Designing a Platform/Adaptive Trial for PAD: The PAEDIS International Platform Trial Development Project

Rationale for initiating the PAEDIS trial development project, key aims, and objectives per work package.

By Athanasios Saratzis, MBBS, FHEA, PhD, FRCS

Peripheral artery disease (PAD) affects one-fifth of people aged > 55 years, and its prevalence is steadily increasing in many countries.[1-3] PAD is the most common cause of amputation in the United Kingdom and the United States and a leading cause of cardiovascular morbidity worldwide.[4] It makes up 75% of current vascular health care workload across primary, community, and secondary care. More than half of those with symptomatic PAD are expected to die, have an amputation, or cardiovascular event within 5 years, which has not improved despite advances in care.[2,5-8] People with symptomatic PAD present with intermittent claudication or chronic limb-threatening ischemia, which is limb- and life-threatening and requires urgent revascularization.[4] Those with claudication require exercise therapy and occasionally revascularization to alleviate symptoms.[9] All patients with symptomatic PAD require risk factor modification and medications to reduce cardiovascular risk and PAD progression.

Most revascularization procedures for PAD are performed via an endovascular (minimally invasive) approach. New endovascular technologies and medications are regularly introduced in clinical care. However, the clinical and cost-effectiveness of these interventions is often unknown, as they have not been assessed in high-quality, randomized controlled trials (RCTs) with primary outcomes and designs that can assess clinically relevant endpoints such as amputation-free survival or improvement in quality of life. The continuous introduction of new PAD technologies and the fact that they can be used contemporaneously, as well as the heterogeneity of presentation for patients with PAD, further complicate their assessment. Most PAD technologies and new treatments are used in routine care without adequate scrutiny. As such, PAD has been identified as a key research priority in a recent James Lind Alliance Priority Setting Partnership with the Vascular Society of Great Britain and Ireland.[1] Further, as noted as part of this application and our ongoing National Institute for Health and Care Research (NIHR)–funded research, patients in focus groups and surveys are concerned about the lack of evidence to support decision-making when they are offered treatment.

Overall, the lack of high-quality randomized evidence assessing the effectiveness and long-term results of new PAD technologies and medications may lead to increased adverse outcomes, increased health care costs, and uncertainty regarding decision-making.[10] One means of addressing this need is a platform trial design. An ideal PAD trial should generate evidence rapidly, account for disease heterogeneity and variation in treatment effects, assess multiple potentially interacting treatments concurrently, take patients' views into account, and create a durable infrastructure for ongoing evidence generation. We plan to initiate such a platform trial to assess new PAD technologies and medications,

which will improve patient care, end treatment uncertainty, and decrease health care costs. This will act as a model design to allow delivery of future ambitious trials in other vascular disease areas.

WHY IS A COMPLEX TRIAL URGENTLY NEEDED IN PAD?

We performed a systematic search and reviewed all PAD guidelines in September 2022 to identify complex vascular trials, and currently available PAD treatments/medications. We recently published three international studies (52 centers, 3,289 patients) investigating new invasive treatments for patients with aortoiliac or infrainguinal PAD[11-13] and have identified the following:

- Symptomatic PAD is the most common arterial pathology requiring specialist treatment[14]
- There is variation in PAD medications and types of revascularization offered to patients[15]
- Modern pharmacotherapies for PAD have not been assessed in high-quality trials
- Most endovascular PAD treatments have not been tested in a randomized trial
- Some new PAD treatments might be associated with unknown risks
- Only 15% of patients seen in real-world practice across multiple sites in Europe would be eligible for randomization in the major industry-funded paclitaxel trials[16]
- Interactions between endovascular technologies and medications have never been assessed[17]

Key challenges in delivering a platform trial to address the aforementioned issues include (1) patients with PAD are usually frail, have multiple comorbidities, and are socioeconomically deprived; (2) several new interventional and pharmaceutical PAD treatments are made available yearly; (3) there are no core outcome sets for patients with PAD; and (4) the opinions and views of patients or health care professionals have not been explored.

AIMS AND OBJECTIVES OF THE PAEDIS TRIAL DEVELOPMENT PROJECT

The main objective of the PAEDIS trial development project is to identify the optimal design and pathway for research delivery for a large-scale platform RCT assessing the clinical effectiveness and cost-effectiveness of interventions for patients with symptomatic PAD. The objectives per work package (WP) are listed herein.

WP1: Evidence Synthesis

Perform evidence synthesis to identify:

- Ongoing and completed complex RCTs relating to any cardiovascular disease
- Interventions to be assessed in the future platform trial (both interventional and pharmaceutical)
- Comparators
- Outcomes of interest, including relevant health states for economic modeling

WP2: Establish Stakeholder Groups

Work package 2 includes the setup of lay and expert groups to guide research design. It aims to:

- Use our existing PAD lay groups to set up a new project-specific patient and public involvement panel
- Institute an international group of professional stakeholders to lead trial design

WP3: Define Trial Characteristics and KPIs

Define the trial's ideal characteristics and key performance indicators (KPIs) regarding:

- Screening, randomization, and treatment allocation mechanisms
- Requirements needed to be met before an intervention is deemed appropriate to enter the trial
- Outcome assessments, treatment delivery assessment per arm, and health economic data collection
- Cost-effective design and model structure, sustainability, and longevity, including the use of existing resources (eg, routinely collected data, existing cohort studies, National Vascular Registry integration)

The trial investigators are actively looking for patients with PAD, as well as health care professionals or industry partners, to support our trial development process. Contact paedis@imperial.ac.uk or as875@le.ac.uk if you are a patient or health care professional interested in helping us develop this research.

