Lessons learned from the feasibility phase of the REvascularization CHoices Among Under-Represented Groups Evaluation (RECHARGE) trial program

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ABSTRACT

Background The REvascularization CHoices Among Under-Represented Groups Evaluation (RECHARGE) program is enrolling 1200 women, Black and Hispanic patients, in 2 parallel randomized trials of percutaneous coronary intervention vs coronary artery bypass grafting.

Methods Funded by a phased Patient-Centered Outcomes Research Institute award, the pilot phase was designed to assess the feasibility of enrolling groups historically under-represented and challenging to enroll in prior revascularization trials, evaluate willingness of patients to accept randomization, refine patient and stakeholder engagement, and scale site infrastructure and data collection across diverse centers. We report key insights from the pilot phase.

Results Physician and patient treatment preferences, often shaped by prior experience and evidence not directly applicable to these cohorts, were the main reasons eligible patients were not randomized. Many sites also lacked consistent multidisciplinary Heart Team processes for coronary disease, requiring new workflows to establish equipoise between percutaneous coronary intervention and coronary artery bypass grafting. Successful recruitment required intentional trust-building and tailored patient-facing materials, while engagement of non-academic centers demanded added financial, educational, and start-up support. During the 2-year pilot phase, 91 US and 17 Canadian sites were selected, and 65 were activated. Median activation time was 10.8 months (Interquartile range [IQR] 9.1-13.6). The pilot enrollment goal of 60 participants was exceeded, with 141 patients randomized within 13 months at a mean rate of 0.27 patients/site/month, prompting expansion to up to 150 sites for the full program.

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Conclusion The lessons learned from the pilot phase of the REvascularization CHoices Among Under-Represented Groups Evaluation program can inform the design and implementation of future randomized trials seeking to enroll traditionally under-represented populations.

Trial Registration REvascularization CHoices Among Under-Represented Groups Evaluation: The RECHARGE Trial; NCT06399705 (RECHARGE:M) and NCT06399692 (RECHARGE:W).(Am Heart J 2026;301:107515.)

Key Points

- The Question: Can dedicated randomized trials of PCI versus CABG successfully enroll women, Black, and Hispanic patients with multivessel or left main coronary artery disease who have been historically under-represented in prior revascularization trials, and what lessons from the feasibility phase can inform the design and implementation of future trials seeking to enroll traditionally under-represented populations?
- The Findings: In the 2-year pilot phase, 91 U.S. and 17 Canadian sites were selected, 65 were activated, and the pilot enrollment goal of 60 participants was exceeded, with 141 patients randomized within 13 months. Physician and patient treatment preferences were the main reasons eligible patients were not randomized; many sites lacked consistent multidisciplinary Heart Team processes for coronary disease, while successful recruitment required intentional trust-building, tailored patient-facing materials, and added financial, educational, and start-up support for non-academic centers.
- The Implications: The lessons learned from the pilot phase of the RECHARGE program can inform the design and implementation of future randomized trials seeking to enroll traditionally under-represented populations. Designing trials dedicated to under-represented patient groups, with tailored trial design and engagement activities, may be key to providing robust and informative data to support patient-centered revascularization choices.

Rationale for REvascularization CHoices Among Under-Represented Groups Evaluation (RECHARGE)

Each year, over one million US patients undergo coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[1] Although landmark trials have reported broadly similar long-term outcomes with both approaches,[2–4] the timing and distribution of risks and benefits differ. PCI is associated with fewer procedural complications and faster recovery while CABG provides more durable protection with lower risks of recurrent cardiac events and repeat procedures.[5–7] These trade-offs are modulated by coronary anatomy, functional status, and comorbidities, such that informed patient preference is universally endorsed when selecting a revascularization strategy.[8,9]

