Protocol

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Diversity in clinical trial inclusion for peripheral artery disease lower extremity endovascular interventions: a systematic review protocol

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Aim: This review provides a study protocol for a systematic review of peripheral artery disease (PAD) clinical trials to examine the eligibility criteria, demographic representation, and enrollment strategies among PAD patients undergoing lower extremity (LE) endovascular interventions. **Methods:** This systematic review will be conducted according to the Cochrane Collaboration methodology for systematic reviews and following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). Eligible studies will include randomized controlled trials (RCTs) between January 2012 and December 2022. The primary outcome will be a description and summary of the frequency of the reporting of demographic characteristics. The feasibility of a meta-analysis or meta-regression will be explored, but if determined to be infeasible, the Synthesis Without Meta-analysis (SWiM) reporting guideline will be followed for the reporting of findings. **Discussion:** The findings may help to quantify existing inequities in clinical trial participation that may be addressed through optimizing enrollment strategies for future PAD trials. **Systematic review registration:** PROSPERO (CRD42022378304)

Plain language summary

What is this article about? This study aims to review clinical trials focused on peripheral artery disease (PAD) patients who have received below-the-knee catheter-based interventions. It investigates the criteria for trial inclusion, how different groups of patients are represented in these trials, and the methods used for recruiting participants.

How will the results be gathered? To achieve this, established methods for systematic reviews will be followed. This review will focus on randomized controlled trials published between 2012 and 2022. This study will explore the feasibility of pooling all studies together to find important patterns. If not, a guideline to summarize the study findings will be used.

Why is this research important? This research is important because it helps identify any existing disparities in clinical trial participation. By understanding these disparities, principal investigators can suggest ways to improve how participants are selected for future PAD trials. Ultimately, this will lead to more effective PAD treatments and enhance the quality of life for patients with this condition.

Tweetable abstract: Investigating diversity gaps in PAD trials: Smaller trials may miss vital insights. Our study explores demographic representativeness for better healthcare equity. #ClinicalTrials #HealthEquity #PADResearch

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Keywords: peripheral artery disease • demographic representation • diversity • equity in healthcare • lower extremity endovascular interventions • systematic reviews • clinical trials

Peripheral artery disease (PAD) imposes a significant disease and economic burden and is associated with adverse outcomes such as amputation and death [1,2]. Medical management and endovascular therapy may reduce the risk of adverse events such as amputation, major cardiac events and death [3–6]. Clinical trials have demonstrated the potential benefits and effectiveness of endovascular interventions for treating PAD [7,8].

While clinical trials provide evidence to inform clinical decision-making and support optimal patient outcomes, diverse populations are often underrepresented in these trials [9–11]. Factors such as mistrust, lack of reliable information, time and resource constraints, and lack of awareness all impact enrollment and participation in clinical trials [12]. This underrepresentation may result in clinical studies not accurately reflecting the real-world patient population, posing a critical challenge in translating outcomes to the wider population. For instance, while women comprise nearly 51% of the US population [13], they represent only 33% of enrollment in medical device clinical trials [12,14]. Similarly, although Black and Hispanic individuals account for roughly 33% of the US population [13], they make up less than 10% of clinical trial participants [14].

As treatment of PAD with endovascular intervention is increasing globally, disparities in treatment and health outcomes are notable. Health outcomes vary disproportionately by racial and ethnic groups, negatively impacting medically underserved populations [15,16]. The impact of these varies by clinical indication. For instance, Black patients are significantly more likely to have PAD than non-Hispanic White patients [17,18], often present with more advanced symptoms, are less likely to be diagnosed/treated [17], and often experience worse outcomes [19]. Both Black race [20,21] and Hispanic ethnicity [22] are associated with increased odds of amputation, while higher mortality rates and increased medical expenses have been observed in individuals of Asian and Pacific Islander ethnicity who are hospitalized for PAD [22].

Women are more likely than men to undergo above-the-knee amputations (AKA), which have a greater impact on mobility than below-the-knee amputations (BKA) [23]. Compared with men, women with PAD often present at an older age, report more PAD-related disability, and are less likely to receive certain treatments [24]. Also, despite comprising a substantial proportion of the PAD population, older adults (over 75 years) are often underrepresented in clinical trials.

