

# The Effect of Lifestyle and Risk Factor Modification on Occlusive Peripheral Arterial Disease Outcomes: Standard Healthcare vs Structured Programme: for a Randomised Controlled Trial Protocol

**Marah Elfgi** (✉ [marahelfghi@gmail.com](mailto:marahelfghi@gmail.com))

Galway University Hospital <https://orcid.org/0000-0003-1383-5683>

**Fionnuala Jordan**

National University of Ireland Galway

**Denise Dunne**

NIPC

**Irene Gibson**

National University of Ireland Galway

**Jennifer Jones**

Brunel University

**Gerard Flaherty**

National University of Ireland Galway

**Sherif Sultan**

Galway University Hospital

**Wael Tawfick**

National University of Ireland Galway

---

## Study protocol

**Keywords:** Peripheral arterial disease, PAD, atherosclerosis, risk factors, lifestyle and risk factor modification intervention programme, Randomised controlled trial

**Posted Date:** November 9th, 2020

**DOI:** <https://doi.org/10.21203/rs.2.19288/v2>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

---

**Version of Record:** A version of this preprint was published on February 13th, 2021. See the published version at <https://doi.org/10.1186/s13063-021-05087-x>.

# Abstract

## Background

Peripheral arterial disease (PAD) affects more than 200 million of the global population. PAD represents a marker for premature cardiovascular events. Patients with PAD, even in the absence of a history of myocardial infarction or ischemic stroke, have approximately the same relative risk of death from cardiovascular causes as patients with a history of coronary or cerebrovascular disease. Despite the high prevalence of PAD and the strong association with cardiovascular morbidity and mortality, patients with PAD are less likely to receive appropriate treatment for their atherosclerotic risk factors than those who are being treated for coronary artery disease.

Atherosclerotic risk factor identification and modification play an important role in reducing the number of adverse outcomes among patients with atherosclerosis. Risk reduction therapy decreases the risk of cardiovascular mortality and morbidity in patients with PAD. In this study we aim to evaluate the effectiveness of a lifestyle and risk factor modification intervention programme in achieving treatment goals for PAD risk factors

## Methods

This is a randomised, parallel group, active-control trial to compare the effectiveness of the risk factor modification intervention programme to standard healthcare in a tertiary vascular care centre, in the reduction of modified risk factors in PAD patients. The primary outcome of this study is to evaluate the effectiveness of a lifestyle and risk factor modification intervention programme in achieving treatment goals for PAD risk factors at 3 and 12 months. The secondary outcomes are to compare the impact of the programme on clinical outcomes in PAD patients at 12 months. Secondary outcomes include amputation-free survival, clinical improvement, haemodynamic improvement, need for revascularisation procedures, outcomes of revascularisation procedures, changes in quality of life and the incidence of adverse events.

## Discussion

This study will provide clear evidence on the effectiveness of a lifestyle and risk factor modification intervention programme in achieving treatment goals for PAD risk factors, through a high quality, well-powered clinical trial.

## Trial registration

This trial was registered (11/07/2017) on the European Clinical Trials Database

(EudraCT number 2017-002964-41) and ClinicalTrials.gov (NCT03935776) which was registered on 02 May 2019.

## Administrative Information

<b>Title {1}</b>	Effect of Lifestyle and Risk Factor Modification on Occlusive Peripheral Arterial Disease Outcomes: a Randomised Controlled Trial Protocol
<b>Trial registration {2a and 2b}</b>	This trial was registered (11/07/2017) on the European Clinical Trials Database (EudraCT number 2017-002964-41) and ClinicalTrials.gov (NCT03935776) which was registered on 02 May 2019
<b>Protocol version {3}</b>	version 2.0 (14 March 2018)
<b>Funding {4}</b>	As sponsor of one of the co-investigators medical doctorate scholarship, Ministry of Higher Education and Scientific Research, Libyan Embassy will provide funding for the trial. The funding organization will have no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.
<b>Author details {5a}</b>	WT conceived and led the study design. ME, DD, IG, JJ, GF, WT, SS contributed to the design of the study and protocol. ME drafted the manuscript. All authors contributed to manuscript revision and read and approved the final manuscript.
<b>Name and contact information for the trial sponsor {5b}</b>	Department of Vascular and Endovascular Surgery, Galway University Hospital, Galway, H91 YR71, Ireland Tel:+35391542535
<b>Role of sponsor {5c}</b>	The sponsor will oversee the running of the trial, while ensuring compliance with regulatory bodies and ethical regulations. The sponsor will supervise recruitment, monitor adherence to protocol and report any adverse events.

