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Strategies to improve regional representation in heart failure randomized controlled clinical trials

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The regional enrollment of participants in pivotal randomized controlled trials (RCTs) often does not represent the regional distribution of cardiovascular diseases. Over the past four decades, trials have enrolled participants primarily from North America and Europe, limiting the global generalizability of findings. In this Perspective, we review the evolution of regional participation in RCTs, using heart failure as a case study to assess temporal trends, current gaps in representativeness and opportunities for improvement. We assess the regulatory, logistical and financial barriers to clinical trial enrollment in underrepresented regions. We examine the manner in which global regions have been classified in trials, and propose a standardized regional classification system for reporting and subgroup analysis. To improve regional representativeness, we suggest targeted strategies that address barriers faced at the national, regulatory, sponsor or funder, institution and patient level. We also recommend the use of a representativeness index during trial planning and site selection to enhance regional representativeness. Expanding trial participation beyond historically dominant regions could be a key step in improving trial efficiency, external validity and global health equity.

The generalizability of randomized controlled trials (RCTs) depends on how adequately the enrolled participants represent people living with the disease[1,2]. However, RCTs in cardiovascular diseases frequently underrepresent key demographic groups, with well-documented geographic, socioeconomic and ethnic disparities. Low- and middle-income countries (LMICs), which are faced with the greatest global burden of cardiovascular diseases, remain underrepresented[3,4]. This lack of inclusivity limits the generalizability of trial findings and represents a missed opportunity to strengthen research infrastructure and healthcare capacity in underrepresented regions[5,6].

One of the best-documented conditions with regional disparities in trial enrollment is heart failure. Despite the predominance of this condition in LMICs, most participants in influential heart failure trials are enrolled in North America and Europe. The underrepresentation of LMICs in practice-changing RCTs means that regions burdened by heart failure do not contribute to trial evidence and do not receive the

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short- and long-term benefits of research engagement[7]. For instance, African or Middle Eastern countries are very rarely represented, limiting the external validity of trial-based recommendations for these populations[6,8]. International guidelines strongly recommend the use of key pharmacotherapy classes for the treatment of heart failure, yet they often fail to acknowledge the geographic biases in the evidence base[9–11].

In this Perspective, we explore the evolution of regional representation in RCTs, using heart failure as a case study. We synthesize nearly 40 years of trial data and focus on the heart failure pharmacotherapy trials that informed class I recommendations in the 2021 European Society of Cardiology, 2021 Canadian Cardiovascular Society, 2021 Japanese Circulation Society/Japanese Heart Failure Society, and 2022 American College of Cardiology/American Heart Association guidelines[9–12].

We highlight persistent gaps, discuss their causes and propose actionable multilevel solutions to foster representative participation in future cardiovascular trials. We argue that expanding trial enrollment beyond historically dominant regions can enhance research efficiency and the development of regionally relevant treatment strategies, ultimately improving patient outcomes worldwide.

Contrast between the regional burden of heart failure and representativeness in randomized clinical trials

Asia and Africa bear the highest burden of heart failure but remain underrepresented

Although Asia (50%) and Africa (at least 14%) account for most patients with heart failure worldwide, their representation in clinical research remains disproportionately low (Fig. 1a). These regions are underrepresented in key aspects of influential RCTs, including trial sites (Asia 17%, Africa 1%) (Fig. 1c), enrolled participants (Asia 13%, Africa 1%) (Fig. 1b) and authorship (Asia 5%, Africa 0–1%)[8]. By contrast, despite accounting for less than 30% of the global population with heart failure, Europe and North America represent over 70% of trial sites and enrolled patients and more than 90% of study authors[7,8,13] (Fig. 1b,c).

Shifts in regional representation of heart failure clinical trials and persistent disparities

Historically, RCTs that informed the use of key pharmacotherapy classes in heart failure enrolled patients primarily in Europe and North America[8] (Fig. 1e). This applies to trials of beta-blockers, mineralocorticoid receptor antagonists and/or renin–angiotensin–aldosterone system inhibitors. Over the past decades, regional representation in trials has increased, as evidenced by the enrollment patterns in trials testing the efficacy of inhibitors of sodium–glucose cotransporter 2 (SGLT2), an angiotensin receptor neprilysin inhibitor (ARNI), and other contemporary pharmacotherapies (Fig. 1e). For example, the representation of South America in contemporary pivotal trials now reflects the relative prevalence of heart failure in the region. By contrast, Asia, despite improvements in its participation over time, continues to be underrepresented. Africa remains the most neglected region, showing little to no progress in trial participation despite its substantial burden of disease. Of note, the prevalence of heart failure in African countries is likely underestimated owing to data gaps; therefore, estimates of trial representativeness in Africa are likely overestimated (Fig. 1d).

