Cross-sectoral rehabilitation intervention for patients with intermittent claudication versus usual care for patients in non-operative management. - The CIPIC Rehab study: study protocol for a randomised controlled trial

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Study protocol

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Abstract

Introduction: Intermittent claudication (IC) caused by Peripheral Artery Disease (PAD) is a common cardiovascular disease. Patients with IC have reduced walking capacity, restricted activity levels and mobility, and reduced health-related quality of life. The disease leads to social isolation, the risk of cardiovascular morbidity, and mortality. Non-operative management of IC requires exercise therapy and studies show that supervised exercise training is more effective than unsupervised training, yet many patients with IC lack motivation for changes in health behavior. No studies investigating the effects of existing cardiac rehabilitation targeted patients with IC have been published. The aim of this paper is to present the rationale and design of the CIPIC Rehab Study, which examines the effect of a cross-sectoral rehabilitation programme versus usual care for patients in non-operative management for IC. Methods and analysis: A randomised clinical trial aims to investigate whether cardiac rehabilitation for patients with IC in non-operative management versus usual care is superior to treatment as usual. The trial will allocate 118 patients, 1:1 individual randomisation to either the intervention or control group. The primary outcome is maximal walking distance measured by the standardised treadmill walking test. The secondary outcome is pain-free walking distance measured by the standardised treadmill walking test, healthy diet measured by a fat-fish-fruit-green score, and level of physical activity measured by activity score within official recommendations. Statistical analyses will be blinded. Several exploratory analyses will be performed. A mixed-method design is used to evaluate qualitative and quantitative findings. A qualitative and a survey-based complementary study will be undertaken to investigate patients' post-discharge experiences. A qualitative post-intervention study will explore experiences of participation in rehabilitation. Discussion: The study is the first to assess the effect of a cardiac rehabilitation programme designed for patients with intermittent claudication. The study will describe how to monitor and improve rehabilitations programme for patients with intermittent claudication in a real-world setting. Mixed method strategies can allow for both exploration and generalization in the same study, but the research design is a complex intervention and any effects found can not be awarded a specific component.

Background

Peripheral Artery Disease (PAD) is a chronic occlusive arterial disease caused by progressive atherosclerosis (1). The most common symptom is Intermittent Claudication (IC), defined as a cramping leg pain that occurs during walking and is relieved by a short period of rest. IC affects 2% of the population (age 50-60) and increases with age to 6-7% (age 65-75) of the population in Western Europe and USA (2). Patients with IC have diminished walking capacity, restricted activity levels and mobility, and reduced health-related quality of life (3, 4). It leads to social isolation and unless health behavior and relevant medications are prescribed, it may lead to worsening of disease with the risk of atherosclerotic complications and death (1, 3-8). Motivation is an important but neglected factor as studies indicate that many patients with IC are not motivated for health behavior changes in accordance with current recommendations (6, 7, 9). Due to the risk of complications and limited patency of revascularisation

(depending on procedure and anatomic location), current guidelines recommend that patients not requiring surgical revascularisation due to critical limp ischaemia be managed conservatively without surgical intervention (10). Current practice for managing IC in Danish hospital settings involves brief advice to 'stop smoking and keep walking', combined with preventive medications including cholesterol lowering treatment with statins and antiplatelet therapy (10, 11). Non-adherence to these recommendations increases the risk of progression from IC to critical ischaemia and limb amputation (1). It also produces a substantial economic burden on society due to reduced working ability, hospitalisation, and associated personal and social consequences for the individual patient (12, 13). A recent Cochrane review (14) concluded that for patients with IC exercise is important regardless of whether treatment is revascularisation or overall conservative management. Supervised exercise training (SET) programmes are effective for alleviating symptoms, increasing walking distance, reducing cardiovascular risk factors and improving quality of life. Additionally, SET is relatively inexpensive and cost-efficient compared with other more invasive therapies (13-16). Although evidence for SET is strong, studies exploring the effects of cross-sectoral rehabilitation intervention on patients treated for IC are lacking. IC rehabilitation is still poorly implemented and knowledge about how to set up an effective programme in a community-based setting is poor (17, 18).