While these differences may not be surprising, it is important to recognize their potential impact on treatment and patient care. However, there is limited global evidence from systematic reviews that identify inclusive trial designs reflective of the patient population in PAD randomized controlled trials (RCTs) [24,25]. No previously published studies have explored the demographic characteristics and enrollment strategies for the recruitment of eligible patients in RCTs. The US FDA and US Congress are implementing regulatory levers to increase diversity in clinical trials [26]. There are several illustrative examples of investments aimed at improving diversity in clinical trial participation, including initiatives by Pfizer and Boston Scientific to achieve a diverse patient population and advance health equity [27,28].

Given RCT enrollment is limited through strict inclusion and exclusion criteria that do not reflect the real-world population, it is critical that future clinical trials prioritize representative and diverse enrollment. Therefore, a systematic review identifying PAD clinical trials and evaluating their design is vital for reducing uncertainty about demographic representativeness in PAD trial enrollment. Specifically, this review will assess the eligibility criteria, demographic representativeness, and enrollment strategies in trials of PAD patients undergoing lower-extremity (LE) endovascular interventions, including superficial femoral artery (SFA), femoropopliteal (FPA), popliteal and tibial artery interventions.

This study aims to address the following questions:

- What are the inclusion and exclusion criteria for PAD LE endovascular intervention clinical trials?
- What are the baseline demographic (age, sex, race/ethnicity, etc.) and clinical characteristics (diabetes, Rutherford classification, etc.) of all patients (enrolled and excluded) in PAD LE endovascular intervention clinical trials over the past 10 years?
- What enrollment strategies are used for PAD LE endovascular intervention clinical trials?

Methods

Protocol & registration

This systematic review will be conducted according to the Cochrane Collaboration methodology for systematic reviews [29] and following the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols

(PRISMA-P) [30]. This protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022378304).

Inclusion & exclusion criteria

Types of studies

Studies eligible for inclusion are RCTs with a parallel group design comparing the outcomes of LE endovascular interventions with a sample size greater than 50 patients published in the last 10 years (between January 2012 and December 2022). RCTs will be eligible for inclusion if the primary outcome of interest is reported at 12 months and is one of the following clinical outcomes: patency rate/vessel patency, target lesion revascularization (TLR), all-cause mortality, amputation (amputation rates, amputation-free survival, minor or major amputations), serious adverse events/major adverse events, change in ankle-brachial index, or improvement in Rutherford category. For RCTs with multiple publications, only those reporting the 12-month primary end point will be eligible for inclusion. Studies reporting the clinical outcomes before or after the 12-month period of interest will be excluded.

Additionally, studies reporting clinical outcomes that do not meet the inclusion criteria, such as late lumen loss, binary restenosis, stenosis, etc., studies reporting benefits, such as resource use, quality of life, quality-adjusted life years, costs, etc., and studies reporting diagnostic/angiographic assessment will be excluded. Non-controlled studies (case reports, observational, non-randomized, retrospective, and other non-comparative studies, letters, commentaries, editorials, abstracts and conference proceedings), RCTs conducted before January 2012 or without a clinical trial registration number, studies published in languages other than English, and studies with a sample size of 50 or less will be excluded. Additionally, RCTs with a single-group assignment, single-arm design, or pragmatic study design will be ineligible.

Population

Adults ($\geq$18 years) diagnosed with PAD, critical limb ischemia, intermittent claudication, severe limb ischemia, or chronic limb-threatening ischemia will be included.

Interventions

Peer-reviewed studies that report on LE endovascular interventions for femoral/popliteal/tibial (percutaneous transluminal angioplasty [PTA], drug-eluting stent [DES], drug-coated balloon [DCB] and bare-metal stent [BMS]) in one treatment arm will be eligible for inclusion. Only studies with a comparator using an LE endovascular intervention (BMS, DCB/drug-eluting balloon [DEB], PTA and DES) will be included. RCTs that use non-LE interventions, such as coronary procedures, atherectomy, graft, bioresorbable scaffolds, etc., either alone or in combination with other interventions, will be excluded from this review. The choice of these interventions was made to align this study with the clinical relevance and standard practices in the management of PAD. These interventions represent common and important treatment modalities for PAD.

Outcomes

The primary outcome will be a description/summary of the frequency of the reporting of demographic characteristics (age, sex, race, etc.) and baseline clinical characteristics of interest in PAD trials. These selected outcomes are clinically meaningful and widely used to assess the effectiveness and safety of these interventions in PAD patients.