Regional variation in the management of heart failure, event rates and outcomes

Heart failure outcomes vary by country income level

Patients with heart failure in low-income countries (LICs) have twice the risk of death and one-third the rate of hospitalization compared to those in high-income countries (HICs)[14–17]. Death is a competing risk for hospitalization; however, the risk of 30-day mortality following any-cause hospitalization is also four to five times higher in LICs than in HICs, suggesting that hospitalization is limited to higher-risk patients in LICs[17].

Income inequality is an important determinant of outcomes

Within a country, income inequality has an important role in the therapeutic management and prognosis of heart failure. Guideline-directed medical therapy is more widely implemented in countries where income inequality is lower, heart failure outcomes are better and event rates are lower[14,16,18]. An analysis of RCTs involving more than 17,000 patients revealed that compared to countries in the lowest tertile of income inequality (measured by the Gini coefficient), those in the highest tertile experienced a 46% to 57% greater risk of cardiovascular death or heart failure hospitalization. They also had a 30% to 46% greater risk of all-cause mortality[14,18]. These findings were adjusted for recognized prognostic variables, including income, education index, hospital bed density and health worker density[14,18]. Patients from countries with the combination of high income inequality and low- to middle-income levels faced a twofold to threefold increase in mortality rates compared to those from HICs with low income inequality[14]. Results from global registries were comparable, showing a 25% increase in 1-year mortality following heart failure hospitalization in regions with greater income inequality[16].

Healthcare resource distribution and access to trials vary greatly across regions

The percentage of gross domestic product (GDP) allocated to healthcare varies by a factor of two to four across countries. For example, in Asia, healthcare spending as a percentage of GDP ranges from 2.8% in Indonesia to 6.6% in South Korea[19]. In Europe and the Middle East, it varies from 2.9% in Kazakhstan to 11.9% in Switzerland. Differences in GDP and the share allocated to healthcare result in substantial variations in national healthcare budgets. The portion of the budget allocated to medications and hospitalizations also varies between countries, and the rate of treatment utilization is strongly correlated with health expenditure per capita[19,20]. Even in countries with active clinical and research programs, healthcare centers and research resources are often concentrated in urban, high-resource areas, which may not represent the broader national population.

Healthcare workforce disparities

The number of health workers varies widely between regions, with more than 10 per 1,000 population in Europe and North America; around 2 per 1,000 in South and Central America, Asia, the Middle East and North Africa; and 1 per 1,000 in sub-Saharan Africa. HICs and middle-income countries (MICs) have an average of 97 and 67 cardiologists per million people, respectively. The number of cardiologists also differs greatly between countries within a given region, as illustrated by Europe, where there are 24 cardiologists per million people in Ireland compared to 350 per million people in the Republic of Georgia[21]. Within countries, there are interregional and urban–rural gaps in access to cardiovascular specialists, research centers and trained research personnel[22]. In the USA, 60% of older adults rely on care from 38% of the country's cardiologists; and in Canada, the provinces with the highest GDP have the greatest concentration of cardiologists[22,23]. This disparity in cardiologist density may account for the variation in mortality after hospitalization for heart failure[23–25].

Implications for clinical trials

The regional differences in healthcare infrastructure, resource allocation and income inequality have important implications for trial enrollment, event rates and estimates of treatment effect (Fig. 2). However, conducting clinical trials in LMICs is not always less costly. In settings without comprehensive public health coverage, sponsors often need to reimburse routine investigations, such as electrocardiography, echocardiography or laboratory tests, which are typically covered by national health systems in countries with stronger universal healthcare structures, such as Canada or those in northern Europe.

