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How to make cardiology clinical trials more inclusive

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Cardiovascular clinical trials continue to under-represent children, older adults, females and people from ethnic minority groups relative to population disease distribution. Here we describe strategies to foster trial representativeness, with proposed actions at the levels of trial funding, design, conduct and dissemination. In particular, trial representativeness may be increased through broad recruitment strategies and site selection criteria that reflect the diversity of patients in the catchment area, as well as limiting unjustified exclusion criteria and using pragmatic designs that minimize research burden on patients (including embedded and decentralized trials). Trial communications ought to be culturally appropriate; engaging diverse people with lived experience in the co-design of some trial elements may foster this. The demographics of trialists themselves are associated with participant demographics; therefore, trial leadership must be actively diversified. Funding bodies and journals increasingly require the reporting of sociodemographic characteristics of trial participants, and regulatory bodies now provide guidance on increasing trial diversity; these steps may increase the momentum towards change. Although this Perspective focuses on the cardiovascular trial context, many of these strategies could be applied to other fields.

Despite calls for clinical trial populations to resemble those living with disease, cardiovascular disease trials continue to enrol primarily White male patients[1]. Representative enrollment in trials is defined as a participation-to-prevalence ratio of 0.8–1.2 (ref. 2). The distribution of a disease across demographic groups may vary across regions, so participation-to-prevalence ratio estimates should reflect the region in which enrollment occurred.

Cardiovascular trials have been largely homogenous, with minimal changes in the composition of trial participants over time. Children, older adults, females and people from ethnic minority groups remain under-represented in trials relative to disease distribution. In a review of 740 cardiovascular trials completed since 2010 only 38% of participants were women[3]. Similarly, in a meta-analysis of 28 statin trials only 8% of participants were over 75 years old, which does not reflect the population in need of lipid-lowering therapy in clinical practice[4]. Although the majority of trials report the sex composition of trial participants[1], in an analysis of 224 heart failure randomized controlled trials (RCTs) only one-third reported results from sex subgroup analyses[5]. Even if such analyses have limited statistical power due to under-enrollment of women, signals could be generated regarding large sex-based differences in efficacy.

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The racial and ethnic composition of trial populations has been under-reported and when data are available they are largely homogenous. A review of 153 cardiovascular RCTs published between 1986 and 2019 reported inclusion of an average of 20% non-White participants (defined as Black, Hispanic, Asian and other people), with no significant change in temporal trends over this time period[1]. Moreover, race/ethnicity was reported in just over half of the trials[1]. Similarly, in a review of 414 heart failure RCTs published between 2000 and 2020 in journals with high impact factors, less than 40% reported race and ethnicity data, and among these less than 20% of participants were Black, Indigenous or people of color; however, both reporting on race or ethnicity and representative enrollment increased with time[6]. Analysis of 460 trials on acute coronary syndromes published between 2001 and 2018 found that only 4% of participants were Black patients, 10% were Asian patients and 8% were Hispanic/Latino patients[7]. Although some of these trends are due to a lack of planning for representative enrollment or omission of large geographic regions from the clinical trial enterprise, collection of ethnicity data is not allowed by law in some jurisdictions, posing a limit to investigators.

Age-based exclusion criteria may limit the applicability of trial results to a substantial portion of the targeted patient population, a proportion that is likely to grow over time due to increasing longevity. For example, a review of 251 heart failure trials found that 25% excluded patients based on an arbitrary upper age limit[8]. Closer examination revealed that 43% had poorly justified age criteria that could exclude older patients. Such age-based criteria could unintentionally exacerbate the under-representation of women in cardiovascular trials since ischemic heart disease, heart failure and other cardiovascular conditions occur later in life among women than in men. Similarly, exclusion criteria related to comorbidities can contribute to under-representation of racial or ethnic groups that have a high burden of specific comorbidities.

In this Perspective, we focus on defining and listing possible barriers to—and facilitators of—representative trial participation, including age, sex, ethnicity, socioeconomic status and regionality. We identify key areas in which members of the research enterprise can take actions to improve the representativeness of participants enrolled in cardiovascular clinical trials. A key focus of this will be to review trial design strategies that could improve the representativeness of cardiovascular trials.

Why representativeness in clinical trials matters

Trials lacking participants similar to those in routine clinical practice may not yield appropriate efficacy or safety estimates that reflect those in real-world clinical settings. In addition to the impaired generalizability of study results, there is the ethical obligation of ensuring that under-represented groups benefit from inclusion in clinical trials[2,9,10]. The efficacy and safety of an intervention may be affected by sex, ancestry, ethnicity, cultural and behavioral norms, comorbidities, baseline usual care standards, access to care, socioeconomic status and healthcare systems. Clinical trials are commonly conducted in a very small proportion of eligible patients, with little evidence to guide uptake in excluded patient groups (Fig. 1). Subgroups may be imbalanced and subgroup analysis may lack adequate statistical power for meaningful results. Post-approval real-world data have the potential to provide generalizable evidence, but these data do not have the methodological rigour to make causal inferences; they also take a long time to accrue evidence.

For example, analyses based on data from the EMPEROR-Reduced trial, which evaluated the SGLT-2 inhibitor empagliflozin in patients with chronic heart failure and a decreased ejection fraction, suggested that empagliflozin is less effective in decreasing the risk of a primary endpoint of heart failure hospitalization or cardiovascular death in Europe than in the other studied countries[11,12]. Subsequent analysis found that differences in healthcare utilization patterns across regions varied in the setting of worsening heart failure, which was more likely to be treated in an outpatient setting in Europe than in other regions; regional differences narrowed when heart failure events included both hospitalization and outpatient care for worsening heart failure[13]. These insights would not have been possible if broad geographic regions had not been included in the trial.