Rehabilitation

Secondary prevention initiatives including rehabilitation for patients with PAD are recommended in current guidelines (5, 19). Community-based supervised exercise appears to be at least as effective as exercise programmes provided in hospital settings (20). Importantly, a study recently reported that attending a hospital-based supervised exercise programme was difficult for patients due to time spent on transportation and logistics (21). This indicates that intervention in the local community improves patients' motivation and adherence (22). Therefore, given the evidence for the beneficial effect of supervised exercise training for patients after acute coronary syndrome, the hypothesis is that patients with IC could also benefit with regard to maximal walking distance, pain-free walking distance, health related quality of life, and physical function. Patients perspectives on participating in the intervention could shed light on the factors that facilitate or hinder exercise and recommended health behaviour. Knowledge of this may increase both the quality and patient adherence to the conservative management of IC, thereby attenuating the burden of disease and improving quality of life for patients with IC.

STUDY OBJECTIVES

The objectives of the trial are to investigate the effects of a cross-sectoral exercise and lifestyle intervention based on the established rehabilitation programme for patients with ischemic heart disease versus usual care without rehabilitation in patients with IC. The primary hypothesis is that, compared with the control group, a specialised rehabilitation programme for the intervention group improves maximal walking distance in the treadmill walking test after the completed intervention. The three secondary hypotheses are that pain-free walking distance (PWD), diet and level of physical activity improve in the intervention group compared with the control group after 6 and 12 months. Exploratory analyses will test

the hypothesis that IC rehabilitation improves quality of life, health behavior, physical activity and reduces anxiety and depression after 6 and 12 months. The effects, benefits, and motivational factors of conservative management will be examined and patient experiences of the intervention, including factors that support or hinder adherence to the intervention explored.

Methods

DESIGN

The CIPIC Rehab Study is designed to develop evidence-based knowledge on rehabilitation among patients with IC. It is a cross-sectoral, multidisciplinary, randomised clinical trial designed to examine the effects of an IC rehabilitation programme compared with usual care for patients in non-operative treatment for IC. Accordingly, the trial combines quantitative and qualitative research methods. The mixed methods are integrated by applying the Explanatory Sequential Design(23, 24). The rationale for this approach is that the quantitative findings provide a general understanding of the research problem through statistical results, and qualitative findings refine and explain the results by exploring participants' views in greater detail. Qualitative research coupled with randomised controlled trials can contribute to developing and evaluating complex healthcare interventions; it may be particularly useful in evaluating interventions that involve social and behavioural processes that are difficult to explore or capture using quantitative methods alone (25, 26). A pragmatic worldview is the philosophy underpinning the study (23).

Study population and eligibility criteria

Consecutive patients at the Department of Vascular Surgery in Copenhagen, Denmark (Rigshospitalet) will be screened for inclusion and approached for study participation.

Inclusion criteria are; patients with newly diagnosed IC treated conservatively; age $\geq$ 18 years; speak and understand Danish; able to provide informed written content; citizens of eight municipalities of Greater Copenhagen belonging to the Healthcare Centre, and able to perform physical exercise. Exclusion criteria are: Failure to understand and cooperate according to the trial instructions; comorbidity complicating physical activity and exercise training, and lack of informed content.

Study procedure

When the informed content is signed, baselinedata will be collected including questionnaire administrated by the primary investigator. After baseline data collection randomisation is conducted. Computer-generated block randomisation in four blocks has been done by an independent statistician and delivered in envelopes blinded from investigator. Randomisation is conducted by ongoing inclusions numbers marked at the envelopes.