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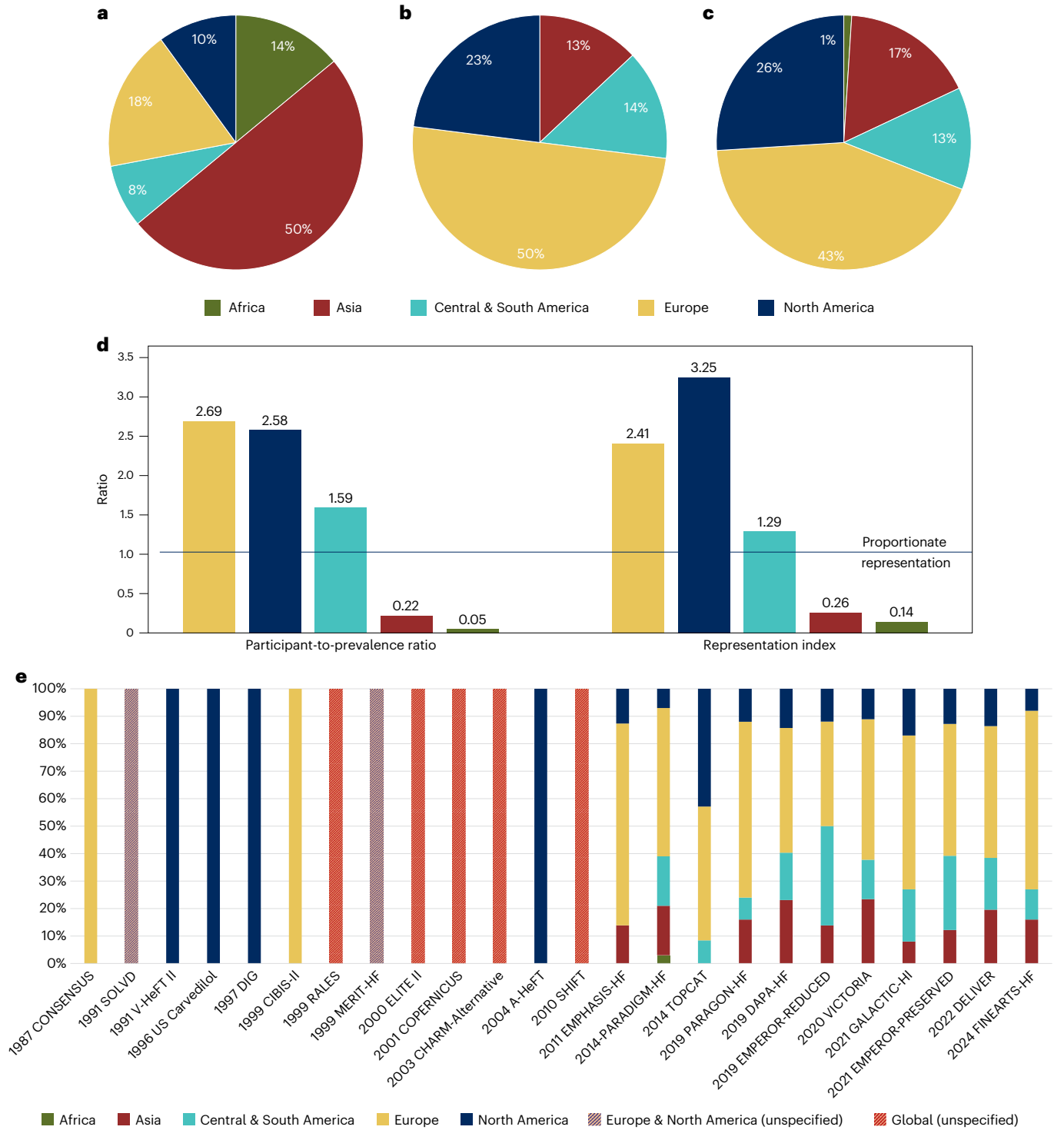

Fig. 1 | Contrast between the regional burden of heart failure and representativeness in heart failure randomized clinical trials. a, Regional distribution of people with heart failure based on GBD 2021 data. **b**, Regional representation among participants in pivotal heart failure clinical trials. **c**, Regional representation of trial sites in pivotal heart failure clinical trials. **d**, Regional representation in pivotal heart failure randomized clinical trials, based on the representation index and the participant-to-prevalence ratio. The representation index is the ratio between the proportion of trial sites in a given region and the proportion of global heart failure cases in that region, while the participant-to-prevalence ratio is the ratio between the proportion of trial participants in a given region and the proportion of global heart failure cases in that region. **e**, Geographic distribution of participants in pivotal heart failure randomized clinical trials by region.

In addition, when trial participation requires access to an expensive standard-of-care treatment that is not reimbursed by healthcare systems, costs can escalate and favor enrollment in well-resourced systems, further limiting representativeness.