## Background

Peripheral arterial disease (PAD) affects more than 200 million of the global population<sup>1</sup>. PAD represents a marker for premature cardiovascular events<sup>2</sup>. Patients with PAD, even in the absence of a history of myocardial infarction or ischemic stroke, have approximately the same relative risk of death from cardiovascular causes as patients with a history of coronary or cerebrovascular disease<sup>2</sup>. Despite the high prevalence of PAD and the strong association with cardiovascular morbidity and mortality, patients with PAD are less likely to receive appropriate treatment for their atherosclerotic risk factors than those who are being treated for coronary artery disease<sup>3,4</sup>.

As PAD represents a peripheral manifestation of atherosclerosis, most traditional and novel cardiovascular risk factors are strongly associated with this condition<sup>5-7</sup>. Smoking, diabetes, hyperlipidaemia, hypertension, unhealthy diet, and physical inactivity were identified as significant modifiable risk factors that should be targeted for secondary prevention<sup>8-12</sup>.

Atherosclerotic risk factor identification and modification play an important role in reducing the number of adverse outcomes among patients with atherosclerosis<sup>13</sup>. Risk reduction therapy decreases the risk of cardiovascular mortality and morbidity in patients with PAD<sup>13</sup>. Because of the efficacy of these techniques, several expert committees have recommended their use in patients with PAD<sup>8-12</sup>. Despite clear guidelines, several studies have shown that patients with PAD are routinely undertreated for these risk factors<sup>4</sup>, which may contribute to high rates of morbidity and mortality.

Previous studies concluded that modifiable risk factor programmes help cardiac patients achieve their risk factor modification targets, with subsequent reduction in cardiovascular events<sup>16-18</sup>. To our knowledge, currently, there is still no evidence to support that the implementation of a structured modifiable risk factor reduction program will lead to improved outcomes in PAD patients. However, due to the similar atherosclerotic burden in cardiac and PAD patients, we hypothesize that these risk factor modification programmes would similarly improve risk factor target achievement in PAD patients and subsequently improve their clinical outcomes and reduce their amputation rates when compared to standard healthcare.

The possibility of lifestyle and risk factor modification intervention should have a positive impact on patients' clinical well-being and on their quality of life.

## **Study objectives**

### ***Primary objective***

The primary objective of this study is to evaluate the effectiveness of a lifestyle and risk factor modification intervention programme in achieving treatment goals for PAD risk factors compared to the standard healthcare management.

### ***Secondary objectives***

Secondary objectives are to compare the impact of the programme on clinical outcomes in PAD patients, specifically:

- Amputation-free survival
- Clinical improvement<sup>19</sup>
- Haemodynamic improvement<sup>19</sup>
- Need for revascularisation procedures
- Changes in quality of life<sup>20</sup>
- The incidence of adverse events

## **Methods**

### **Study design**

This is a randomised, parallel group, active-control trial to compare the effectiveness of the risk factor modification intervention programme to standard healthcare in a tertiary vascular care centre, in the reduction of the prevalence of modifiable risk factors in PAD patients.

This trial will randomise patients with PAD in an equal ratio to one of two treatment arms. One arm will be randomised to undergo a risk factor modification intervention programme at a community based centre. The other arm will be provided with standard healthcare advice, in the outpatient PAD clinic in a tertiary referral vascular centre. Patients randomised into the risk factor modification intervention programme will have the intervention administered for 12 weeks. Patients will then be followed for 12 months to determine further PAD outcomes. The participant flowchart through the study is shown in Figure 1. SPIRIT figure for this trial is given in Figure 2.

### **Study setting**

Potential participants will be identified from the outpatient PAD clinic at the University Hospital Galway, Ireland (UHG). Patients will be screened and randomised at the outpatient PAD clinic in UHG.

The risk factor modification intervention programme will be administered in a nurse led community-based centre (Croí Heart and Stroke Centre, Galway, Ireland), in the presence of a physiotherapist and dietitian. The control arm will be managed in the outpatient PAD clinic, UHG. The coordinating centre will be the Department of Vascular and Endovascular Surgery, UHG, and the School of Medicine at the National University of Ireland Galway (NUI Galway). Patients are directly supervised during the intervention. The twelve-week and one-year assessments will take place at the outpatient PAD clinic in UHG.

# Eligibility criteria

## ***Inclusion Criteria***

- Aged 18 years or more
- Provide written informed consent
- PAD: diagnosed by at least one of the following:
  - Ankle-brachial index of less than 0.90 in at least one lower extremity<sup>9</sup>
  - Toe brachial index of less than 0.60<sup>9</sup>
  - Evidence of arterial occlusive disease in one lower extremity detected by duplex ultrasonography, computed tomographic angiography, or magnetic resonance angiography<sup>9</sup>
    - Symptomatic PAD ( Rutherford category 2 and above<sup>21</sup>)
    - Patients should have at least one of the following risk factors:
      - Blood pressure > 140/80 mmHg
      - Fasting blood sugar (FBS) >53 mmol/mol
      - Glycosylated haemoglobin (HbA1c) >7%
      - Total cholesterol >5 mmol/L
      - Low density lipoprotein (LDL) cholesterol >2.6 mmol/L
      - Triglycerides >1.7 mmol/L
      - High density lipoprotein (HDL) <1.0 mmol/L in men and <1.2 mmol/L in women
      - Physical activity less 30 minutes for 5 days per week
      - Body mass index (BMI) 25>kg/m<sup>2</sup>
      - Waist circumference >80 cm in women, and >94 cm in men.
      - Current smoker or exposure to tobacco in any form
      - Unhealthy diet, Mediterranean diet score less than 10 points