Analysis of the Digoxin Investigation Group trial revealed an increased risk of death in female participants, but not male participants, receiving digoxin versus placebo. This was probably due to higher serum digoxin levels in female participants, highlighting clinically important sex differences in treatment effects and the importance of representative enrollment[14].

The exclusion of regions outside North America and Europe from trial participation represents a missed opportunity to expand research and clinical infrastructure in low-resource regions and to potentially speed up trial enrollment rates. Health inequities in the groups under-represented in clinical trials are propagated, with long-term financial and social costs as measured by life expectancy, disability-free life years and years in the labor force[10]. These inequities are also amplified in pooled analyses and datasets that inform artificial intelligence (AI) algorithms, which become prone to bias[15].

Strategies to improve representativeness in clinical trials

Increasing cardiovascular trial representativeness requires action at the levels of trial design, funding, conduct, publication and dissemination, as well as at the societal level[2,9]. Although the following section highlights some strategies that could be addressed by different groups, we recognize that there is often overlap between them and these changes will need to be made by multiple partners involved in the clinical trial process.

Trial design elements that foster diverse representation include broad recruitment strategies, streamlined and justifiable inclusion and exclusion criteria, cultural competency training of investigators (including for consent processes) and efficient trial processes that minimize research burden on participants, particularly those faced with caregiver responsibilities or socioeconomic deprivation[16]. In addition, there should be broad representation on trial committees of both investigators and patient representatives. Interim analyses to monitor the representativeness of participants should be included in trial protocols.

Recruitment

Patient recruitment is one of the most time-consuming and costly stages of a clinical trial. Trialists and sponsors can be faced with difficulties when trying to identify sites in under-served areas and enrolling under-represented patients. Clustering of trial centers in urban locations and research-intensive settings can lead to selection bias. There are several strategies that can be used to identify areas with a high burden of disease and to engage patients who belong to under-represented groups.

Use of digital technology. Social media platforms are increasingly being integrated into research, but remain underutilized. These platforms have broad reach and offer no-cost avenues to advertise trials and potentially recruit or engage patients from diverse communities[17]. Engaging key opinion leaders, health equity associations, community champions and patient advocacy groups in social media campaigns could foster outreach to historically marginalized groups. Links to online trial screening questionnaires could allow patients to self-screen and connect with investigator teams. Most social media users state they would share data with researchers, but confidentiality, privacy and data protection remain concerns[17]. Digital health equity can be a barrier in some regions, and improved digital access and literacy are needed[18].

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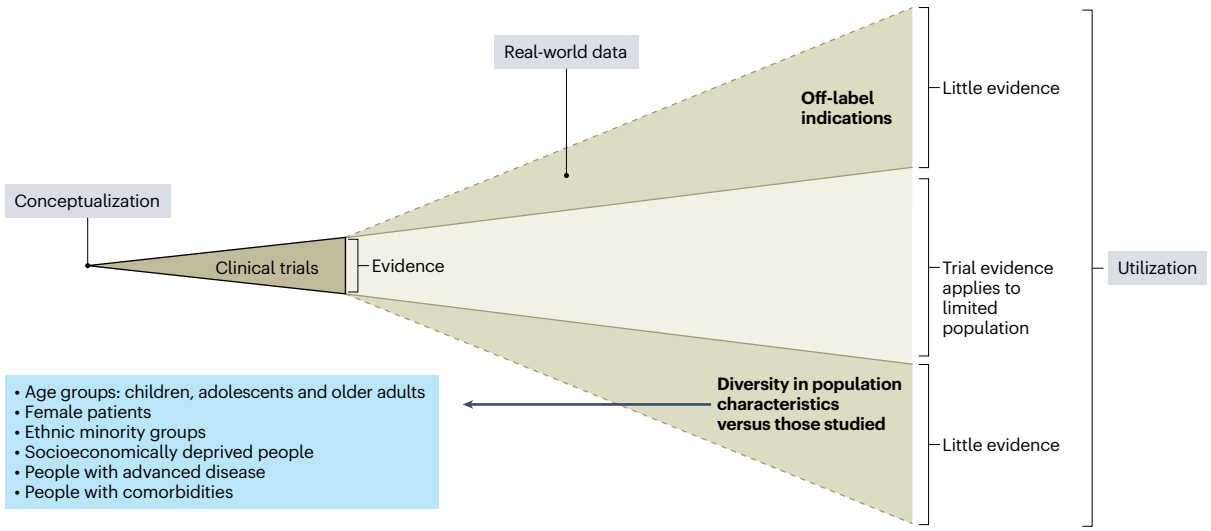

Fig. 1 | Summary of the evidence generation process. Clinical trials generate evidence from the subset of patients in the population that meet trial eligibility criteria. Estimates of treatment effect in patients excluded from trials are generated from real-world data, including registries and EHRs, but causal inferences cannot be reliably made. Knowledge gaps relating to treatment effects remain in many patient subgroups.

Communications on social media platforms and online traffic can be analysed using novel AI/machine learning algorithms to identify sites or regions with high disease burden or interest in trial participation. Patients and medical staff in these regions can be automatically alerted regarding trial opportunities, which could speed up recruitment and potentially decrease bias at the trial invitation stage[19]. AI using big data, including health data, can also be used to characterize and predict disease trajectories for a precision-based approach to trial recruitment. For example, AI was successfully used to link phase 2 trial results to real-world data from millions of patients in Europe and the United States and predict the long-term risks in a population similar to the trial[20]. Thus, the recruitment of patients at risk decreased the number of participants needed for a phase 3 trial for asundexian (a factor XI inhibitor) for the reduction of stroke risk[20].