Setting

All RCTs conducted in any country will be included in the review.

Data sources

The information sources for this review will include various trial registries, including ClinicalTrials.gov [31], National Institute of Health grants and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) [32], which will be accessed through Drevidence™ [33]. Bibliographic databases, such as MEDLINE and EMBASE via OVID and the Cochrane Controlled Register of Trials (CENTRAL), will be searched. Google Scholar will be used to search for protocols or publications that may not be indexed in the trial registry. Additional trials will be identified through manual searches of eligible publications.

Table 1. Search strategy.

PICO strategy	Search terms
Patients	SFA lesions OR FPA lesions OR Severe Limb Ischemia OR popliteal lesions OR tibial lesions OR peripheral arterial disease OR Peripheral artery disease PAD OR critical limb ischemia OR intermittent claudication OR critical limb OR limb ischem OR claudication OR chronic limb-threatening ischemia OR limb ischemia or limb threat OR ischaemia AND (leg OR legs OR limb OR limbs)
Interventions	Peripheral interventions OR stents OR drug eluting stents OR drug coated stents OR drug coated balloons OR drug-coated balloons OR balloon angioplasty OR plain balloon OR bare metal stent OR paclitaxel eluting stent OR paclitaxel-coated balloon OR PTA OR percutaneous transluminal angioplasty OR uncoated PTA OR lower extremity OR endovascular procedures OR angioplasty, balloon
Comparators	Endovascular intervention OR bare metal stent OR BMS OR drug-coated balloon OR DCB OR drug-eluting balloon OR DEB plain old balloon angioplasty OR POBA percutaneous transluminal angioplasty OR PTA OR drug-coated stent OR DCS OR drug-eluting stent OR DES
Outcomes	Patency rate OR vessel patency OR target lesion revascularization OR TLR OR all-cause mortality OR all-cause death OR amputation OR amputation rates OR amputation-free survival OR minor amputation OR major amputation OR serious adverse event OR major adverse event OR wound healing

DCB: Drug-coated balloon; DEB: Drug-eluting balloon; DES: Drug-eluting stent; FPA: Femoropopliteal; PAD: Peripheral artery disease; PICO: Patient/population, intervention, comparison and outcomes; POBA: Plain old balloon angioplasty; PTA: Percutaneous transluminal angioplasty; SFA: Superficial femoral artery: TLR: Target lesion revascularization.

Search strategy

A draft of the search strategy to identify the appropriate population, interventions, comparators and outcomes is provided in Table 1. Additional filters will be applied to restrict the search to RCTs or clinical trials published in English between January 2012 and December 2022. To enhance the quality and timeliness of the searches, an information specialist (librarian) will be consulted to refine the search strategy (Table 1).

Study management

Covidence [34], a web-based systematic review management software, will be used for removing duplicates, data screening, extraction and quality assessment. The tool offers a range of features, such as duplicate removal, full-text screening, risk of bias assessment and data extraction forms. EndNote 20 will be used to transfer references from PubMed to Covidence, and for importing hand searches into Covidence. Title and abstract screening will be performed independently by two reviewers. Full-text screening will be performed independently by two reviewers against the eligibility criteria. Disagreements, if any, will be resolved by a third reviewer.

Data extraction & assessment

A pre-specified, standardized data extraction form customized in Covidence will be used to extract data. The following features will be extracted:

- Trial characteristics: trial source, reporting of study results, indexing of peer-reviewed or study protocols to trial registry, intervention and comparator, blinding, concealment allocation, start and end date of the trial, follow-up, sample size, study sites, recruitment status (active not recruiting, completed, recruiting, suspended, not yet recruiting, unknown, etc.), type of randomization (1:1, 2:1, 3:1, or not reported), masking (single, double, or not reported), trial phase, principal investigator characteristics (sex, affiliation, country), etc.
- Protocol characteristics: methods of recruitment of patients (hospitals or clinics, academic institutions, community settings), withdrawal strategies, strategies for follow-up of patients (telephone, letter, office or clinic visits), availability of participant facing materials in other languages, information on barriers to transportation, patient reimbursement or compensation, types of reimbursement or compensation, patient navigation or coaching strategies adopted, information on cultural competency training for clinical research associates or principal investigators, information on methods for handling missed or late visits, reasons for excluding patients (missed visits, investigator removal, defaulted clinical follow-up, surgery, death, withdrawal, early termination, etc.)
- Eligibility criteria of patients (inclusion and exclusion criteria for the recruitment of patients)
- Baseline demographic characteristics (age, race/ethnicity, sex, age, region, etc.) of patients enrolled and excluded
- Baseline clinical characteristics (intermittent claudication, critical limb ischemia, Rutherford classification, diabetes, hyperlipidemia, hypertension, smoking status, obesity, coronary artery disease, history of congestive heart failure, chronic obstructive pulmonary disease, etc.) of patients enrolled and excluded
- Clinical outcomes: patency rate/vessel patency, target lesion revascularization (TLR), all-cause mortality/death, amputation (amputation rates, amputation-free survival, minor or major amputations), serious adverse