Factors such as access to healthcare, hospitalization thresholds and overall mortality risk directly influence baseline event rates and estimated treatment effects. However, these elements are rarely accounted for in current trial designs and reporting. This heterogeneity

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Barriers		Solutions
• Language • Limited access to trial sites • Mistrust in researchers • Fear of research harm • Unremunerated research time and burdensome research processes	Patients	• Join patient-led advocacy groups and trial advisory boards • Seek opportunities for trial participation • Request reimbursement for transportation and loss of income
• Limited research infrastructure • Limited capacity for trial coordination • Limited training or mentorship to develop trialists • Limited salary or research support for trialists	Institutions	• Invest in research infrastructure, biobanks, core laboratories • Partner with AROs and CROs • Remote training and mentorship • Fair research support for trialists • Academic merit for site investigators
• Restricting enrollment to target market regions and well-known trial sites • Limited inclusion of LMIC investigators in trial design • Uncertainty around insurance and indemnification coverage	Industry sponsors	• Partner with regional AROs and CROs • Use RRI to guide site selection • Fund investigator-initiated trials in LMICs • Include LMIC investigators and patients in trial advisory boards
• Regional variation in regulatory standards for trial conduct • Regional trial enrollment quotas for regulatory approval in high-income regions	Regulators	• Remove regional enrollment quotas for regulatory approval • Implement global regulatory standards for trial conduct • International partnerships to work toward accreditation of more trial sites in LMICs
• Geopolitical instability • Limited funding for research or clinical infrastructure • Limited regulatory oversight of RCTs • Bureaucratic processes	Governments	• Adapt international trial standards to regional context • International partnerships for research funding initiatives • Research and clinical infrastructure investments • Centralized ethics boards

Fig. 2 | Comprehensive strategies for overcoming barriers to clinical trial engagement in LMICs. Factors at the patient, academic institution, sponsor or funder, regulator and country level are acknowledged (left) and proposed solutions are offered (right). AROs, academic research organizations; CROs, contract research organizations; RRI, regional representation index.

in standard-of-care practices across regions, particularly when hospitalization for heart failure is used as a key outcome in sample size calculations, is a major concern[26]. In regions where hospitalization is limited to high-risk patients due to constrained resources, event rates may differ considerably from those observed in regions with better access to care. Because the sponsor's primary objective is to test the efficacy and safety of an intervention without the influence of extrinsic or contextual factors, heterogeneity introduced by the region of enrollment and variation in clinical trial regulatory standards is a disadvantage. Therefore, the challenge lies in achieving a pragmatic balance between representativeness and methodological rigor.

The benefits of global research representativeness

Generalizability

The underrepresentation of patients from LMICs in practice-changing trials has implications for the global generalizability of the trial results. From a scientific perspective, increasing regional representativeness in clinical trials could enhance the reproducibility of results across diverse populations faced with varied environmental, healthcare system, socioeconomic, ancestral and other factors[5] (Table 1). The evidence base for international guidelines predominantly reflects the healthcare systems and outcomes in HICs, often rendering these guidelines less relevant or applicable for LMICs[6,27]. Therapeutic recommendations may fail to address the unique challenges in LMICs, including resource limitations, differences in disease presentation and variations in healthcare infrastructure. Patient-reported outcomes, such as quality of life and dyspnea, differ according to socioeconomic, cultural and educational factors; demonstrating a consistent treatment effect across multiple circumstances is important[28]. By neglecting to adequately include LMIC populations in clinical research, influential trials risk perpetuating a cycle of inequity, ultimately undermining the development and implementation of truly inclusive evidence-based care.

Trial efficiency

Broadening regional inclusion in trials could improve trial efficiency, particularly in LMICs, where higher clinical event rates can accelerate meaningful findings. The low saturation of trials in these regions could improve enrollment rates. Given the frequency of events, trials can be smaller or have shorter durations to achieve adequate statistical power, thereby reducing costs. Furthermore, treatment effect estimates could be more generalizable to individuals living with the disease. Additionally, investigator fees—set in relation to local salary standards—could offer large cost savings to sponsors while supporting the salaries of motivated clinician researchers, enabling them to dedicate time to research and build research capacity[7]. However, to avoid diverting clinicians from patient care to research for financial reasons, fees should be aligned with regional standards and accompanied by defined research time.

Better assessment of regional heterogeneity in treatment effect

Tests for subgroup analyses are often underpowered to detect heterogeneity, and imbalances in subgroup sizes can further reduce the statistical power to detect heterogeneous treatment responses. Additionally, the near-total absence of patients from Africa severely limits the ability to conduct any meaningful analysis of treatment effects in that region. In this case, the ability to reliably detect a true subgroup–treatment effect interaction is usually low[29,30], but the absence of a statistically significant interaction does not imply the absence of a clinically meaningful difference in treatment effects[31]. Including a greater number of patients from Africa and Asia, where the burden of heart failure is highest, would help increase overall trial enrollment while limiting costs for sponsors. These regions often offer lower operational and recruitment costs than North America and Europe, which can facilitate larger sample sizes without substantially increasing budgets. Moreover, broader geographic representation would enhance the ability to detect potential heterogeneity in treatment responses across diverse populations. This approach would not only improve the external validity of trial results but also provide insights into differential treatment effects that may arise from ancestral, environmental or healthcare system-related factors.