The use of big data is often limited by the reliability and quality of the data and validation of outcomes; poor-quality data can result in AI bias that can be propagated in iterative cycles and result in harm[15,21–23]. International harmonization and regulatory efforts are underway for the collection, management and AI applications of data. In addition, the largest amount of data feeding AI is produced in digitalized communities and countries with the capacity to generate high-quality data. It misses entire populations from countries with limited digital access, affordability and literacy, contributing to biased AI solutions[15,21–23]. Researchers need to be alert to this paucity of data and work to address the data bias/gap by encouraging, producing and feeding in relevant data from under-served communities and geographies. In addition, diversity within AI research and development teams can help with identifying and decreasing bias in AI/machine learning algorithms[24].

Although digital research data are subject to patient privacy laws, digital data in the general population (for example, from social media use or website visits) are routinely sold to commercial entities for targeted advertisements. The use of such digital data to identify areas with a high burden of disease and unmet needs is arguably both ethical and useful. Real-time information from mobile devices (for example, geolocation or step count) could be used to recruit patients into trials targeted to their medical conditions and needs. Such strategies could be tailored to increasing health equity in specific demographic groups, educating patients about trials using culturally competent language and facilitating self-enrollment. These strategies will need to be deployed thoughtfully, respecting patient privacy and considering digital health equity to avoid further marginalizing individuals and communities with suboptimal access to digital technologies[18].

Routinely collected health data (including electronic health records (EHRs) and pharmacy and diagnostic laboratory records), administrative and health insurance databases and national registries can be used to map the prevalence of a particular condition in a given area and to recruit patients for trials[25]. Trials embedded in routine healthcare settings such as pharmacies and hospitals may have broader recruitment pools and make it easier for investigators to screen patients[26,27]. EHRs and pharmacy records can be programmed to identify patients who may be eligible for trials and may mitigate clinician biases in terms of which patients are referred into a trial.

Engagement of patients. There are several patient-level barriers to trial participation that could be mitigated through meaningful engagement of patients and community groups in trial design, and through transparency in data collection and reporting. Historically marginalized groups that have been mistreated or subjected to ethical violations in research may not have adequate trust in the clinical trial enterprise[28]. Engaging community leaders and scientists from historically marginalized communities can be effective in strengthening relationships and building trust. For example, the Coronavirus Prevention Network paired Black scientists and faith leaders with communities around the United States to raise awareness about COVID-19 vaccines. Transparent communication with participants on the rationale for and type of data collection, along with privacy safeguards, could enhance trust.

Culture, language, religious beliefs, age, sex, education, socioeconomic status, geography and ethnicity can all play a role in research engagement. These factors may influence whether the patient is referred to a trial and whether they understand, trust or consent to trial participation. Socioeconomic deprivation may limit participation in trials that involve time off work, lost wages and costs of travel[2]. Attitudes toward healthcare and physicians, such as those related to previous negative experiences with healthcare professionals or healthcare settings, along with historic research misconduct and marginalization in some ethnic groups, can leave patients unwilling to participate in research[29].

Patients and community leaders should be engaged on trial advisory boards to inform trial design and communications in a manner that increases representativeness[16,30]. People with lived experience can add valuable insights regarding barriers to enrollment and patient-centered

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trial communications, processes and outcomes. Trial partnerships with patients and community members have the potential to foster trust[16] if guided by respectful dialogue and clarity around bidirectional roles and responsibilities for knowledge co-production[31,32]. Patient groups may have concerns regarding the rationale for data collection, protection of privacy, data ownership and sharing; these could be addressed with clarity in patient-centered trial documents co-designed with patients.

Site selection. Community settings frequently used by specific demographic groups could serve as trial engagement or recruitment sites for prevention or health service trials. These include community centers, pharmacies, grocery stores, sports arenas, coffee shops, barbershops and places of worship.

Site selection is an important step in recruiting a representative sample of patients, as the distribution of representative patients at risk differs markedly among sites and countries. Trialists typically recruit sites that have a track record of successfully meeting enrollment targets; thus, clinical trials typically have rich engagement with a small number of research-intensive centers in large metropolitan institutions within a country, which can result in a very select study population. Adding rural sites and sites with a high proportion of under-represented and historically marginalized sociodemographic groups, for example, can ensure a trial population that, overall, reflects the disease distribution in a country[33,34]. Collaboration with local residents can help in identifying barriers to participation.

Concerns around the quality of research that may result from inexperienced sites in under-served areas can be mitigated by investments in training and infrastructure for these sites[33]. In particular, investments in electronic medical research records, research facilities, databases and other resources can promote research readiness[2]. This capacity building at the site can lead to long-term relationships and multi-trial involvement.

Eligibility criteria

Protocols for cardiovascular trials frequently have standard exclusion criteria, such as age (typically excluding pediatric patients and older adults), pregnancy/lactation, the potential to become pregnant, substantial medical comorbidities or inadequate literacy in the language of the country in which the trial is being conducted. Such criteria serve a purpose, but can disadvantage certain populations, such as females or people from minority racial or ethnic groups who may have a higher prevalence of chronic conditions such as poorly controlled hypertension or kidney disease[29,35,36]. Exclusion criteria should be selected carefully and justified in the context of the individual trial to avoid under-representing some demographic groups relative to others. The under-representation of older adults from cardiovascular trials due to age or comorbidity-based exclusion criteria is a concern given that the incidence and prevalence of most cardiovascular diseases increases with age. Similarly, standard exclusion of patients with elevated liver enzymes in cardiovascular trials may lead to under-representation of patients with non-alcoholic fatty liver disease—a condition frequently consubstantial to cardiovascular–renal–metabolic disease. Thus, exclusion criteria should be reviewed with consideration given to the clinical characteristics of people to whom the trial results will be generalized and for whom regulatory approval will be sought. The ideal demographic distribution of trial populations should reflect the distribution of the disease in the wider population, aiming for a participation-to-prevalence ratio of 0.8–1.2 (ref. 2).