events/major adverse events and wound healing. Reporting of clinical outcomes by demographic characteristics (age, sex and race) will be assessed.

The data extraction template will be piloted by two reviewers using a few eligible studies and modified based on feedback, comprehensibility and user experience. Two independent reviewers will perform data extraction, and a third reviewer will verify the data for quality assurance. All discrepancies or inaccuracies between the reviewers will be resolved by a third reviewer.

Risk of bias of individual studies

Two independent reviewers will evaluate the methodological quality of eligible studies for potential bias using the Cochrane risk-of-bias tool for randomized trials (RoB 1) [35]. This tool evaluates the quality of RCTs across several domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain will be rated as 'low risk of bias', 'high risk of bias' or 'unclear risk of bias'. The overall risk of bias is determined by considering all domains. The RoB 1 tool will be customized in Covidence, where data extraction will take place. Any disagreement will be resolved independently by a third reviewer or through consensus.

Data synthesis & confidence in cumulative estimate

A PRISMA flow chart will be used to report the study selection process for the included and excluded trials, highlighting the reasons for exclusion. The unit of analysis will be the included clinical trial. Depending on the completeness of the data, the feasibility of a meta-analysis will be explored to assess the potential variability of the patients enrolled in RCTs by demographic characteristics (sex, age and race). In the event the necessary data are unavailable, the extracted data will be described and summarized using descriptive analyses (frequencies for categorical data and interquartile ranges and medians for continuous data). The Synthesis Without Meta-analysis (SWiM) [36] in systematic reviews reporting guideline will be followed to report the findings. The SWiM guideline has emerged as a methodological framework for systematic reviews that aims to synthesize evidence while avoiding the use of statistical pooling or meta-analysis or meta-regression. This approach utilizes narrative synthesis techniques to summarize and present the findings from individual studies, considering the quality of evidence and consistency in results across studies. The feasibility of either the SWiM or meta-analysis approach will be assessed in consultation with a biostatistician.

Meta-bias(es)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [37] will be used to evaluate the quality of evidence and strength of recommendations in the included studies. The GRADE approach is based on several factors such as study design, risk of bias, inconsistency, indirectness, imprecision and publication bias. The tool has four levels of quality of evidence (high, moderate, low and very low) and four levels of strength of recommendations (strong, weak, conditional and good practice). The GRADE profiler (GRADEpro) software will be used to assess the quality and overall level of recommendation of the evidence. GRADEpro is a software tool that facilitates the development and management of systematic reviews, health technology assessments and clinical practice guidelines. A summary of findings table will be used to summarize the treatment effects and the quality of evidence for each outcome.

Dissemination

The results of this systematic review will be presented at scientific conferences and reported using the PRISMA for abstract [30]. The key findings will be reported using the PRISMA guidelines and published in a peer-reviewed journal.

Discussion

This is the first study to investigate the demographic representation of patients in PAD clinical trials on LE endovascular interventions. The findings from this study will inform addressing existing inequities in clinical trial participation and optimizing enrollment strategies to increase demographic representativeness in future trials. Inadequate representation of specific populations in clinical trials may lead to insufficient evidence on the effectiveness of treatments and inappropriate management of PAD in underrepresented groups. Therefore, this influenced the

decision to exclude studies with less than 50 participants. This criterion ensures the analysis focuses on trials with a sufficient sample size to provide meaningful and statistically robust insights, as smaller trials are more prone to statistical variability and may not accurately represent the diversity of patient populations.