Opportunity for standardized regional classification

There is no standard classification of regions across clinical trials. Europe is sometimes divided into eastern and western Europe; North and South America are occasionally combined; and Asia may be treated as a distinct region, divided into subregions or grouped with Pacific regions. Three countries—Israel, South Africa and Turkey—may have been excluded from the regional analysis of the PARADIGM-HF (Prospective Comparison of ARNI with Angiotensin-Converting Enzyme Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial due to geopolitical factors, making it challenging to associate them with a specific geographic region[32]. Additionally, in a secondary analysis evaluating the effect of dapagliflozin by region (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial), Saudi Arabia was arbitrarily grouped with Europe[33]. A more standardized approach to defining geographic regions would provide a foundation for more consistent reporting across trials, enabling reliable comparisons between studies and facilitating meta-analyses. We acknowledge that each region exhibits variations in

Table 1 | Factors relevant to clinical trial execution and outcomes that vary across global regions

Category	Parameters
Country	– Geopolitical and economic stability – Transportation and delivery systems – Healthcare quality and funding – Disease prevalence and outcomes – Functioning academic or clinical research organizations
Regulators	– Regulatory standards for trial conduct – Regional trial enrollment requirements for regulatory approval of health products
Sponsors or funders	– Priorities related to target market regions – Relationships with research organizations or trial sites – Insurance and indemnification coverage – Complexity of trial protocol and data requirements
Institutions	– Track record in clinical trial execution and adherence to regulatory standards – Clinical trial contracting processes and costs – Clinical trial recruitment efficiency – Healthcare and research resources and personnel
Patients	– Ancestry and ethnicity – Socioeconomic status – Lifestyle – Language and literacy – Disease etiology and comorbidities – Medication adherence – Level of trust in research ecosystem

ancestry, ethnicity, culture, healthcare systems and resource availability. Nonetheless, a reproducible geographic framework would enhance comparability between studies while preserving interpretability. This system is not intended to replace other indicators of inequality—such as income-based metrics (for example, the Gini coefficient), human development indices or resource-level classifications—but to complement them by offering a spatial perspective that supports globally coherent clinical research.

Market and regulatory considerations

Increasing geographic representativeness in RCTs and demonstrating clinical benefits and cost-effectiveness across regions could facilitate the market entry and reimbursement of treatments that would otherwise be inaccessible in LMICs[34,35]. This can drive the adoption of guideline-directed medical therapy, especially in low-income regions with high income inequality, where implementation is currently weakest[15,16]. This is crucial for addressing the unique healthcare challenges in LMICs. However, regulatory requirements can pose challenges to achieving this diversity. For instance, the US Food and Drug Administration mandates a minimum proportion of participants from the USA, while Japan enforces similar local recruitment criteria. The European Medicines Agency tends to focus primarily on EU-centric populations. While these policies ensure that high-income populations targeted for market entry are adequately represented in clinical trials, they further exacerbate the underrepresentation of Africa and other low-resource countries.

Barriers and possible solutions to increase trial engagement in LMICs

Future RCTs should strive for increased enrollment outside Europe and North America, with a particular focus on Africa, the Middle East, and Southeast and East Asia, where the burden of heart failure is increasing but trial enrollment remains low[36] (Fig. 2). As a starting point, investigators should reach a consensus on regional classification for clinical trials to standardize recruitment zones, subgroup reporting, regional analyses and inferences. Such a classification should account for differences in geography, ancestry and socioeconomic conditions within each continent, as these factors are relevant to heart failure treatment response. The World Health Organization (WHO) framework is a reasonable starting point for further classifying regions. We propose the following classification of regions: North America; Central and South America; Middle East and North Africa; Central and South Africa; Europe; Southeast Asia; East Asia; and the Pacific, including Australia and New Zealand (Table 2).

The challenges to trial execution in LMICs across clinical, financial, operational and patient-related domains must be acknowledged. Overcoming these barriers requires a comprehensive, multifaceted approach involving governments, sponsors, academic institutions and patients[7,37], each of whom has a critical role in shaping the future of clinical research in LMICs (Fig. 2).