Unjustified exclusion criteria related to female reproductive potential are independently associated with the under-enrollment of women in clinical trials and should be avoided. A review of 283 published trials found that almost 40% reported exclusion criteria related to female biology, including being of childbearing age or having the biological potential to become pregnant[29]. Verbatim criteria that exclude women with intact reproductive organs from trial participation unless they are on birth control are rarely justified; instead of protection by exclusion mindsets, consideration should be given to informative discussions and informed consent by women[36,37]. Pregnancy and lactation are very different physiological states and should be considered separately—when necessary—instead of being combined into a single exclusion criterion; for example, drugs that have evidence of teratogenicity may not be secreted in milk or be harmful to a breastfeeding child.

Table 1 | Justification scheme for excluding individuals from clinical trials

Justified reason for exclusion	Unjustified reason for exclusion
• Lack of consent • Potential for harm to participant ◦ Unacceptable or known risk from the intervention ◦ Unacceptable risk from withholding the intervention (that is, if assigned to placebo group) • Individual is unlikely to benefit from the intervention ◦ Individual does not have the condition or type of disease that will respond to the intervention ◦ Individual is not at risk for the outcome or is at imminent risk of death or the outcome being assessed in the trial • Effect of intervention will be difficult to interpret ◦ Individual is unlikely to be adherent ◦ Individual is on concomitant treatment that will influence the effect of the intervention ◦ Individual has a comorbidity that will make treatment response difficult to detect	• Exclusion based solely on ≥1 of the following (in the absence of another justifiable reason for exclusion) ◦ Age ◦ Sex or sex-specific conditions (menstruation, pregnancy or lactation) ◦ Race, ethnicity or religion ◦ Spoken or written language ability ◦ Education level ◦ Socioeconomic status ◦ Cognitive abilities ◦ Physical abilities or disabilities ◦ Chronic comorbid health conditions ◦ Geographic region or location

Based on refs. 2,29.

Exclusion criteria should be justified using evidence from preceding animal and early-phase trials[2,29]. Justification schemes for eligibility criteria can guide trialists in selecting criteria that are not overly restrictive[2,29] (Table 1). Streamlined and simple eligibility criteria can decrease the burden on sites. The justification of eligibility criteria should also be considered by research ethics boards that assess a trial protocol.

Informed consent

Informed consent documents have traditionally been long and complex forms, largely mandated by study sponsors. The trial description for patients and the informed consent processes should consider literacy levels, language and cultural barriers. Digital consent tools may be preferred by some patients and should routinely be made available. A research-trained patient should help to develop patient information materials for the study and should be included as a member of the trial steering committee to help guide the language in consent documents[16,38]. Steps should be taken to ensure that patients who are unable to sign have a valid proxy method of giving their informed consent to be eligible to participate in clinical trials.

Trialists and frontline personnel may benefit from cultural competency training to guide trial processes and communications with diverse patients[16]. Education on cultural differences, beliefs and terminology can improve people's knowledge, skills and confidence when engaging with community members[28]. Several programs are available to help people understand the needs of diverse communities before undertaking cardiovascular trials, and several institutions provide toolkits for culturally sensitive communications, guidance and training[39].

Research culture at the macro or micro level may play an important role in consent and engagement of patients in trials. Across disease states, patients with cancer appear to consider trial participation

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Table 2 | Quality checks when using synthetic control datasets

	More favorable	Intermediate	Less favorable
Data source	• Patients from large, well-conducted RCTs • Baseline characteristics similar to those of the target population	• Patients from high-quality prospective cohorts or registries • Patient characteristics somewhat sparse	• Small number of patients or covariates • Substantial missing data
Similarity of datasets	• Similar clinical and geographic setting and demographics • Equivalent disease and outcome definitions	• Adequate sample size and covariates to confirm match • Manageable differences in disease and outcome differences	• Differences in important covariates, outcomes or disease definition • Too few data for reliable adjustments
Synthetic control methods	• Use of contemporaneous control data • Adequate size and high similarity or robust adjustment of external control data	• No contemporaneous control data • Minor dissimilarity or some adjustments needed • Acceptably robust sensitivity analysis	• No contemporaneous control data • Important dissimilarity • Unacceptable or no adjustments
Relevance and reliability	• High patient and outcome similarity • No apparent bias • Appropriate patient and covariate sample sizes	• Data sample or analytical adjustments not fully able to represent target population • Biased external control outcomes	• Dataset not representative of main disease or outcome definitions • Sufficient adjustments not feasible

Adapted from ref. 44.

desirable; this may be a function of the high degree of integration between oncology care and trials at academic centers or the perceived importance and urgency of trial participation by patients. Education and awareness about the seriousness of disease and the benefits of trial participation, as well as regular opportunities for trial participation at the point of care, may increase research readiness and consent.