To date, most clinical trials comparing PCI and CABG have predominantly enrolled White men, with limited participation of women, racial, and ethnic minority populations. For example, the Evaluation of XIENCE vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial,[2] the largest contemporary comparison of PCI and CABG, enrolled only 23% women and 8% non-White patients. The synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial[10] and the Nordic–Baltic–British Left Main Revascularisation (NOBLE) trials[11] included approximately 22% women and did not even report race. More broadly, women have accounted for ~21% of participants in cardiac surgery randomized trials, and fewer than half of cardiovascular trials have reported race or ethnicity.[12,13]

Outcomes after PCI and CABG may differ by sex, race, and ethnicity. Women experience higher rates of adverse events after both CABG and PCI, potentially related to differences in anatomy, comorbidity burden, and procedural risk.[14–33] Black and Hispanic patients experience worse outcomes after both CABG and PCI than White patients, potentially due to differing clinical profiles at enrollment and barriers to accessing rehabilitation and longitudinal cardiovascular care.[34–52] Patient priorities for the reductions in various major cardiovascular events (eg, death vs stroke vs MI vs repeat revascularization) vs improvement in quality-of-life (QOL) may also vary

by sex, race, ethnicity, and influenced by socioeconomic factors and differing life objectives.[53] Despite these biological, cultural, and socioeconomic differences, no prior revascularization trials have been performed to assess the comparative safety of PCI vs CABG and their impact on cardiovascular outcomes and changes in QOL in these under-represented groups.

Thus, given differences in clinical characteristics, procedural outcomes, social conditions, and life priorities, the results of PCI vs CABG observed in White men in prior clinical trials should not necessarily be translated to women or racial/ethnic minority patients. This paucity of data notwithstanding, ~250,000 women and >200,000 racial/ethnic minority US patients undergo coronary revascularization each year. Moreover, given the increasing importance of shared decision-making, women, and racial/ethnic minority group patients are asked to choose between PCI and CABG with little data to inform their risks and benefits in patients like them.[54] The RECHARGE program was, therefore, designed to provide, for the first time, high-quality evidence on the comparative effectiveness of PCI and CABG in women, Black and Hispanic patients.

Key elements of trial design

RECHARGE (Figure 1) is an integrated program consisting of 2 parallel, individually powered, multicenter, randomized superiority trials: RECHARGE:Women, enrolling ~600 women of any race and ethnicity, and RECHARGE:Minorities, enrolling ~600 Black or Hispanic patients of either sex. Women who are also Black or Hispanic will contribute data to both trials, further increasing study power. This structure accommodates potential heterogeneity in treatment effects between sex and racial/ethnic groups and permits separate analysis and reporting in each cohort.

Eligible participants are adults with multivessel or left main coronary artery disease requiring revascularization, in whom the local multidisciplinary Heart Team has determined that clinical and technical equipoise between PCI and CABG exists. Patients with ST-segment elevation MI within 3 days or cardiogenic shock are excluded, as are patients with prior PCI within 12 months or any prior CABG, as well as those requiring additional cardiovascular procedures, except left atrial appendage exclusion or atrial fibrillation ablation. Otherwise, there are few exclusion criteria. After informed consent, patients are randomized 1:1 to PCI vs CABG using permuted blocks, with stratification by site and the presence of left main disease and minority status (in both trials) and by sex (in RECHARGE:Minorities). Procedures follow contemporary best practices and guideline-directed therapies, with a strong emphasis on optimal secondary prevention, irrespective of assigned strategy. Follow-up will continue through 5 years under the current award, and all patients have been consented for potential 10-year follow-up.

The RECHARGE trial program is funded by the Patient-Centered Outcomes Research Institute (PCORI) as a phased large award for comparative effectiveness research that required substantial pre-study evidence generation prior to grant submission, followed by a pilot feasibility phase before transitioning to full-scale enrollment. This manuscript describes the learnings from the pre-grant submission and pilot phase of this ongoing trial program (Clinicaltrials.gov identifiers NCT06399692 and NCT06399705) to share insights that may be useful to future trials seeking to enroll more diverse participants.

