Resting blood pressure and heart rate measured using an automated blood pressure cuff and a heart rate monitor at baseline and after 16 weeks
14. Left ventricular (LV) function including volumes, ejection fraction, strain, diastolic function, measured by echocardiogram at baseline and after 16 weeks
15. Left ventricular (LV) manual measures will be compared with artificial intelligence by measuring echocardiogram at baseline and after 16 weeks

Completion date
31/03/2023

Eligibility

Key inclusion criteria
1. Males and females with a diagnosis of chronic lymphocytic leukaemia, defined by International Workshop on Chronic Lymphocytic Leukemia (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)
2. Age >18 years old
3. Asymptomatic early-stage disease monitored without anti-CLL treatment
4. 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))
5. Access to an appropriate electronic device (e.g. laptop, tablet or smartphone) with an appropriate wireless internet connection (and data allowance if relevant) capable of streaming video
6. All participants will have completed the full appropriate vaccination schedule including seasonal influenza, pneumococcal and COVID-19

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
40

Key exclusion criteria
1. World Health Organisation (WHO)/ Eastern Cooperative Oncology Group (ECOG) performance status >1
2. Pregnancy
3. Deemed unsafe to exercise according to the Physical Activity Readiness Questionnaire (PARQ)
4. 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)
5. Cognitive impairment deemed a risk by the healthcare team for participation in the trial (e.g. diagnosis of neurodegenerative disease)
6. Unable to understand explanations and/or provide informed consent

7. Any condition and/or behaviour that would pose an undue personal risk or introduce bias into the trial
8. Recent blood counts at levels that are deemed to pose an undue risk by the healthcare team

Date of first enrolment
01/10/2021

Date of final enrolment
01/12/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Bath
Department for Health
Claverton Down
Bath
United Kingdom
BA2 7AY

Study participating centre
Royal United Hospital
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
Great Western Hospital
Marlborough Rd
Swindon
United Kingdom
SN3 6BB

Study participating centre
Southmead Hospital
Southmead Rd
Bristol

United Kingdom
BS10 5NB

Sponsor information

Organisation
University of Bath

ROR
https://ror.org/002h8g185

Funder(s)

Funder type
Charity

Funder Name
World Cancer Research Fund; Grant Codes: SG_2019_1884

Alternative Name(s)
World Cancer Research Fund UK, World Cancer Research Fund International, WCRF International, WCRF, WCRF UK

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		05/12/2024	20/12/2024	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version 2	22/03/2021	22/09/2021	No	Yes
Protocol file	version 2	22/03/2021	22/09/2021	No	No