Trial design

Factors involved in a patient's willingness to participate in a clinical trial may include early access to new treatments, the opportunity to receive high-quality healthcare and altruism; however, traditional explanatory trials that are designed to maximize estimates of efficacy and safety are highly selective in eligibility, controlled in delivery and data intensive; these trials place a research burden on patients that causes many to opt out. Trials could be designed in a manner that minimizes the research burden on patients and increases the efficiency of recruitment. Patient-reported outcomes could be collected remotely using digital health technology. Such strategies were adopted in the Patient-Centered Care Transitions in Heart Failure (PACT-HF) RCT in 2015–2016 and Canagliflozin Impact on Health Status, Quality of Life, and Functional Status in Heart Failure (CHIEF-HF) decentralized RCT in 2020–2021, which enrolled 49 and 45% female participants, respectively[26,27,40]. Efforts to minimize research visits that gather data from patients may be of particular benefit to patients who have caregiver responsibilities, are unable to bear the cost of research visits or rely on family for transportation; such patients tend to be women, socioeconomically deprived groups and older adults, the very groups that are under-represented in trials[41].

Synthetic control groups. Historical, or synthetic, control groups (often derived from real-world data) can be attractive because they allow all recruited participants in the trial to receive the active intervention. This is especially relevant to rare diseases, for which recruitment pools are limited or patients may be reluctant to join a trial for fear of receiving the placebo. For example, the mitogen-activated protein kinase inhibitor selumetinib was granted regulatory approval for children with neurofibromatosis type 1 based on the single-arm, phase 2 SPRINT trial and a historical control group[42]. Sources of external control groups could include existing standardized RCT data, administrative datasets and EHRs, among others[43]. However, historical control groups are inherently fraught with the risk of bias and systematic error because of the lack of randomized evidence. In fact, accepting a lower level of evidence for under-represented groups may be hazardous. Considerations must be given to the validity and reliability of the synthetic dataset—especially if derived from a historic dataset—as the phenotype of diseases may change over time. Importantly, the processes of data collection, baseline patient characteristics and comprehensiveness and reliability of data must all be similar in the synthetic control and intervention groups, to allow appropriate interpretation of the results[44] (Table 2).

Embedded trials. Pragmatic trials embedded within healthcare systems or disease registries can benefit from broad recruitment pools with representative populations, and routinely collected data can minimize the research burden to patients[45]. Patients could be identified by screening EHRs, consent could be obtained remotely and the intervention could be delivered in everyday clinical settings without encumbering patients—as was done in the PACT-HF and CHIEF-HF trials[26,27,40]. Links between enrolled patients and EHRs or administrative databases can be used to determine clinical outcomes, including mortality. Countries such as Australia, Canada and the United Kingdom collect clinical data on people across their lifespan and these data are linked across sources via unique health card numbers for each individual[26,27]. A benefit of using these data is that long-term follow-up beyond the trial duration can be obtained and a large number of outcomes can be collected with minimal incremental cost.

Conversely, some regions or countries may not have EHRs or registries, thus limiting these trials to localized areas with data accumulated in one healthcare database. Many countries have national death registries and hospitalization records and some also have prescription drug registries. However, there continues to be a need for international collaboration and consensus on the type of data collected at the national level to increase the feasibility of data harmonization for multi-national research analyses.

Registry-based RCTs can also help to broaden the recruitment pool and alleviate the research burden on trial participants. For example, the VALIDATE-SWEDEHEART RCT enrolled patients with non-ST or ST segment elevation myocardial infarction undergoing percutaneous coronary intervention pre-treated with a P2Y12 antagonist[46]. Using the SWEDEHEART registry, all relevant patients were assessed. Almost 70% of patients were asked to participate and a verbal consent process was used. Follow-up data were obtained for almost 99% of the patients via telephone or hospital and registry records[46,47] (Fig. 2). Data on race or ethnicity were not collected in the SWEDEHEART registry[48], but a representative sample of older adults and women were included[49,50]. Overall, there was no difference in major adverse cardiovascular events with either bivalirudin or heparin—a finding consistent among older adults[47,49]; in contrast, among women, there was a lower risk of adverse outcomes in the bivalirudin group, related to a significant decrease in bleeding[50].

Decentralized trials. Decentralized trials can bring clinical trials to patients, increasing access and enhancing representativeness. Trial participation, from recruitment to follow-up, can occur in communities

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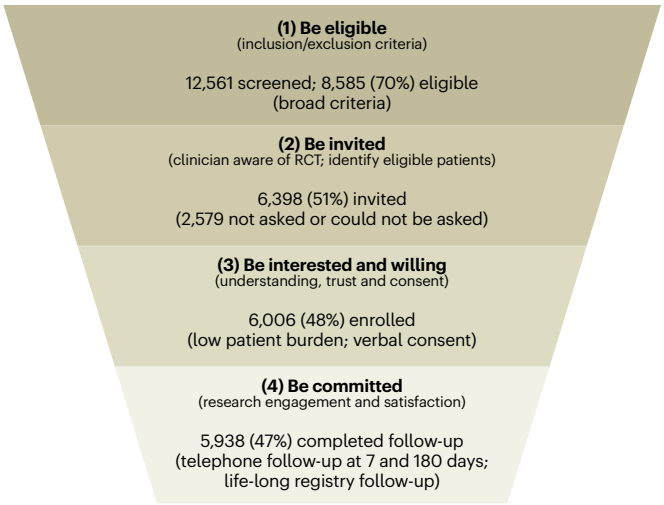