## ***Exclusion Criteria***

- Involvement in another clinical trial in the previous six months
- Legal incapacity
- Inadequate English language ability to understand the content of the intervention programme
- Significant cognitive impairment or mental illness
- Refusal to participate in a certain part of the intervention
- Patient suffering from a comorbidity that could affect either their physical participation in the intervention arm or influence outcomes (e.g. ischemic heart failure or severe chronic kidney disease with an estimated glomerular filtration rate of less than 30 mL/min<sup>22</sup>)
- Patient is immobile
- Contraindication to anticoagulation and antiplatelet medications or any of the risk factors treatment.

## Study screening

Patients with Symptomatic PAD (Rutherford category 2 and above<sup>21</sup>) will be invited to join the study. Invited patients will be provided with a pre-designed information leaflet. This leaflet will be fully explained to the patient at the initial assessment. The study researchers will answer any questions about the study. Informed consent will be obtained from the patient on a formatted consent form. Patients will be given the freedom to give consent either on the same day or at a later date in accordance with a study within a trial (SWAT), entitled "Same-day Consent vs Delayed Consent in a Randomised Trial: A Study within a Trial"<sup>23</sup>. This SWAT aims to ensure the rigorousness of the consent process and will run in conjunction with this randomised controlled trial.

Researchers will screen the patient for inclusion and exclusion criteria and administer a series of the following:

1. Record PAD risk factors such as smoking, hyperlipidaemia, diabetes, hypertension, increased body weight, as well as the patient's current medication.
2. Document the Rutherford category<sup>21</sup>, claudication distance and absolute walking distance for each patient, to assess the severity of PAD.
3. Schedule appointments for baseline health assessments over the following month.

## Randomisation

After meeting the inclusion criteria, screened patients will be randomised to one of two treatment arms. One arm will receive the 12-week intensive risk factor modification intervention programme. The control arm will be provided with standard care in the outpatient PAD clinic. This is an intention to treat designed study, where patients are analysed as randomised. Each screened patient will be given a unique screening number.

Screened patients will be randomised in a 1:1 ratio of study intervention: control according to a randomisation scheme. The randomisation scheme will be produced using the PROC PLAN® procedure of the SAS® software package (version 9.2.2) using a simple randomisation strategy. The scheme will be concealed from all patients and study personnel until after database lock.

Patients will be allocated to intervention via an automated telephone system, which will not deliver the randomised allocation except after registering the subject screening number. Each screened patient who is recruited to the trial will be given a unique patient trial number.

The statistician will remain blinded to the treatment allocation until all the data have been

analysed to minimise bias. Outcome assessors and data analysts will be blinded, however, in the event of an adverse event outcome assessors will be unblinded.

## Baseline, prior to intervention

All randomised patients will undergo a full baseline assessment prior to their intervention:

1. PAD assessment;
  - a. Ankle brachial index (ABI)
  - b. Digital pressure
  - c. Rutherford category<sup>21</sup>
  - d. Wound ischaemia and foot infection classification (Wifl)<sup>24</sup>
2. Blood samples including:
  - a. Fasting blood lipids,
  - b. Fasting glucose
  - c. HbA1c

3. Blood pressure documentation
4. Anthropometric measurements including:
  - a. BMI
  - b. Waist Circumference
5. Sub-maximal functional capacity exercise testing including:
  - a. Shuttle test<sup>25</sup>
  - b. Claudication distance<sup>26</sup>
  - c. Absolute walking distance<sup>27</sup>
6. Behavioural and psychological survey using the Hospital Anxiety and Depression Scale (HADS)<sup>28</sup>.
7. Health related quality of life assessment: Dartmouth Quality of Life score<sup>20</sup>.
8. Smoking status assessment using the Fagerstrom Test for Nicotine Dependence<sup>29</sup>.
9. Physical activity assessment: Godin and Shepard Leisure Exercise Questionnaire<sup>30</sup>.
10. Nutritional assessment through the Mediterranean Diet Questionnaire<sup>31</sup>.