Control group – usual care

Patients randomised to the control group will initially receive the department's usual, brief advice about exercise therapy (walking), smoking cessation, and preventive medical treatment with antiplatelet therapy and statins. The IC patients will receive written information about medication, walking exercise, and a logbook for self-reporting of walking behaviour in the outpatient clinic at the Department of Vascular Surgery, Rigshospitalet. Patients in the control group will follow standard follow-up procedure for patients treated for IC.

Experimental intervention group

The intervention group initially receives the usual care in the outpatient clinic at the Department of Vascular Surgery; additionally, patients' home communities offer courses in smoking cessation. Patients will receive a pedometer and be asked to self-report walking behaviour and steps in a logbook. The patient brings the logbook to the consultation with the physiotherapist who initiates the startup training, supplies the motivation and explains the goal for the physical activity. Patients in the intervention group will follow the specialised cardiac rehabilitation programme for patients with IC. The intervention is based on experiences of cardiac rehabilitation and guidelines of The Danish National Board of Health and European Society of Cardiology (19). Theories about personalised feedback and self-efficacy will be used as a method for encouraging behavioral changes to improve health outcomes (27).

Physical exercise training component

Training sessions will take place at a Healthcare Centre within the municipality of Greater Copenhagen. The main goal of the exercise is to improve the patient's physical capacity and health behavior, such that this subsequently results in physical and psychological health benefits. Supervised exercise training is also targeted, relieving the fear and uncertainty the patient may feel towards physical activity. Two specialised cardiac rehabilitation physiotherapists with specific insight into IC will plan and supervise participants exercise. This entails patients actively engaging, in groups with up to ten in 24 supervised physical exercise sessions, each lasting one hour with two weekly sessions. The exercises include varied forms of physical exercise all combined to accommodate the patients' own goals regarding walking distance. The physiotherapists will administer and record a six-minute walking test and 30 second chair-stand-test prior to and at completion of the intervention. Pedometer and self-reported walking behaviour are a part of the consultation used to increase or sustain daily physical exercise at least 30 min/day. The results will be used as part of an individual motivational interview with each patient after completion of the 24 training sessions.

Supervised Exercise training programme

The exercise training protocol will consist of 10-15 minutes warm up, followed up by a 45-50 minutes combination of strength and circuit training. The exercise training program is based on national guidelines for cardiac rehabilitation (28). The warm up will be based on either bicycling, with a focus on

using the forefoot when pedalling, or walking in different variations, i.e. walking on toes, heels, walking sideways, walking lunges and walking at different paces. In strengthening the large muscle groups there will be a primary focus on the leg muscles. The strength exercises for the upper body will primarily be performed as an intermission, in the exercise for the lower body. Different exercise equipment will be used to create resistance in the exercise training, i.e. elastic bands, bodybar, dumb bells, and strength training machines. The exercise will vary from 1x15, 2x15, and 3x10 repetitions, based on low to moderate intensity of 40-60 % of the maximum muscle strength (28). The circuit training will primarily be based on activity for the lower limbs, i.e. walking and running at different paces and variations, walking combined with an exercise i.e. high knee lifts, kick back, calf raise, and different relay races in teams. The circuit training will also involve interval training, of varying lengths, depending on both the different exercises and the patients' individual limits due to lower limb pain. Two of the sessions will be based on using and practising pole striding and a nearby outdoor training park. In addition to the physical activity component the program will also contain components of health education for improving the self-efficacy of physical activity in the patients and therefore seek to affect health behavior. Five of the sessions will contain 10-15 minutes of health education which will include the use of tools developed by Steno Diabetes Center, Copenhagen. These tools were developed for supporting the patients in making long-term health related changes, and for the use of health professionals in health education for patients with chronic illness (29). Furthermore, the health education will contain motivational, group-based dialogue with the patients about their health behavior and ability to participate in physical activity in their own neighbourhood. There will also be motivational conversations concerning the patients' daily use of and achievements with the pedometer and logbook handed out to each patient at the start of the intervention.