Government-level challenges

Governments in LMICs face substantial challenges in establishing and maintaining research infrastructure, including the financial costs associated with developing public policy, funding research institutions, and creating the necessary regulatory and ethical frameworks[38]. These costs are compounded by the need for advanced medical facilities, biobanks, research equipment and reliable communication networks—all of which are often underfunded in LMICs. Additionally, banking constraints and exchange rate fluctuations can complicate the transfer of funds, leading to administrative delays that hinder trial operations. Political instability can hinder the development of sustainable research ecosystems. Even in MICs and HICs, rural regions lack research coordinating centers, trained personnel and infrastructure. For example, in Mexico, more than 80% of clinical trial sites are located in the three capital cities (Mexico City, Monterrey and Guadalajara), neglecting rural and underserved regions where the disease burden may differ due to disparities in healthcare access, comorbidities and socioeconomic factors. Similar patterns exist in Brazil (São Paulo, Rio de Janeiro) and Argentina (Buenos Aires), where urban-centric trial coordination limits the inclusion of rural participants[39].

Governments must be encouraged to prioritize healthcare and clinical research infrastructure, including in rural regions, as part of their national development goals (Fig. 2). This can be achieved through funding partnerships and commitments. Partnerships with the WHO (similar to those adopted for COVID-19 vaccine trials), industry, academic research organizations and contract research organizations can provide support. Incentives from international bodies and industry could motivate governments to make these long-term investments, which may include funding for research institutions, regulatory frameworks and centralized research ethics boards. Much of this capacity could be created without the cost of physical infrastructure by using decentralized trial designs with remote operations[40].

The creation of multidisciplinary research centers, supported by external methodological and operational expertise and focused on conditions with a high population burden—including cardiometabolic, oncologic and infectious diseases—could strengthen national research capacity. Such centers could reduce structural costs, attract sponsors, and ensure compliance with international quality standards while providing on-site training and mentoring. This model could serve as a scalable framework for improving both equity and sustainability in global clinical research.

International regulatory standards could be adopted for conducting clinical trials. Additionally, investment in clinical infrastructure, such as electronic medical records, data storage and biobanks, benefits both research and clinical care[41]. Public campaigns to foster research-ready cultures can further enhance these efforts, and high-quality local and regional registries and epidemiological data repositories have contributed to building research capacity in LMICs[42]. Global registries have provided real-world data from underrepresented regions, complementing the evidence generated from RCTs[43–45]. Historically, the predominance of infectious diseases in LMICs, particularly in Africa and Asia, may have delayed the development of cardiovascular

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Table 2 | Proposed regional classification scheme to standardize regional analyses in RCTs

Regions	Countries
North America	Canada, USA
Central and South America	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
Europe	Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Moldova, Monaco, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Russia, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, UK, Uzbekistan
Central and South Africa	Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Ivory Coast, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Republic of the Congo, Rwanda, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, South Africa, South Sudan, Eswatini, Togo, Uganda, Tanzania, Zambia, Zimbabwe
North Africa and Middle East	Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, Yemen
Southeast Asia	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste
East Asia	China, Japan, Mongolia, South Korea, Taiwan
Western Pacific	Australia, Brunei, Cambodia, Cook Islands, Fiji, Kiribati, Laos, Malaysia, Marshall Islands, Micronesia, Nauru, New Zealand, Niue, Palau, Papua New Guinea, Philippines, Samoa, Singapore, Solomon Islands, Tonga, Tuvalu, Vanuatu, Vietnam

research networks. However, the Global Burden of Disease (GBD) data reveal the high prevalence and ongoing increase of cardiometabolic disease and heart failure in these regions; competing risk from life-limiting communicable diseases no longer explains the underrepresentation of LMICs in cardiometabolic and heart failure RCTs. By promoting a supportive policy environment and improving infrastructure, governments can help globalize clinical research and make their countries more attractive for RCTs.

Regulatory agency challenges

Regulatory agencies in North America and Europe have established policies for ethnic representativeness but commonly mandate that sponsors include a substantial proportion of trial participants from within their region, promoting the overrepresentation of these groups in trials. Japan has similar regulatory requirements. In LMICs, bureaucratic inefficiencies and overlapping regulatory requirements often delay the initiation of trials.