## **Intervention**

### ***Risk Factor Modification Structured Programme***

The risk factor modification intervention programme is a 12-week intensive lifestyle programme. This is a nurse-led, community-based, lifestyle and risk factor modification intervention modelled on the European Society of Cardiology demonstration project, a large clinical trial called EuroAction<sup>14</sup>. The programme includes:

- Phase 1: Initial individualised assessment by the multidisciplinary team (MDT), will include previously mentioned baseline assessment in addition to the following:
  - Dietician will assess, current eating habits and food diary
  - Exercise specialist will assess, seven-day activity recall, barriers to exercise, seven-day pedometer and Functional Capacity Test
- Phase 2: The intervention including:
  - Weekly exercise class and educational workshops.
  - Serial blood pressure, body mass index, waist circumference, glucose and lipid measurements with goal setting.
  - Weekly MDT meetings.
  - Targeted and protocol-based pharmacotherapy to support lifestyle changes.

### ***Standard healthcare***

The control group will receive the standard healthcare advice provided to PAD patients in the outpatient PAD clinic. In this study, standard care will be conducted by the researchers which include:

- Advising patients to quit smoking, regular exercise and healthy eating, but neither structured intervention nor organised cessation plans will be addressed.
- Non-specific interventions, such as providing patients with educational material on general health problems.

### ***Twelve-week assessment***

On completion of the 12 weeks in both groups, patients are reassessed for risk factors, therapeutic management and lifestyle changes similar to baseline.

### ***One-year assessment***

Similar to the baseline and twelve-week assessment in addition to assessment and documentation of clinical outcomes which include:

1. If the patient underwent a major amputation and level of amputation
2. If required a revascularisation procedure.
3. Any residual stenosis of more than 30 %<sup>19</sup>
4. If developed a major adverse cardiovascular event (MACE) or major adverse limb event (MALE)
5. Health related quality of life
6. Cost-effectiveness of the programme

### **Endpoints**

#### *Primary endpoint*

Achieving target Improvement in lifestyle risk factors at twelve-week and at one-year. Target improvement will be considered if the patient achieves any one or more of the following:

1. Smoking cessation
2. BMI 20-25 (kg/m<sup>2</sup>). BMI is calculated by dividing body weight in kilograms by the square of height in meters
3. HbA1c less than 7%
4. Total Cholesterol less than 5.0 mmol/L

Patients will be reassessed for the primary endpoint at one year. If they fail the criteria by which they were deemed at twelve weeks to have achieved the primary endpoint, they will then be considered to not have achieved the one-year primary endpoint.

We will report the primary endpoint for both time points.

#### ***Secondary endpoints***

Secondary endpoints of PAD outcomes are based on the Society for Vascular Surgery (SVS) reporting standards<sup>19</sup>:

1. Amputation free survival; defined as time spent free from any major above ankle amputation<sup>19</sup>
2. Hemodynamic improvement: defined as an increase in the ABI by at least 0.10<sup>19</sup>
3. Clinical improvement: which is defined as an upward shift by at least one Rutherford category. However, PAD patients suffering from actual tissue loss (Rutherford category 5<sup>21</sup>) should move up two Rutherford categories to be considered improved<sup>32</sup>.
4. Re-intervention or stenosis rate; any re-intervention or stenosis among patients who already underwent vascular surgery<sup>19</sup>
5. Freedom from major adverse cardiovascular events (MACE). MACE is defined as any major cardiovascular event such as myocardial infarction, cerebrovascular accident or death<sup>19</sup>.
6. Major adverse limb events (MALE). MALE is defined as any major amputation or revascularization procedure<sup>19</sup>.
7. Revascularisation-free survival; defined as time free from any revascularisation procedure regardless of if it were an endovascular intervention or an open surgery<sup>19</sup>.
8. Change from baseline of the following risk factors:

a-BMI (measured in kg/m<sup>2</sup>)

b-HbA1c (measured as a percentage)

c-Total Cholesterol (measured in mmol/L)

9. Health related quality of life<sup>20</sup>; assessed using the Dartmouth Cooperative Information Project (COOP) charts at enrolment and after one year. The COOP charts measure six core aspects of functional status: physical fitness, feelings, daily activities, social activities, change in health, pain, and overall health. The instrument consists of six charts, referring to the above mentioned aspects of functioning. Each chart consists of a simple title, a question referring to the status of the patient and an ordinal five-point response scale illustrated with a simple drawing. Each item is rated on this five-point ordinal scale ranging from 1 (no limitation at all) to 5 (severely limited); for 'change in health' score 1 means 'much better' and score 5 'much worse'. The designers do not advocate summing the responses to gain a single index figure of health status

### ***Safety endpoints***

1. Incidence and severity of adverse events
2. Incidence of side effects due to medication commenced during the trial, for the modulation of any PAD risk factor. This includes any drug interaction of these medications with any previously assumed medication the patient was using regularly prior to commencing the trial.