Education in groups and individual consultation

The aim of the intervention is to provide emotional support, improve coping skills, and respond to physical symptoms. Education and information about the disease prepares the patient for expected symptoms and sensations and dialogue and shared reflections facilitate strategies for coping with symptoms and experiences associated with the condition for example when leg pain is part of the treatment for getting better. The group education is a two-hour long session, about the pathophysiology of IC, medications, health behavior, disease management, quality of life, and coping with the disease. The principal investigator (MS), who is an experienced cardiac rehabilitation nurse with specific knowledge of IC to ensure protocol compliance, will perform the intervention. Information given will also be based on national guidelines and standard treatment of patients with IC. A clinical dietician will advise participants in a two-hour long group session about healthy diet and atherosclerosis, and in addition give access to individual consultation.

Albert Bandura's Social Cognitive-Behavioral Theory and self-efficacy inspires the intervention. Its focus is on the dynamic interaction of person and behaviour, the individual's actual ability to perform the appropriate behaviour, learning a new skill, or knowledge by observing others, external responses to the individual's behaviour that either encourage or discourage the behaviour, expectations: the anticipated consequences of a behaviour, and self-efficacy: the person's confidence in his or her ability to perform a

behaviour (27, 30). Consequently, the individual, the group, spouses, and surroundings in a rehabilitation setting are important. Spouses are therefore invited to participate in group-sessions as well as in individual sessions.

Studies show that text messages can facilitate lifestyle changes (31-33). After completion of exercise training, participants are offered personalised motivational follow-up text messages. The content, frequency, and duration of the text-messages are agreed upon individually for the next eight months and will be reassessed at follow-ups after three and six months.

Outcomes and data collection

Data will be collected at admission, discharge, six months and twelve months administrated by the primary investigator (see **Table 1**). The primary and the secondary outcomes reflect the primary modifiable factors of the intervention, and a number of explorative outcomes will be collected to evaluate the effect and meaning of the intervention (see **Table 2**). The post discharge experiences of patients in the intervention group will be explored through semi-structured qualitative interviews. Patient flow illustrated in **Figure 1**

Quantity	Time of measure	Type of quantity
Demographic		
Sex	Baseline	Binary (M/F)
Age, height, weight, Body Mass Index (BMI)	Baseline	Continuous
Marital, occupational, educational status	Baseline	Categorical
Clinical		
Charlson Comorbidity Index(34)	Baseline, 6, 12	Categorical
Hypertension	Baseline 6, 12	Binary (Y/N)
Smoking+ Fagerströms test, alcohol (Time-Line-Follow Back)	Baseline, 6, 12	Categorical
Medication (routine drugs; antiplatelet; statins and other medication)	Baseline, 6, 12	Categorical
Nutritional screening 'HjerteKost': fat-fish-fruit-green score (35)	Baseline, 6, 12	Categorical
Paraclinical		
Blood work (biomarkers, cholesterol, HBa1C, Hg, thyroid)	Baseline, 6, 12	Continuous
Physical function		
The standardized Treadmill Walking Test(36, 37)	Baseline, 6, 12	Continuous
Six min walking test (Before and after Supervised exercise training)(38)	Baseline, 3	Continuous
Sit to stand test (Before and after supervised exercise training)(39)	Baseline, 3	Continuous
Level of physical activity (0-7 times a week)	Baseline, 6, 12	Categorical
Questionnaires		
HADS, Hospital Anxiety and Depression Scale(40)	Baseline, 6, 12	Categorical
VascuQol, The Vascu -Quality of Life questionnaire(41)	Baseline, 6, 12	Categorical
PAM13, The Patient Activation Measure(42)	Baseline, 6, 12	Categorical
Pedometer, Text message (intervention group)	3 months, 6	Binary (Y/N)
Participation in dietician and nurse session (intervention group)	3 months	Binary (Y/N)

Table 1 The CIPIC Rehab Study -exploratory quantities subjected to post hoc analysis