Internally consistent policies that acknowledge the interconnectedness between geographic and ethnic representativeness could help achieve research and health equity goals (Fig. 2). Securing a proportional sample of participants from each region could be a mutually agreeable solution for all stakeholders, but better international coordination between regulatory agencies is needed to ensure representative data. This includes the strategic selection of trial sites to account for intrinsic (genetic, physiological) and extrinsic (environmental, dietary, healthcare access) factors that influence treatment response. In countries with inefficient bureaucracy, streamlining ethics approvals through centralized committees and adopting harmonized regional standards aligned with established frameworks could accelerate participation while maintaining rigorous trial conduct.

Industry funder or sponsor challenges

Industry funders or sponsors have historically hesitated to invest in research recruitment in LMICs, opting instead to conduct RCTs in HICs that align with the target market and offer established research infrastructure and a proven record of success[7,37]. Additionally, sponsors may face uncertainties regarding data quality, as demonstrated in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial. Insurance and indemnification coverage for both participants and researchers in LMICs may further deter investment. Still, trials focusing on implementation or pragmatic evidence generation can be conducted even in regions that are not fully equipped to participate in explanatory or policy-changing trials. Machine learning algorithms can be deployed to check data quality and provide feedback on performance.

Sponsors could establish partnerships with local nongovernmental bodies, academic institutions and clinical research organizations to facilitate high-quality trial execution and ensure data integrity. Culturally competent trial processes and communications[37] can further help engage underrepresented racial and ethnic groups, fostering more meaningful participation in global clinical research. Additionally, sponsors should invite LMIC investigators as coauthors and members of trial committees to ensure that these regions benefit from the research and contribute to global scientific advancements. Incentives for local investigators should not rely on compensation alone; mechanisms must be put in place to maintain trial integrity and prevent inappropriate trial enrollment, as appears to have occurred in the TOPCAT trial[46,47].

Site selection is a key determinant of trial representativeness, as reflected by the alignment between the representation index and the participant-to-prevalence ratio[8] (Fig. 1d). The representation index, defined as the ratio between the proportion of trial sites in a given region and the proportion of global heart failure cases in that region, offers a standardized way to identify geographic imbalances in planned recruitment. Sponsors and investigators can estimate the representation index of the trial site during the planning phase and use it as a guide to improving regional representativeness. However, the site recruitment plan should be interpreted within the broader context of regional feasibility, infrastructure quality and compliance with Good Clinical Practice standards, which influence trial integrity and data quality. Although the representation index assesses geographic representativeness, its interpretation must be coupled with an evaluation of macro-level logistical, socioeconomic and cultural factors that enhance or hinder trial operations in a given region. Factors such as the national economy, political stability, healthcare and research infrastructure, transportation networks, and access to necessities that minimize competing risks from avoidable intervening health events require contextual understanding. Coupling the representation index analysis with readily available structural markers (for example, the

Human Development Index, indices of governance and GDP per capita) may be a step forward in fully describing the context that includes clinical trial engagement. Instead of aiming for a fixed representation index of 1, sponsors and investigators should seek progressive improvement in representation, starting in regions with a high disease burden. To address the rural–urban imbalance in trial participation, sponsors and local investigators could prioritize decentralized trial designs, telemedicine-enabled follow-up and capacity-building partnerships with regional hospitals. Without the intentional inclusion of diverse geographic settings and contextual adaptations, trials risk reinforcing historical inequities.

Sponsors could include patient advocacy groups from different regions on advisory boards to learn from their lived experiences related to trial participation (Fig. 2). Early patient involvement in reviewing informed consent materials, procedural descriptions and follow-up processes can ensure that the study is understandable and acceptable, thereby strengthening ethical standards and participant engagement.

Institutional and investigator challenges

Institutions and investigators in HICs maintain formal collaborative networks based on mutual gains from grant winnings and academic output rather than a mission of research equity. Investigator-initiated RCTs are often conducted with stringent trial budgets determined by publicly funded grant agencies that prioritize the principles of equity and diversity. However, these agencies do not allocate funds to building capacity or conducting research in resource-limited regions. Trial investigators often favor well-known centers with a track record of recruiting patients into trials, and many do not know how to identify new centers or regions.

LMICs face a shortage of trained clinicians, researchers and research coordinators[38]; research training programs may be inaccessible, and attending specialized courses abroad can be expensive and may require departmental support that is not always forthcoming. Once well trained in research, investigators commonly emigrate to HICs for better opportunities, and the lower number of specialists per capita makes it challenging to lead research trials in subspecialty fields. Additionally, investigators may be discouraged from investing time in trials where access to the studied treatment will be limited after the RCT, particularly when academic returns, such as publications or participation in steering committees, are minimal. Finally, the systems and personnel responsible for ensuring adherence to regulatory processes and data integrity can be suboptimal.