The consequences of disparities in clinical trials create significant ripple effects across various aspects of healthcare. When certain demographic groups are underrepresented in these trials, it can result in limited knowledge about how these therapies work in those populations [9,11]. This could lead to missed opportunities for potentially life-saving or life-improving interventions, or could cause delays or barriers in accessing innovative treatments for specific patient groups [38]. Furthermore, when trial populations fail to mirror the diversity of the broader patient population, it can lead to the development of policies or care guidelines based on evidence that may not be generalizable to underrepresented groups [39]. Ultimately, these disparities impact patient outcomes, influence healthcare policy and affect resource allocation. Addressing these disparities is not solely an ethical concern, but also essential for achieving equitable healthcare outcomes and improving the overall health of diverse patient populations.

It is important for healthcare providers to be aware of disparities in clinical trial inclusion for PAD and consider the potential impact on treatment decisions for patients from underrepresented groups. Moreover, underrepresentation of certain groups in clinical trials may limit the generalizability of the findings to real-world populations, leading to suboptimal care and perpetuation of health inequities. Additionally, a lack of diversity in clinical trials can also lead to mistrust in the healthcare system among certain populations, ultimately leading to decreased participation in clinical trials.

Diversity in clinical trial participation is essential to ensure the safety and efficacy of treatments in all patient populations. Recent increased investment in clinical trial inclusion and resources, such as the FDA guidance on clinical diversity, demonstrate the importance of this issue. Thus, the potential impact of this study is to support evidence-informed practice and policy decision-making in PAD, including factors such as trial site selection and clinical trial design that may improve treatment efficacy. Furthermore, this study will emphasize the need for principal investigators to explore innovative approaches to increase clinical trial diversity, such as establishing trust through partnerships with entities or agencies that have the network and expertise to engage underrepresented groups. Lastly, the findings will highlight the importance of adopting multiple enrollment strategies, such as community engagement, to identify patients for PAD trials and increase demographic representation across trial sites.

Summary points

- Patient populations included in clinical trials do not generally represent the real-world populations they are intended to treat or important sub-populations (based on sex/gender, race/ethnicity and socioeconomic class).
- Peripheral artery disease (PAD) imposes a significant health and economic burden on broad patient populations. The epidemiology, treatment patterns, and outcomes of PAD differ by race, sex/gender and age. Therefore, diverse representation within PAD trials is imperative.
- This research provides a study protocol for a systematic review of PAD clinical trials to examine the eligibility criteria, demographic representation, and enrollment strategies among PAD patients undergoing lower-extremity endovascular interventions.
- This systematic review will be conducted according to the Cochrane Collaboration methodology for systematic reviews and following the PRISMA.
- Eligible studies will include randomized controlled trials (RCTs) with a parallel group design and with sample sizes greater than 50 published in peer-reviewed journals or on clinicaltrials.gov starting between January 2012 and December 2022.
- The primary outcome will be a description and summary of the frequency of the reporting of demographic characteristics.
- The feasibility of a meta-analysis or meta-regression will be explored, but if determined to be infeasible, the Synthesis Without Meta-analysis reporting guideline will be followed for the reporting of findings.
- The findings may help to quantify existing inequities in clinical trial participation that may be addressed through optimizing enrollment strategies for future PAD trials. Improved representation may lead to improved patient management and outcomes, potentially reducing health disparities.

Author contributions

AO Williams, CM Jacobsen and LM Hargens designed the methodology. AO Williams, CM Jacobsen and AM McGovern extracted and analyzed data. S Duval, MR Jaff and C Long contributed to validating the methodology. S Duval analyzed the data. All authors contributed to the interpretation of the data, edited and revised the manuscript.

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Competing interest disclosure

AO Williams, AM McGovern, CM Jacobsen, LM Hargens and MR Jaff are employees of and own stock in Boston Scientific. S Duval is a contractor to Boston Scientific and a Professor at the University of Minnesota. C Long is a Physician and Assistant Professor of Surgery, Director of Vascular Surgery Fellowship Program Director of Vascular Surgery and Integrated Residency Program Co-Director of Duke Center for Aortic Disease Duke Vascular and Endovascular Surgery Duke University Medical Center. The authors have no other competing interests or relevant affiliations with any organization/entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

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Data sharing statement

Data supporting the findings of this study are available from the corresponding author (AO Williams) upon reasonable request.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Aday AW, Matsushita K. Epidemiology of peripheral artery disease and polyvascular disease. *Circ. Res.* 128(12), 1818–1832 (2021).