Table 2 Focus group Interview topics
Supervised Exercise Training: Physiotherapist. Content and education
Education session: Nurse and dietician. Content and education
Patients' experiences of participating in the intervention group.
Knowledge and uncertainty about IC
Experiences of factors and barrier that supported or hindered adherence to the intervention.
Factors that influence coping strategy, persistent lifestyle changes
Importance of environment and togetherness with similar patients
Empathy, support and motivation
Risk factor management
Coping behaviors
Change interventions
Attitudes, beliefs, how to handle the pain
Feeling better mentally
Accessibility and compliance
Self-monitoring goal setting
Exercise logbook and pedometers. Motivational text message.
Specific walking advice to promote self-managed walking
Quality of life
Solution behavior change techniques
Patient satisfaction of participate in the IC-rehabilitation program and point out if any suggestions for changes.

Results

Primary outcome

Maximal walking distance will be measured by the standardised treadmill walking test based on a graded protocol (3.2 km/hour with 2% increase every 2 minutes). Treadmill assessment has the highest reliability when using a graded protocol together with outcome measurements such as initial claudication distance and absolute claudication distance. Results of treadmill testing are expressed as the initial claudication distance, the moment claudication pain begins and the absolute claudication distance, the moment the test has to stop due to the maximal level of bearable claudication pain (36, 37). The follow-up treadmill walking test will be performed by a research assistant blinded as to the patients' group affiliations.

Secondary outcome

PWD will be measured by the standardised treadmill walking test as described above and with a numeric rating scale for pain (37, 43). Daily physical activity is measured by self-reported number of times per week of walking or physical exercise activity of at least 30 min., as recommended by the National Board of Health(44). Diet will be measured by a diet questionnaire (HjerteKost), a validated Danish instrument with 19 items. The scale offers two scores, a fat and a fish-fruit-green score, each of which can range from 0 to 18. To be able to achieve the term "healthy" the score must be at least 75% in both the fat and the green scores (35). The instrument is validated and recommended by the National Board of Health(28).

Exploratory outcomes

Smoking is measured by self-reported smoking behaviour by the Fagerström Test for Nicotine Dependence. The self-administered questionnaire has good internal validity and a good correlation with nicotine levels as an instrument for measuring addiction to tobacco (45). Alcohol consumption will be measured by The Alcohol Timeline Follow back (TLFB). TLFB has been shown to be a psychometrically sound assessment instrument for obtaining retrospective daily estimates of alcohol consumption. TLFB has been extensively evaluated in various settings, over varying reporting intervals and with diverse drinker populations and has been found to have very good measurement properties(46, 47).

The Hospital Anxiety and Depression Scale

HADS is a 14 item instrument that measures symptoms of anxiety (HADS-A) and depression (HADS-D). The scale offers two subscales each of which can range from 0 to 21. Scores of 0-7 for either subscale are regarded as normal; 8-10 suggest the presence of a mood disorder, and 11 and above suggest the probable presence of a mood disorder. This tool has been translated and validated in many countries and its capacity to detect anxiety and depressive disorders is widely recognized (48).

The Vascu -Quality of Life questionnaire

VascuQoL (VQ6) is a PAD-specific instrument recommended as one of the preferred questionnaires when evaluating quality of life outcomes in patients with PAD. The VQ6 is a six-item questionnaire, developed using a combination of qualitative and quantitative methodology. The VQ6 has acceptable to good psychometric properties regarding data quality, scale assumptions, targeting, validity and reliability. Further, VQ6 seems to be easy to use and comprehend within the target population of patients with PAD(41).

The Patient Activation Measure

PAM- 13 is a 13 item instrument for evaluating educational interventions aimed at improving patient engagement. Patient activation specifies the level of patients' engagement and may contribute to better self-management, higher engagement in treatment and greater patient satisfaction. The European translations of PAM-13 resulted in four instruments with good psychometric capabilities for measuring patient activation. All items have five possible responses with scores ranging from 0 to 4: (1) disagree strongly, (2) disagree, (3) agree and (4) agree strongly or (0) not applicable(42, 49).