To address these barriers, international efforts are needed to develop local research capacity through online or correspondence courses and remote mentorship (Fig. 2). This could include international grant funding calls, advanced degree or research certification programs, international fellowship exchange programs, and remote mentorship and collaborations. The inclusion of research curricula in undergraduate and medical programs can generate early interest in clinical research.

Investment in academic research organizations, partnerships with contract research organizations and the development of clinical trial networks are essential for building a strong research infrastructure. The STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial and the ongoing VICTORY-HF (Virtual Care to Improve Outcomes and Recovery from Heart Failure Hospitalization) trial (NCT05724433) are examples of investigator-initiated trials led in HICs that successfully collaborate with contract research organizations from underrepresented regions to engage in trial enrollment. Furthermore, investment in faculty career development and salary support, opportunities for coauthorship, and recognition of site investigators will help retain talent, build local expertise and motivate researchers to stay engaged in their home countries while participating in global trials[7,48,49].

Challenges for cardiovascular societies

Cardiovascular societies such as the European Society of Cardiology, the American Heart Association and the American College of Cardiology are currently developing a global agenda. Guidelines developed by these societies are heavily promoted in LMICs but are not adapted to the regional context. Guidelines could better highlight missing evidence or include the results of subgroup analyses and meta-analyses to emphasize the generalizability of trial results. Collaborating with local and regional societies to develop official documents (for example, consensus statements) can help identify key knowledge gaps and implementation challenges, thereby stimulating local research interest. Major journals in general medicine and cardiology often have regional editions, mainly in China, and are expanding their presence and readership in local languages; these offer a pathway to growing regional research and authorship[27].

Challenges for patients

Patients in LMICs face unique challenges that limit their participation in RCTs (Fig. 2). In some cultures, health-related beliefs and strong family influence can discourage patients from participating in clinical trials. Language barriers, widespread misinformation about research and mistrust of the medical establishment also contribute to this phenomenon. Some mistrust by ethnic minority groups is rooted in historical mistreatment, structural racism and cultural insensitivity[37,48]. These issues are often compounded by the geographic challenges of reaching participants in rural areas, as well as by the lost wages and personal costs associated with trial participation. The expenses associated with high-quality standard care, often required for trial participation, can also be a barrier—especially in settings where it is difficult to distinguish between routine care and research-related expenses. Additionally, patients may fear that they will not have long-term access to the treatments tested in these trials.

To overcome these barriers, clinical trials should address the local burden of disease and actively engage by educating patients and their families about the importance of trial participation, while also sharing results with them using interpretable and culturally appropriate language (Fig. 2). Sponsors must compensate patients for transportation to trial sites and lost wages, as well as offer comprehensive insurance and indemnification coverage[48,49]. The cost savings achieved by conducting trials in LMICs could be used to provide patients with free long-term access to the treatment if the trial results are positive. Ensuring long-term access to effective treatments tested in trials could help build trust among patients and increase their engagement in research. We must increasingly consider what we owe patients for their contributions to trial evidence, both in the care they receive during the trial and after the results are announced.

Conclusion

LMICs account for most heart failure cases globally. Despite this burden, LMICs are underrepresented in clinical trials, which exacerbates existing healthcare inequities. The barriers to implementation are diverse, spanning government-, regulatory-, sponsor-, institution-, investigator- and patient-related challenges. A key consequence of these barriers is the stark absence of data from RCTs conducted in LMICs, which limits the availability of region-specific evidence on the efficacy and safety of therapies. This gap in data not only undermines the generalizability of trial results but also restricts our ability to tailor international guidelines to the specific needs of LMICs. Tackling these multilevel obstacles through coordinated efforts can improve the inclusion of LMICs in clinical trials and generate broader evidence on efficacy and safety, ultimately promoting research and health equity. At the trial level, standardizing regional classifications and estimating the representation index of trial sites can provide important information during the trial planning stage to increase regional representativeness.

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G.B.: conceptualization, writing—review and editing. L. Monzo: writing—review and editing. R.A.V.N.: writing and editing. G.L.: writing—review and editing. M.C.P.: review and editing. N.G.: review and editing. A. Mebazaa: review and editing. D.A.G.: review and editing. A. Mocumbi: review and editing. K.R.: review and editing. J.B.: review and editing. L. Mbuagbaw: review and editing. F.Z.: conceptualization, writing—review and editing, supervision. H.G.C.V.S.: conceptualization, writing—review and editing, supervision.

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