### **Sample size calculation**

For sample size calculation, the EUROACTION study<sup>14</sup> was used to estimate the coefficient of variation for sample proportions.

Data from the EUROACTION<sup>14</sup> study suggest that twelve-week intervention response rates for the primary endpoint of 54.8% (Intervention programme) and 35.6% (Usual care). 80% statistical power and an alpha level of 5% were chosen. A two-sample comparison of proportions sample size calculation was implemented.

With these parameters, the G\*Power<sup>33</sup> software yields a trial with a maximum sample size of 208 patients completing the intervention (104 per intervention group).

### **Statistical analysis**

All data will be analysed according to the intention to treat principle. The primary outcome, the achievement of treatment goals for PAD risk factors between both groups at 12 weeks and 12 months will be compared using Chi square or Fisher's Exact where appropriate. Secondary outcomes including time to event will be assessed using Kaplan Meier survival curves and Log rank test. An exact 95% confidence interval will be applied for the difference between intervention groups in terms of PAD risk factor reduction.

## **Discussion**

PAD is a very common disease that affects the quality of life of a large segment of the global population<sup>1</sup>. PAD is associated with premature cardiovascular events even in the absence of symptomatic ischaemic heart disease<sup>2</sup>. Due to the atherosclerotic nature of PAD, it is associated with similar risk factors to coronary artery disease<sup>5-7</sup>. Smoking, diabetes, hyperlipidaemia, hypertension, unhealthy diet, and physical inactivity have been identified as significant modifiable risk factors in PAD patients<sup>8-12</sup>.

Atherosclerotic risk factor identification and modification have been shown to play an important role in reducing the number of adverse outcomes among patients with atherosclerosis<sup>13</sup>. Previous studies concluded that modifiable risk factor programmes help cardiac patients achieve their risk factor modification targets, with a subsequent reduction in cardiovascular events<sup>15-18</sup>.

As a result of the efficacy of these techniques, several expert committees have recommended their use in patients with PAD<sup>8-12</sup>. These recommendations for lifestyle modification techniques in PAD patients have included smoking cessation based on level 1B

evidence and healthy diet and physical activity based on level 1C evidence<sup>12</sup>. However, none of these recommendations were based on randomised clinical trials. In fact, the recommendation for smoking cessation in PAD patients was based on observational studies that noted that smokers had a seven-fold increased risk of developing PAD<sup>34,35</sup> and a two-fold higher risk of amputation<sup>36</sup>.

There are no randomised controlled trials that have quantified the direct effect of smoking cessation, directly targeting this specific PAD population. It has been shown that patients with PAD are routinely undertreated for these risk factors<sup>4</sup>, which may contribute to high rates of morbidity and mortality. However, in the absence of level one evidence to support its implementation in this particular cohort of patients, it could be difficult to convince health authorities of the benefits of spending on such programmes. This study will provide clear evidence for the effectiveness of a lifestyle and risk factor modification intervention programme in achieving treatment goals for PAD risk factors, through a high quality, well-powered clinical trial.

The study is designed to be available in large centre setups. However, if the study proves to be beneficial to these patients it can possibly be included in the guidelines of management of PAD patients. As such, there might be a cost to make this service widely available in all medical centres.

Any important protocol modifications will be communicated first to the REC. Following ethical approval, an amended patient information leaflet will be circulated to trial participants. The trial registries and journal will be notified of the amended protocol.

### **Trial registration**

This trial was registered (11/07/2017) on the European Clinical Trials Database (EudraCT number 2017-002964-41) and ClinicalTrials.gov (NCT03935776) which was registered on 02 May 2019. Appendix; Section 1, shows Trial Registration Data Set.

### **Trial status**

The study is ongoing at the time of submitting this manuscript (November 2019). This trial was using protocol version 2.0 ( 14 March 2018) at the time of this submission. Recruitment started in the University College Hospital, Galway, Ireland on 1 June 2018 and is expected to be completed on 1 June 2021. The trial management committee manages and disseminates the protocol amendments.

## **Abbreviations**

ABI	Ankle brachial index
AE	Adverse event
BMI	Body mass index
BRPM	blinded report planning meeting
Cm	Centimetre
CRF	Case report form
CTA	Clinical Trial Authorisation
DI	Decilitre
FAS	Full Analysis (data) Set
HADS	Hospital anxiety and depression scale
HbA1c	Glycosylated haemoglobin
HDL	High-density lipoprotein
ICH	International Conference on Harmonisation
Kg	Kilogram
L	Litre
LDL	Low- density lipoprotein
M	Meter
MACE	Major adverse cardiovascular event
MALE	Major adverse limb event
MDT	Multidisciplinary team
Mg	Milligram
mm Hg	Millimetres of mercury
Mmol	Millimole
NUI	National University of Ireland, Galway
PAD	Peripheral arterial disease
PP	Per Protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SVS	Society for Vascular Surgery
UCHG	University College Hospital, Galway, Ireland
Wifl	Wound ischaemia and foot infection classification

## Declarations

### Acknowledgments

We would like to acknowledge the support provided by the National Institute for Prevention and Cardiovascular Health and the Croí Heart and Stroke Centre, Galway, Ireland.