COMPLEMENTARY STUDIES

Numerous data will be collected to evaluate the effect and meaning of the intervention.

Quantitative data

The quantitative study consists of an individual questionnaire survey conducted as interview by the principal investigator. The survey including data about feasibility: participation (number of times), use of

pedometer (yes/no), logbook (yes/no) and to what extent it has motivated daily psychical exercise, exercise choice after the course, and text messages (Yes/no). Results from the physiotherapist six minute walking test and 30 second chair stand test, before and after in meters/number are also included.

Qualitative explorative data

As a part of the study, brief individual interviews exploring course satisfaction, suggestions for changes, and the relevancy of the various rehabilitation components will be conducted. Furthermore, focus group interviews of patients participating in the intervention group will also be conducted. Prior to interviewing, an interview guide will be developed. It will be used to help explore patient experiences of training and teaching sessions, factors helping or hindering improvement in health behavior, the use of the pedometer, logbook, and text message influenced motivation/adherence, patient satisfaction with the intervention and suggestions for future rehabilitation programmes. Research questions will be developed using knowledge from existing qualitative studies in the field and the individual brief interviews (6, 7, 9, 15, 17, 50, 51) (see **Table 2**). The focus group interviews will be conducted by the principal investigator (MS) and two assistant moderators that register key points and takes field notes(52). Patients will be recruited during their three and six month follow-ups at the Healthcare Centre or at the Department of Vascular Surgery as a convenience sampling with consecutive recruitment of participants according to the groups in which they exercised during the training sessions. To embrace the potential impact of any team spirit developed during the training session, we consider focus groups and recruitment of participants according to training groups to be relevant. The interviews will be held in well-known surroundings in the Healthcare Centre. The size of the focus groups will be five to eight participants to secure an opportunity for each person to share insights, experiences, and observations. Smaller groups allow more in-depth conversation and afford each person a greater opportunity to speak. ‘Information power’ will guide the adequate sample size and the number of focus group interviews (52).

Data collection and data analysis

The interviews will be audio recorded and transcribed verbatim. Interviews are anticipated to last approximately one hour. Thematic analysis according to Braun & Clarke will be used to analyze data (53). This means combining a coding analysis with the content of the focus group discussion (11, 13). Derivation of themes will be identified by an exploratory analysis to present selected patterns relevant for the study aim and collected data. Numbers of data coders, description of the coding tree, software program, illustrated themes/ findings, quotations identification, consistency between the data presented and the findings, as well as the clarity of major and minor findings will be a part of the analysis (54, 55). The thematic analysis will be used as a systematic approach to the analysis of quality data from the focus group interviews. That involves identifying themes or patterns of meaning by coding and classifying data textually, according to themes and interpreting the resulting thematic structures by seeking commonalties, relationships, overarching patterns, theoretical constructs, or explanatory principles (56).

STATISTICAL ANALYSIS

A trial-independent statistician will make a blind analysis of the data and the primary and secondary analyses will be performed according to the intention-to-treat principle. We will use general regression models for the continuous outcomes and logistic regression models for binary outcomes. In the analysis of the primary outcome, the outcome (maximal walking distance at six months) will be analysed with adjustment for baseline maximal walking distance, gender og age (included continuously). For the three secondary outcomes - PWD distance, level of physical activity and diet at six months - the analysis will be done similarly with adjustment for baseline values, gender and age (continuous). As exploratory analyses of maximal walking distance, pain-free walking distance, smoking behavior, diet and patient related outcome measures, mixed general and generalised models with repeated measurements will be used including measurements at baseline, six and twelve months in the same model. These models will also be used for all other explorative outcomes. In these models, the interaction between intervention group and time is of primary interest, indicating different developments after intervention start. In the case of significant results in the primary outcome, sensitivity analyses will be performed to estimate the potential effect of data missing at random by a worst-case scenario. Let X be the group where a beneficial effect is observed, and Y be the other group. Missing values in group X will be imputed by the minimum value found in the material and missing values in group Y will be imputed by the maximum value found. The primary outcome will be tested first using a significance level of 0.05. Analyses of the secondary and exploratory outcome measures as planned above will be analyzed with no p-value adjustment due to multiplicity. Instead, the interpretation of these results will be assessed in the light of multiple testing, i.e. statistically significant effects will be interpreted in the context of increased risk of type I error. The clinical effect size will be reported by Cohen's d. Per-protocol analyses of the primary and secondary outcomes will be performed.