•• **Provides essential epidemiological insights into peripheral artery disease (PAD) and its association with polyvascular disease.**

2. Bauersachs R, Zeymer U, Brière JB, Marre C, Bowrin K, Huelsebeck M. Burden of coronary artery disease and peripheral artery disease: a literature review. *Cardiovasc Ther.* 2019, 8295054 (2019).

3. Anand SS, Caron F, Eikelboom JW *et al.* Major adverse limb events and mortality in patients with peripheral artery disease: The COMPASS Trial. *J. Am. Coll. Cardiol.* 71(20), 2306–2315 (2018).

•• **Considerable interest as it discusses major adverse limb events and mortality in patients with PAD, particularly in the context of the COMPASS trial.**

4. Muller-Hulsbeck S, Keirse K, Zeller T, Schroe H, Diaz-Cartelle J. Twelve-month results from the MAJESTIC Trial of the Eluvia Paclitaxel-Eluting Stent for treatment of obstructive femoropopliteal disease. *Journal of endovascular therapy: an official journal of the International Society of Endovascular Specialists.* 23(5), 701–707 (2016).

5. Muller-Hulsbeck S, Keirse K, Zeller T, Schroe H, Diaz-Cartelle J. Long-term results from the MAJESTIC Trial of the Eluvia Paclitaxel-Eluting Stent for femoropopliteal treatment: 3-year follow-up. *Cardiovasc. Intervent. Radiol.* 40(12), 1832–1838 (2017).

6. Stavroulakis K, Torsello G, Bosiers M, Argyriou A, Tsilimparis N, Bisdas T. 2-Year outcomes of the eluvia drug-eluting stent for the treatment of complex femoropopliteal lesions. *JACC Cardiovascular interventions.* 14(6), 692–701 (2021).

7. Muller-Hulsbeck S, Benko A, Soga Y *et al.* Two-year efficacy and safety results from the IMPERIAL randomized study of the eluvia polymer-coated drug-eluting stent and the Zilver PTX Polymer-free Drug-Coated Stent. *Cardiovasc. Intervent. Radiol.* 44(3), 368–375 (2021).

8. Giannopoulos S, Mustapha J, Gray WA *et al.* Three-Year Outcomes From the LIBERTY 360 Study of Endovascular Interventions for Peripheral Artery Disease Stratified by Rutherford Category. *Journal of endovascular therapy: an official journal of the International Society of Endovascular Specialists.* 28(2), 262–274 (2021).
9. Bierer BE, Meloney LG, Ahmed HR, White SA. Advancing the inclusion of underrepresented women in clinical research. *Cell Rep Med.* 3(4), 100553 (2022).

• **As it addresses the critical issue of advancing the inclusion of underrepresented women in clinical research.**

10. McCarthy CR. Historical background of clinical trials involving women and minorities. *Acad. Med.* 69(9), 695–698 (1994).
11. The Society for Women's Health Research United States Food and Drug Administration Office of Women's Health. Dialogues on diversifying clinical trials: successful strategies for engaging women and minorities in clinical trials 2011. (2023). https://www.fda.gov/media/84982/download
12. Clark LT, Watkins L, Piña IL *et al.* Increasing Diversity in Clinical Trials: Overcoming Critical Barriers. *Curr. Probl. Cardiol.* 44(5), 148–172 (2019).

•• **This reference is highly relevant as it discusses strategies to increase diversity in clinical trials and overcome critical barriers.**

13. United States Census Bureau. US Census Bureau Quick Facts 2023. https://www.census.gov/quickfacts/US
14. Zhang T, Tsang W, Wijeysundera HC, Ko DT. Reporting and representation of ethnic minorities in cardiovascular trials: a systematic review. *Am. Heart J.* 166(1), 52–57 (2013).
15. Havranek EP, Mujahid MS, Barr DA *et al.* Social Determinants of Risk and Outcomes for Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation* 132(9), 873–898 (2015).