## **Funding**

As sponsor of one of the co-investigators medical doctorate scholarship, Ministry of Higher Education and Scientific Research, Libyan Embassy will provide funding for the trial. The funding organization will have no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

## **Availability of data and materials**

The final datasets underlying publications, resulting from this trial, will be shared as an anonymous copy upon reasonable and approved request. A request may be made through email to the Principal Investigator and can only be made upon meeting the terms and conditions for the ethics approval of this trial.

## **Authors' contributions**

WT conceived and led the study design. ME, DD, IG, JJ, GF, WT, SS contributed to the design of the study and protocol. ME and WT are responsible for data management.

ME drafted the manuscript. Steering committee includes WT, SS and GF. Endpoint adjudication committee includes WT, GF and FJ. The data monitoring committee will be GF, JJ and IG, they will review the collected data for completeness and accuracy, they are independent from the sponsor. All authors contributed to manuscript revision and read and approved the final manuscript

## **Ethics approval and consent to participate**

Ethical approval has been obtained from the Merlin Park Hospital, Clinical Research Ethics Committee (approval number: C.A. 1912).

The procedures detailed in this protocol are designed to ensure that investigators abide by the principles of the Good Clinical Practice guidelines of the International Conference on Harmonisation (ICH). The trial will adhere to the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza 2013)<sup>37</sup>, as well as the demands of national drug and data protection laws and other applicable regulatory requirements.

The investigator is responsible for ensuring that no patient is subject to any trial related examination or activity before that patient has given informed consent. Written consent must be given by the patient after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the patient.

The investigator will inform the patient of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it may entail. The patient must be given every opportunity to clarify any points he/she does not understand and if necessary, as for more information.

Patients will be required to sign and date the informed consent form. Participants will also be asked for permission for the research team to share relevant data with people from the Universities taking part in the research or from regulatory authorities, where relevant. This trial does not involve collecting biological specimens for storage. After completion, informed consent forms will be kept and archived by the investigator in the investigator's trial master file. We are conducting a study within the trial Study within a Trial "*Same-day Consent vs Delayed Consent in a Randomised Trial: A Study within a Trial*", to ensure of the rigorousness of the consent process<sup>23</sup>.

It should be emphasised that the patient is at liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give, or who withdraw written informed consent will not be included or continued in the trial, however, they will be assured of continued appropriate medical care.

## **Consent for publication**

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## Open Access

This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

## References

1. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *The Lancet*. 2013;382(9901):1329-40.
2. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. *Arteriosclerosis, thrombosis, and vascular biology*. 1999;19(3):538-45.
3. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *Jama*. 2001;286(11):1317-24.
4. Becker GJ, McClenny TE, Kovacs ME, Raabe RD, Katzen BT. The importance of increasing public and physician awareness of peripheral arterial disease. *Journal of Vascular and Interventional Radiology*. 2002;13(1):7-11.
5. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation*. 1985;71(3):516-22.
6. Ix JH, Allison MA, Denenberg JO, Cushman M, Criqui MH. Novel cardiovascular risk factors do not completely explain the higher prevalence of peripheral arterial disease among African Americans: The San Diego Population Study. *Journal of the American College of Cardiology*. 2008;51(24):2347-54.
7. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative Research Group. *Circulation*. 1993;88(3):837-45.
8. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). *Circulation*. 2006;113(11):e463-e654.
9. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *European Journal of Vascular and Endovascular Surgery*. 2007;33(1):S1-S75.
10. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline). *Vascular Medicine*. 2011;16(6):452.
11. Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, Mills JL, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication. *Journal of vascular surgery*. 2015;61(3):2S-41S.
12. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European heart journal*. 2016;37(29):2315-81.