Fig. 2 | Broadening the recruitment pool with registry-based RCTs. This figure shows the steps involved in participating in a traditional RCT. The data below each step show enrollment in the VALIDATE-SWEDEHEART registry-based RCT. Of 12,561 patients who were screened (that is, diagnosed with non-ST or ST segment elevation myocardial infarction scheduled for percutaneous coronary intervention), 8,585 patients were eligible and 6,006 patients were enrolled. Enrolled patients represented almost 50% of the screened patients, representing high efficiency. VALIDATE-SWEDEHEART data from refs. 46,47.

rather than in trial centers, enhancing enrollment and engagement, as well as retention in low-resource or remote regions[51]. Decentralized trials can be fully conducted remotely through the use of digital tools, internet access and mobile medical units[51]. Some key elements include recruitment through online identification, randomization and electronic informed consent, decentralization of procedures, medication delivery to the patient's home or through the use of mobile or local healthcare providers and monitoring and outcome collection via patient-reported or routinely collected EHR data. Representativeness can be enhanced by conducting recruitment efforts in regions with a high proportion of historically marginalized groups[51]. However, digital collection can exclude patients without access to the internet.

Examples of decentralized cardiovascular trials include ADAPT-ABLE[52], CHIEF-HF[40], TIME[53] and the ongoing EVOLVE-MI (NCT05284747) trial. These trials involve patient identification through EHRs, local pharmacy or home delivery and self-administration of study drugs and pragmatic collection of data through EHRs, patient-completed forms and national registries.

Adaptive designs. Another type of trial that can help to improve the representativeness of the patient population is the adaptive trial design. Adaptive clinical trials allow for prospectively planned modifications to the trial design based on the accumulating patient data[54]. This can permit changes to trial enrollment criteria based on interim analysis of patient representativeness. Recruitment can continue with just a single subgroup, or the proportions of different subgroups can be changed, rather than using a fixed prevalence of the subgroup throughout the trial (Fig. 3). Interim analysis can be hastened by computerized algorithms that identify when representative enrollment of a certain subgroup has not been achieved. Within the trial, patients can be sequentially randomized to different interventions, with interim analysis to guide decisions. This can be done in real time.

Societal strategies

There is a need for education to improve population-based health and research readiness across all groups at the societal level, given the potential health benefits associated with trial participation[55]. Measures to combat misinformation and ensure transparency in research and data collection are needed to foster trust in science. Social influencers and celebrities have been used in some jurisdictions to encourage the engagement and enrollment of people from racial or ethnic minority groups in clinical trials.

An important barrier to ensuring representativeness is that data collection on ethnicity is not permitted in some jurisdictions. Even when not forbidden, these data are often not collected, definitions of ethnicity are often unclear and discussions with patients about self-identification are potentially awkward[56,57]. In addition to government policies on inclusion, there is a need to develop standards for defining, classifying and collecting ethnicity data. Meaningful partnerships with and engagement of researchers from historically marginalized groups can foster greater trust. For example, in Canada—in the spirit of 'no research on us without us'—federal grant applications for research on Indigenous peoples requires Indigenous researchers or community members to engage as partners in the application[58].

Like race or ethnicity, socioeconomic data should be collected and reported in trials, as socioeconomic deprivation is a well-known determinant of healthcare outcomes[33]. Data such as education level or annual income can be directly collected from trial participants or—in some countries—gleaned from the patient's zip code.

Ethics approval processes should be simplified and streamlined to foster efficient trial initiation and engagement in regions without adequate research resources. The province of Ontario in Canada has initiated a single, province-wide research ethics review for multi-site and multi-region studies to streamline administrative work and eliminate the need for approval from multiple local research ethics boards; although the intent was sound, the processes remain inefficient with the need for local research ethics boards to review, approve or disapprove the province-wide approval[59].

Role of regulatory bodies

Regulatory requirements and funding are important determinants of trial design and execution. Government, industry and institution sponsors have leverage to require that trial protocols be designed for representativeness, but they must also be willing to invest in systems required to expand research infrastructure to under-represented regions[2,9]. The US Food and Drug Administration has developed draft guidance plans for industry and patients to improve the diversity of enrollment of participants from under-represented racial and ethnic populations in clinical trials[60]. The European Medicines Agency clinical trials regulation requires assessment of the relevance of the clinical trial, including whether the participants represent the population to be treated, and if not an explanation must be provided[61]. In addition, agencies such as the UK-based National Institute for Health and Care Excellence specifically look for diversity in the data being submitted for decision-making and in its guideline development.

Regulatory agencies such as the European Medicines Agency or US Food and Drug Administration or governments could consider developing economic incentives and initiatives such as patent protection or extension when studies are expanded to include under-represented populations. These agencies can provide specific guidance for the enrollment of women and racial groups, including defined target proportions[56,57].

Industry- and trialist-based strategies

Central to increasing representativeness in the design of cardiovascular clinical trials is the mindset and culture in the study team, including how investigators are selected for industry-sponsored trials or supported in academic settings. Although under-represented on trial executive committees, female trial leaders enrol more women and people from racial or ethnic minority groups in trials (adjusting for other trial variables), highlighting the benefits of trial leadership diversity[62–65]. In an analysis of 317 RCTs, 72% under-enrolled female participants relative