- Implementation research and qualitative appraisal within the trial

WP4: Consensus on Trial Design

This WP aims to gain consensus to design the research, including objectives to:

- Finalize the PICO (patient, intervention, comparison, outcome) design of the ideal PAD platform trial
- Finalize the KPIs to assess patient safety, research delivery success, and milestones
- Create a blueprint for collaboration between existing vascular registries, trials, and cohort studies in the National Health Service and abroad to establish recruitment and patient follow-up strategies
- Establish a mechanism via which arms will be added or removed in the platform trial
- Identify how interactions between different treatments will be assessed
- Create a vehicle for efficient and timely international dissemination alongside trial delivery
- Obtain consensus on appropriate core structure for economic modeling

WP5: Finalize Protocol and Funding

The aim of WP5 is to finalize the trial protocol and funding application for the NIHR by the end of November 2023.

SUMMARY

The PAEDIS project is an ambitious attempt to improve the way in which we conduct randomized research for people with PAD. It will hopefully address deficient areas in the existing evidence base and improve clinical care. Anyone interested to help or provide feedback, please get in touch with the PAEDIS team. ■

The PAEDIS trial development project is a collaboration between the Imperial College (London), Leicester, and Leicester Clinical Trials Unit and is funded by the National Institute for Health and Care Research. Prof. Athanasios Saratzis (Leicester) is Chief Investigator, and Prof. Alun Davies (London) is Co-Chief Investigator.

1. Cea-Soriano L, Fowkes FGR, Johansson S, et al. Time trends in peripheral artery disease incidence, prevalence and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK. BMJ Open. 2018;8:e018184. doi: 10.1136/bmjopen-2017-018184
2. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. BMJ. 2018;360:j5842. doi: 10.1136/bmj.j5842
3. National Institute for Health and Care Excellence (NICE). Peripheral arterial disease: diagnosis and management. Clinical guideline [CG147]. Published August 8, 2012. Updated December 11, 2020. Accessed June 12, 2023. https://www.nice.org.uk/guidance/cg147
4. Diabetes UK. Facts and Figures 2019 Diabetes UK. https://www.diabetes.org.uk/resources-s3/2019-02/1362B_Facts%20and%20stats%20Update%20Jan%202019_LOW%20RES_EXTERNAL.pdf
5. Parvar SL, Fitridge R, Dawson J, Nicholls SJ. Medical and lifestyle management of peripheral arterial disease. J Vasc Surg. 2018;68:1595-1606. doi: 10.1016/j.jvs.2018.07.027
6. Dhaliwal G, Mukherjee D. Peripheral arterial disease: epidemiology, natural history, diagnosis and treatment. Int J Angiol. 2007;16:36-44. doi: 10.1055/s-0031-1278244
7. Dua A, Lee CJ. Epidemiology of peripheral arterial disease and critical limb ischemia. Tech Vasc Interv Radiol. 2016;19:91-95. doi: 10.1053/j.tvir.2016.04.001
8. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, et al. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. J Vasc Surg. 2014;60(3):686-95.e2. doi: 10.1016/j.jvs.2014.03.290
9. Saratzis A, Paraskevopoulos I, Patel S, et al. Supervised exercise therapy and revascularization for intermittent claudication: network meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2019;12:1125-1136. doi: 10.1016/j.jcin.2019.02.018
10. Subherwal S, Patel MR, Chiswell K, et al. Clinical trials in peripheral vascular disease. Pipeline and trial designs: an evaluation of the clinicaltrials.gov database. Circulation. 2014;130:1812-1819. doi: 10.1161/circulationaha.114.011021
11. Saratzis A, Rudarakanchana N, Patel S, et al. Interwoven nitinol stents versus drug eluting stents in the femoropopliteal segment: a propensity matched analysis. Eur J Vasc Endovasc Surg. 2019;58:719-727. doi: 10.1016/j.ejvs.2019.06.012
12. Troisi N, Saratzis A, Katsogridakis E, et al. Different endovascular modalities of treatment for isolated atherosclerotic popliteal artery lesions (EMO-POP) registry. J Vasc Surg. 2023;77:231-240.e4. doi: 10.1016/j.jvs.2022.07.170
13. Saratzis A, Argyriou A, Davies R, et al. Editor's choice—covered vs. bare metal stents in the reconstruction of the aortic bifurcation: early and midterm outcomes from the COBRA European multicentre registry. Eur J Vasc Endovasc Surg. 2022;63:688-695. doi: 10.1016/j.ejvs.2021.12.020
14. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg. 2019;58:S1-S109.e33. doi: 10.1016/j.ejvs.2019.05.006
15. Saratzis A, Jaspers NEM, Gwilym B, et al. Observational study of the medical management of patients with peripheral artery disease. Br J Surg. 2019;106:1168-1177. doi: 10.1002/bjs.11214
16. Stavroulakis K, Katsogridakis E, Torsello G, et al. RANDOMization screening for drug coated or drug eluting device randomised trials among patients undergoing endovascular femoropopliteal procedures (RANDOM-STOP study). Eur J Vasc Endovasc Surg. Published online July 3, 2023. doi: 0.1016/j.ejvs.2023.06.038
17. Fuchs S, Olberg B, Panteli D, Busse R. Health technology assessment of medical devices in Europe: processes, practices, and methods. Int J Technol Assess Health Care. 2016;32:246-255. doi: 10.1017/S0266462316000349

Athanasios Saratzis, MBBS, FHEA, PhD, FRCS
Professor of Vascular Surgery
Honorary Consultant Vascular & Endovascular Surgeon
NIHR Leicester Biomedical Research Center
Department of Cardiovascular Sciences
University of Leicester
Glenfield Hospital
Leicester, United Kingdom
saratzis@doctors.net.uk; as875@le.ac.uk
@a_saratzis
Disclosures: None.