13. Lu J, Creager M. The relationship of cigarette smoking to peripheral arterial disease. *Reviews in cardiovascular medicine*. 2003;5(4):189-93.
14. Wood DA, Kotseva K, Connolly S, Jennings C, Mead A, Jones J, et al. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. *The Lancet*. 2008;371(9629):1999-2012.
15. Gibson I, Flaherty G, Cormican S, Jones J, Kerins C, Walsh AM, Costello C, Windle J, Connolly S, Crowley J. Translating guidelines to practice: findings from a multidisciplinary preventive cardiology programme in the west of Ireland. *European journal of preventive cardiology*. 2014 Mar;21(3):366-76.
16. Kotseva K, Connolly SB, Jennings C, Mead A, Jones J, Holden A, et al. EUROACTION: An ESC project in preventive cardiology programme in coronary and high risk patients and their partners. 2007. p. 285.
17. Wood D, Kotseva K, Jennings C, Mead A, Jones J, Holden A, et al. EUROACTION: A European Society of Cardiology demonstration project in preventive cardiology - A cluster randomised controlled trial of a multi-disciplinary preventive cardiology programme for coronary patients, asymptomatic high risk individuals and their families. Summary of design, methodology and outcomes. *Eur Heart J Suppl*. 2004;6(J):J3-J15.
18. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U, et al. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *The Lancet*. 2009;373(9667):929-40.
19. Stoner MC, Calligaro KD, Chaer RA, Dietzek AM, Farber A, Guzman RJ, et al. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. *Journal of vascular surgery*. 2016;64(1):e1-e21.
20. McHorney CA, Ware Jr JE, Rogers W, Raczek AE, Lu JR. The validity and relative precision of MOS short-and long-form health status scales and Dartmouth COOP charts: results from the Medical Outcomes Study. *Medical care*. 1992;MS253-MS65.
21. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *Journal of vascular surgery*. 1997;26(3):517-38.
22. Lewis R. *Understanding Chronic Kidney Disease: A guide for the non-specialist*. M&K Update Ltd; 2012.
23. Elfghi M, Jordan F, Tawflick W. SWAT 84: Same-day Consent vs Delayed Consent in a Randomised Trial. The Northern Ireland Network for Trials Methodology Research. 2018. online, available at: <https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/Fileupload,996661,en.pdf> [accessed on 12/3/2018]
24. Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The society for vascular surgery lower extremity threatened limb classification system: risk stratification based on wound, ischemia, and foot infection (Wifl). *Journal of vascular surgery*. 2014;59(1):220-34. e2.
25. Liu NY-S, Plowman SA, Looney MA. The reliability and validity of the 20-meter shuttle test in American students 12 to 15 years old. *Research quarterly for exercise and sport*. 1992;63(4):360-5.
26. Kruidenier LM, Nicolaï SP, Willigendael EM, de Bie RA, Prins MH, Tejjink JA. Functional claudication distance: a reliable and valid measurement to assess functional limitation in patients with intermittent claudication. *BMC cardiovascular disorders*. 2009;9(1):9.
27. Fabry R, Dubost J-J, Pochon P, Duchene-Marullaz P. Comparison of standard one-minute treadmill exercise and strandness test (absolute walking distance) in relation to site of lesion, walking distance, and diastolic blood flow velocity (Doppler curves). *Angiology*. 1990;41(10):869-76.
28. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatr scand*. 1983;67(6):361-70.
29. 26. Heatherton TF, Kozlowski LT, Frecker RC, FAGERSTROM KO. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Addiction*. 1991;86(9):1119-27.
30. Godin G, Shephard R. Godin leisure-time exercise questionnaire. *Med Sci Sports Exerc*. 1997;29(6):36-8.
31. Martinez-Gonzalez M, Fernandez-Jarne E, Serrano-Martinez M, Wright M, Gomez-Gracia E. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. *European Journal of Clinical Nutrition*. 2004;58(11):1550-2.

32. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, Jones DN. Recommended standards for reports dealing with lower extremity ischemia: revised version. *Journal of vascular surgery*. 1997 Sep 1;26(3):517-38.
33. Faul F, Erdfelder E, Lang A-G, Buchner A. G\* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods*. 2007;39(2):175-91..
34. Shamma NW. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. *Vascular health and risk management*. 2007 Apr;3(2):229.
35. Price J, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease; Edinburgh Artery Study: Edinburgh Artery Study. *European heart journal*. 1999 Mar 1;20(5):344-53.
36. Bendermacher BL, Willigendael EM, Teijink JA, Prins MH. Medical management of peripheral arterial disease. *Journal of Thrombosis and Haemostasis*. 2005 Aug 1;3(8):1628-37.
37. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *The Journal of the American College of Dentists*. 2014;81(3):14.