Sample size and power calculation

The expected average baseline value of maximal walking distance has been set to 120 m with a detected 50% improvement (60 m). There is a wide variance in MWD in this patient group and consequently the standard deviation (SD) is set at 100 m, based on an expected improvement in walking ability of approximately 50% to 200% (18). With a 5% significance level and 80% power it will thus be necessary to include 88 patients to detect an improvement of 60 m. in MWD in the intervention group at the 12 month follow-ups, compared to the control group. Owing to the previously mentioned risk of comorbidities, combined with an expected drop-out, a drop-out of 25% must be expected, therefore the investigators plan to include 118 patients in total (59 in each group).

Discussion

This randomised clinical trial is the first to examine the effect of a cross-sectoral exercise and health behaviour intervention based on the established cardiac rehabilitation programme for patients with IC. The CIPIC Rehab Study will provide evidence on rehabilitation needs of patients treated conservatively for

IC. Insight into the patient benefits and motivational factors of conservative management experiences of the intervention. The results can be used to point out recommendations for a specialised IC rehabilitation programme, which healthcare professionals and policymakers may use to make qualified, evidence-based decisions in everyday clinical practice and as a foundation for national and international guidelines. With a positive outcome, some of the possible effects could be lower morbidity and a decrease in the use of the public health system. This is advantageous for both patients and society. Whether it produces neutral, negative or positive results the study will have implications for clinical practice and follow-up care for patients treated for IC. The study has been designed to meet the criteria for high quality in non-pharmacological randomised clinical trials (57) with central randomisation, blinded assessment of the exercise outcome, and blinded analysis by a study-independent statistician. Detailed information on the intervention received and usual care will be collected, including self-initiated exercise training during the trial period. The secondary outcomes of self-rated mental health are subjective by nature (58-60). The trial is designed with multiple statistical comparisons, therefore results of the explorative analyses will be interpreted with caution.

Trial Status

Recruitment began in April 1th 2017 in accordance to protocol number: H-17004183

Inclusion was initiated in December 5th, 2017 and completed in June 28th, 2019. End of 12-month follow-up of all patients will be completed in the end of June 2020. The results of the trial and complementary studies will be published in relevant international peer-reviewed journals. Authorship will be determined according to the guidelines of the International Committee of Medical Journal Editors.

List Of Abbreviations

Intermittent claudication (IC)

Peripheral Artery Disease (PAD)

Supervised exercise training (SET)

Pain-free walking distance (PWD)

Maximal walking distance (MWD)

Male/Female (M/F)

Yes/No (Y/N)

Hospital Anxiety and Depression Scale (HADS)

The Vascu -Quality of Life questionnaire (VascuQol)

The Patient Activation Measure (PAM13)

The Alcohol Timeline Follow back (TLFB)

Declarations

Ethics approval and consent to participate

The study complies with the Declaration of Helsinki and was approved by the regional research ethics committee (J. No.:H-17004183) and the Danish Data Protection Agency (J.No.:2012-58-0004). Informed written content has been provided and signed.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

MS, LPJ and HS conceived the idea of the study. MS initiated the study design and implementation.

LCT designed the statistical analysis plan in collaboration with MS and SKB. PPB designed the supervised exercise training programme. All authors designed the trial, developed the protocol, revised the manuscript critically and have given their final approval of the version to be published.