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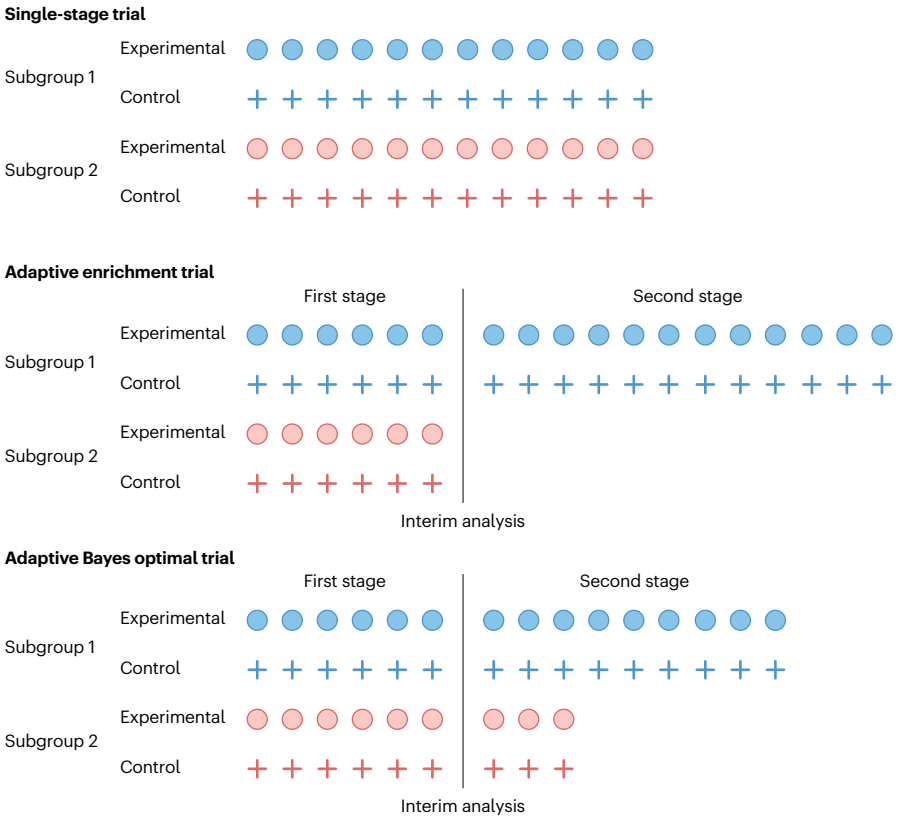

Fig. 3 | Using adaptive trial designs to increase representativeness. This figure shows schematics of three types of trial design. In a single-stage trial, the sampling prevalence rates of each subgroup are fixed throughout the trial. In standard adaptive enrichment trials, patients are recruited with predefined subgroup prevalence rates, but at the interim analysis a decision is made to continue with the same prevalence rates or to sample from a single subgroup. In the Bayes optimal adaptive trial design, the sampling prevalence rates may be changed at the interim analysis. Adapted from ref. 73, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

to the disease distribution and the odds of under-enrolling women were 34% higher in trials with male leaders (adjusted odds ratio = 1.34; 95% confidence interval = 1.12–3.54)[63]. Similarly, enrollment of Black people, Indigenous people and people of color was also significantly greater in trials led by women[6]. Studies have also shown increased recruitment of patients from other ethnic and under-served groups when trial investigators and staff are representative of the people being recruited, especially if they are from the local community[16].

There may be a need for hands-on mentoring and active sponsorship of investigators from under-represented groups; these include females and people from racial or ethnic minority groups, as well as people in lower- and middle-income countries[66,67]. High-quality mentorship through principal investigator dyads—an established investigator paired with an earlier-career-stage investigator from an under-represented group in a trial—could build capacity for diverse trial leadership. Trials with senior women investigators are associated with female first authors and increased representation of women in steering committees in adjusted analyses[65]. Thus, developing capacity for women and investigators from under-represented groups as trial leaders is a way to increase representation among trial populations.

Journals

Trial publications in medical journals have long printed trial results that fail to analyze, report or even acknowledge sex, age and racial or ethnic gaps within the study. Journals are taking steps to improve this oversight. For example, the *New England Journal of Medicine* requires authors to include a supplementary table that provides background information on sex, age, ethnicity and other factors of the patients affected by the disease and the representativeness of the study participants[68]. Such requirements can help to encourage greater efforts during trial design and recruitment to ensure representativeness of trial participants.

Medical societies and academic institutions

Women, people from racial or ethnic minority groups and other under-served groups continue to be under-represented within the cardiology profession and cardiology associations in Europe and North America compared with their proportion in society. A 2020 survey of cardiology departments in European countries found that women accounted for only 35% of European Society of Cardiology (ESC) members, 30% of leaders of cardiology departments and 18% of interventional cardiologists[69]. A similar Australian survey found that women accounted for 36% of specialists, 15% of cardiologists and <5% of interventional cardiologists[70]. Women have cited a lack of opportunity, prejudices of male colleagues, male-dominated culture and a lack of female role models and mentorship as barriers in cardiology fields[71]. This may not be typical in some fields of endeavour, including some other medical disciplines or in the life science industry.

Career advancement for female cardiologists and members of other under-represented groups can be stimulated through meaningful inclusion, equal opportunities for growth and discrimination-free environments[62]. Cardiology societies should develop a data-driven approach that describes (and perhaps sets targets for) the sex and regional distribution of funding awards, authorship positions on guidelines and position statements and speaking engagements at annual conferences. In 2022, the ESC developed gender policies to facilitate more balanced writing groups and speaker representation on ESC position statements and at ESC conferences[72].