## Figures

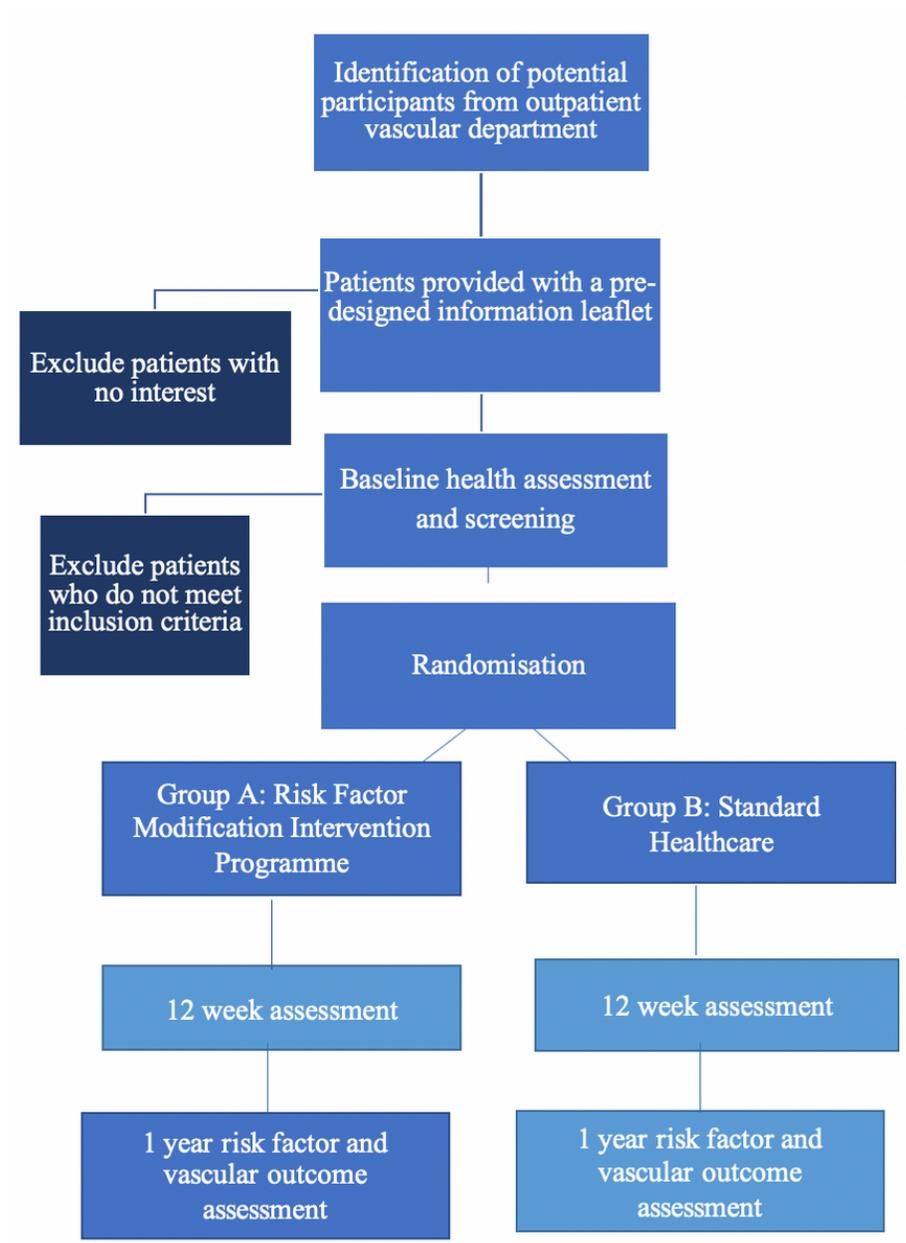


Figure 1

Participant flowchart through the study

TIME POINT	Enrolment	Allocation	Study Period			
	-t1	0	Baseline Week 0	Intervention (12 weeks)	12 weeks follow up	12 months follow up
Eligibility screen	X					
Informed consent	X					
Randomisation		X				
<b>INTERVENTIONS:</b>						
Risk Factor Modification Intervention Programme				—————		
Standard Healthcare (control group)				—————		
<b>ASSESSMENTS:</b>						
PAD assessment: ABI, digital pressure, Rutherford category, and WIfI			X		X	X
Blood samples including: Fasting blood lipids, Fasting glucose and HbA1c			X		X	X
Blood pressure documentation			X		X	X
Anthropometric measurements including: BMI and Waist Circumference			X		X	X
Physical capacity including: Shuttle test, Claudication distance and Absolute walking distance			X		X	X
<b>HADS</b>			X		X	X
Dartmouth Quality of Life score			X		X	X
Fagerstrom Test for Nicotine Dependence			X		X	X
Godin and Shepard Leisure Exercise Questionnaire			X		X	X
Nutritional assessment through the Mediterranean Diet Questionnaire			X		X	X
major amputation						X
revascularisation or a reintervention						X
intervention or stenosis						X
MACE						X
MALE						X
Health related quality of life						X
Cost-effectiveness of the programme						X

Figure 2

SPIRIT figure showing an overview of the assessment schedule at baseline and follow-up in study. ABI: Ankle brachial Index, WIfI: Wound ischaemia and foot infection classification, HbA1c: Glycosylated haemoglobin, BMI: body mass index, HADS: Hospital anxiety and depression scale, MACE: major adverse cardiovascular event and MALE: major adverse limb event

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendices.docx](#)
- [amendedRCTSPIRITchecklist.docx](#)