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Figures

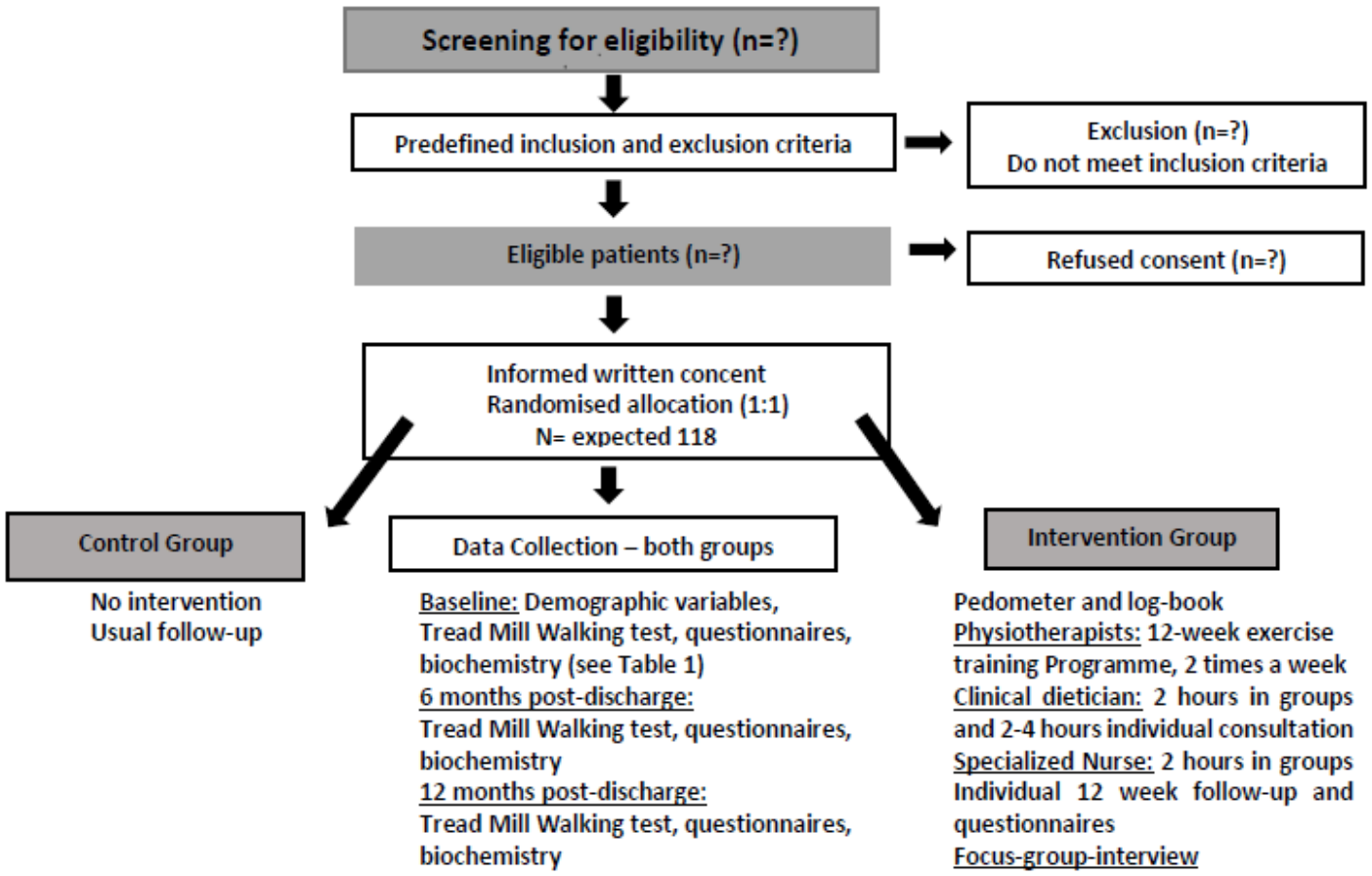

Figure 1

Patient flow.

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