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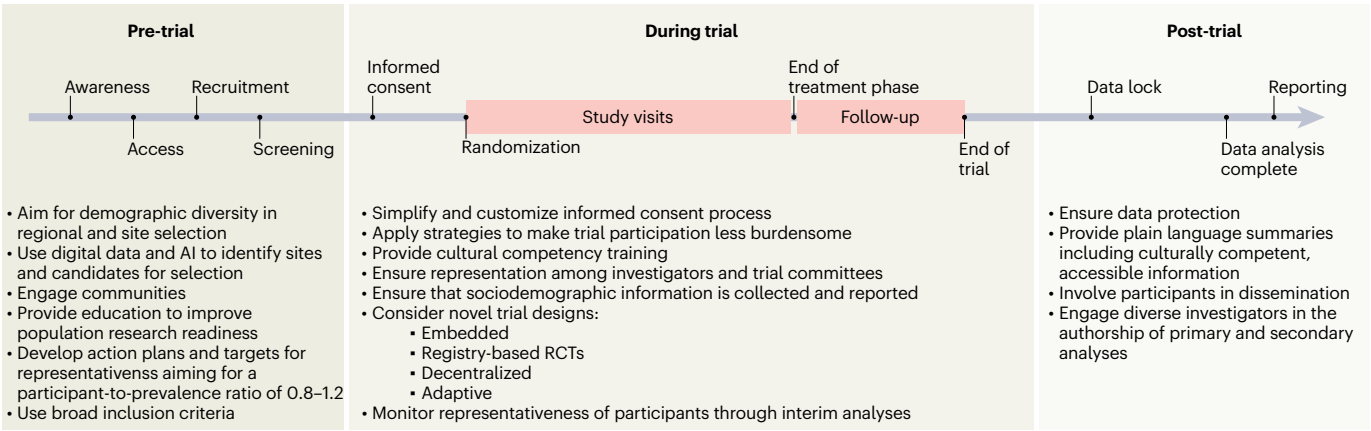

Fig. 4 | Strategies to improve representativeness in cardiovascular clinical trials. Key considerations (adapted from ref. 2) are summarized for each stage of the trial process.

Conclusion

Despite years of data on the under-representation of older adults, females and people from racial or ethnic minority groups in clinical trial populations, trends have not improved substantively. As noted in the sections above, increasing representativeness of trial populations requires actions at the levels of the trial sponsor or funder, leadership team, planning and design, execution and publication (as summarized in Fig. 4). Equitable investments will need to be made to support diverse trialists and to build trial capacity in low- and middle-income countries. The potential of communities and patients themselves must be harnessed to transform the clinical trial enterprise into one that meets the needs of those living with cardiovascular disease.

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F.Z. has received consulting fees from 89bio, Applied Therapeutics, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior Pharmaceuticals, CellProthera, Cereno Scientific, CEVA, CVRx, Merck, Novartis, Novo Nordisk, Owkin, Pfizer and Servier, honoraria for lectures from Bayer, Boehringer Ingelheim, CEVA, CVRx, Merck and Novartis and fees for participating on a data safety monitoring board or advisory board from Acceleron/Merck and has equity interests in G3 Pharmaceuticals, Cereno Scientific, CardioRenal, Eshmoun Clinical Research and CVCT. O.B. has received grants or contracts from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Pfizer and Servier and travel and/or meeting attendance support from AstraZeneca and Servier. S.C. has been employed by Bayer. M.R.C. has been employed by and has stock options in AstraZeneca. H.G. has received honoraria from Menarini and Servier for lectures, participated on a data safety monitoring board for the RIC Africa trial and held a leadership role (Vice President) for the Pan-African Society of Cardiology. A.G. has been employed by and has stock options in Bristol Myers Squibb. T.H. has been employed by, has stock or stock options in and has received travel and/or meeting attendance support from Amgen. K.K. has received institutional grants from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Novo Nordisk, Oramed Pharmaceuticals, Sanofi-Aventis and Servier, consulting fees from Abbott, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Napp, Novartis, Novo Nordisk, Oramed Pharmaceuticals, Roche, Sanofi-Aventis and Servier and travel and/or meeting attendance support from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Napp, Novartis, Novo Nordisk, Roche, Sanofi-Aventis and Servier and has held leadership roles for the Centre for Ethnic Health Research (Director) and South Asian Health Foundation charity (Trustee and Working Group Chair). B.J.K. has been employed by and has received travel and/or meeting attendance support from Boehringer Ingelheim International. C.L. has received grants or contracts from the Swedish Heart Lung Foundation, Swedish Society of Science and Stockholm County Council, consulting fees from AstraZeneca and Medtronic and payment or honoraria for lectures, presentations or speaker bureaus form AstraZeneca, Bayer, Boehringer Ingelheim, Impulse Dynamics, Medtronic, Novartis and Vifor Pharma, has participated on a data safety monitoring board or advisory board for the ABC study by UCR Uppsala Sweden and has held a leadership role (Secretary Treasurer) for the ESC. T.F.L. has received institutional grants from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Menarini Foundation, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi and Vifor and honoraria from Amgen, Dacadoo, Daiichi Sankyo, Menarini Foundation, Novartis, Novo Nordisk, Philips and Pfizer. M.M. has received research grants from Novartis, Novo Nordisk and Health Data Research UK and a fellowship from the British Heart Foundation and has participated on a data safety monitoring board or advisory board for the PAVE-2, STIMULATE-ICP, ASPECT, ORION-4 and ASCEND PLUS trials. R.M. has received travel and/or meeting attendance support from the ESC, Horizon and Digital Health for Heart Health. R.F.O. has held a leadership role (Executive Director) with Women as One. E.P. has held a leadership role (Committee Chair) for the ESC. C.Y. has been Steering Committee Chair for ACTIV trials, sponsored by the National Heart, Lung, and Blood Institute. A.Z. has been employed by and has stock or stock options in Roche Diagnostics. H.G.C.V.S. has received grants from the Canadian Institutes of Health Research and Heart

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