• **Considerable interest as it provides insights into the social determinants of risk and outcomes for cardiovascular diseases.**

16. Institute of Medicine Committee on U, Eliminating R, Ethnic Disparities in Health C. In: *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* Smedley BD, Stith AY, Nelson AR. (Eds). National Academies Press (US), WA, USA (2003).
17. Hackler EL 3rd, Hamburg NM, White Solaru KT. Racial and Ethnic Disparities in Peripheral Artery Disease. *Circ. Res.* 128(12), 1913–1926 (2021).

• **Highly relevant as it discusses racial and ethnic disparities in PAD.**

18. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* 110(6), 738–743 (2004).
19. Rucker-Whitaker C, Greenland P, Liu K *et al.* Peripheral arterial disease in African Americans: clinical characteristics, leg symptoms, and lower extremity functioning. *J. Am. Geriatr. Soc.* 52(6), 922–930 (2004).
20. Arya S, Binney Z, Khakharia A *et al.* Race and Socioeconomic Status Independently Affect Risk of Major Amputation in Peripheral Artery Disease. *J. Am. Heart Assoc.* 7(2), e007425 (2018).
21. Jones WS, Patel MR, Dai D *et al.* Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from U.S. Medicare 2000–2008. *J. Am. Coll. Cardiol.* 60(21), 2230–2236 (2012).
22. Chen L, Zhang D, Shi L, Kalbaugh CA. Disparities in peripheral artery disease hospitalizations identified among understudied race-ethnicity groups. *Front. Cardiovasc. Med.* 8, 692236 (2021).
23. Zayed M, Bech F, Hernandez-Boussard T. National review of factors influencing disparities and types of major lower extremity amputations. *Ann. Vasc. Surg.* 28(5), 1157–1165 (2014).
24. Demsas F, Joiner MM, Telma K, Flores AM, Teklu S, Ross EG. Disparities in peripheral artery disease care: a review and call for action. *Semin. Vasc. Surg.* 35(2), 141–154 (2022).
25. Michos ED, Reddy TK, Gulati M *et al.* Improving the enrollment of women and racially/ethnically diverse populations in cardiovascular clinical trials: An ASPC practice statement. *Am J Prev Cardiol.* 8, 100250 (2021).
26. United States Food & Drug Administration. Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry 2022. (2023). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations

•• **Considerable interest as it provides guidance on diversity plans to improve enrollment in clinical trials.**

27. Pfizer. Diversity in our clinical trials 2023. https://www.pfizer.com/science/clinical-trials/diversity
28. Boston Scientific Corporation. 2021 Annual Report 2022. https://www.bostonscientific.com/content/dam/bostonscientific/corporate/annual-report/2021_Boston_Scientific_Annual_Report.pdf (2023).
29. *Cochrane Handbook for Systematic Reviews of Interventions (Second Edition).* Higgins JPT, Thomas J, Chandler J, et al. (Eds). John Wiley & Sons, Chichester, UK (2019).
30. PRISMA 2020 for Abstracts. Reporting Systematic Reviews in Journal and Conference Abstracts. (2023). https://www.equator-network.org/reporting-guidelines/prisma-abstracts/
31. United States National Library of Medicine. ClinicalTrials.gov 2023. (2023). https://clinicaltrials.gov/

32. World Health Organization. International Clinical Trials Registry Platform 2023. (2023). https://trialsearch.who.int/

33. Dr.Evidence(TM) (2023). https://www.drevidence.com/

34. Covidence (2023). https://www.covidence.org/

35. Higgins JP, Altman DG, Gotzsche PC *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 343, d5928 (2011).

36. Campbell M, McKenzie JE, Sowden A *et al.* Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ.* 368, l6890 (2020).

37. Guyatt G, Oxman AD, Akl EA *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J. Clin. Epidemiol.* 64(4), 383–394 (2011).

- **Relevant as it discusses GRADE guidelines for evidence profiles and summary of findings tables.**

38. Hall AG, Winestone LE, Sullivan EM *et al.* Access to chimeric antigen receptor T cell clinical trials in underrepresented populations: a multicenter cohort study of pediatric and young adult acute lymphobastic leukemia patients. *Transplant Cell Ther.* 29(6), 356.e1–.e7 (2023).

39. Castro-Dominguez Y, Mena-Hurtado C, Algara M *et al.* Representativeness of Peripheral Artery Disease Randomized Clinical Trials Supporting Current Guidelines. *Am. J. Cardiol.* 201, 166–169 (2023).