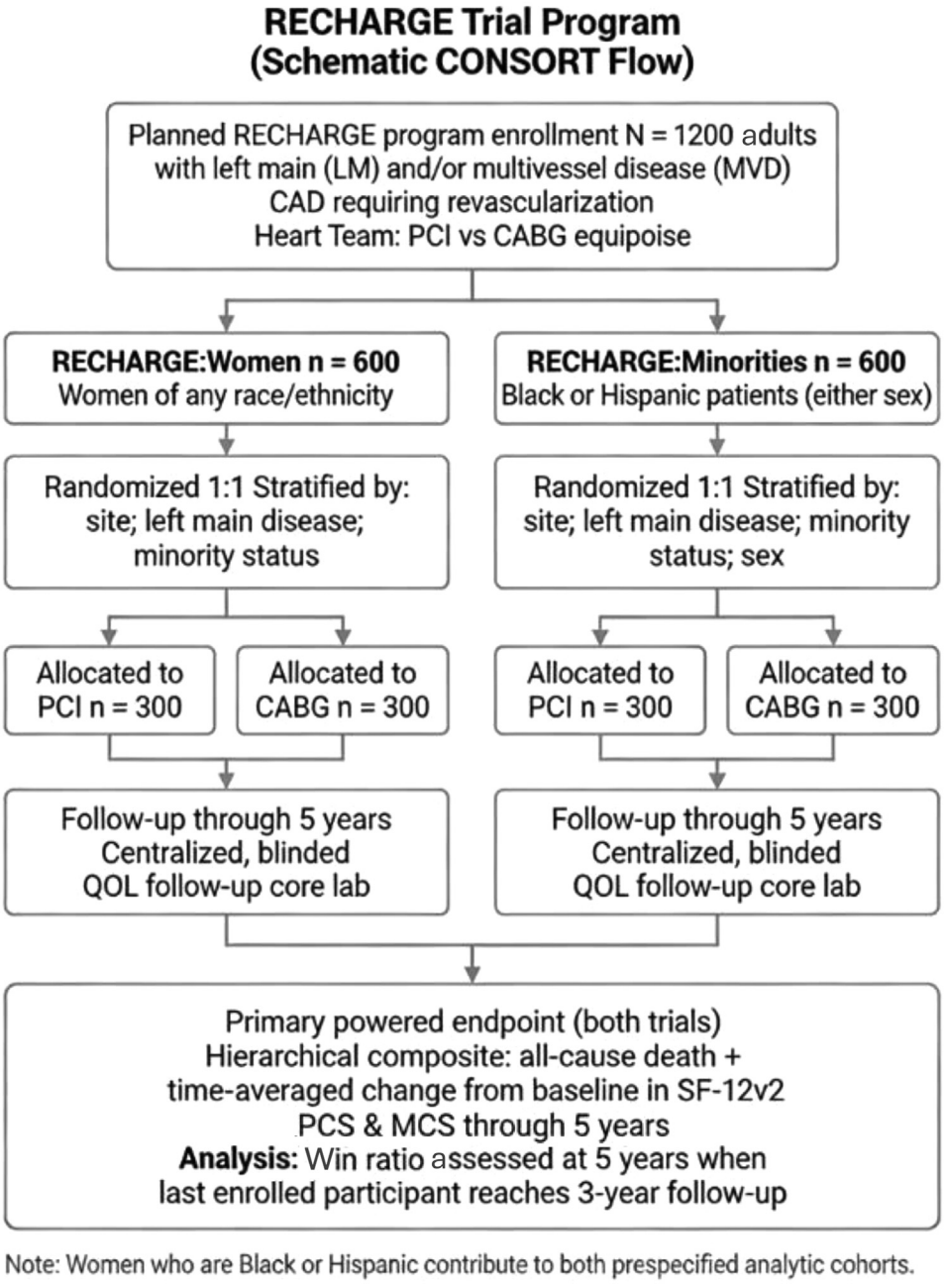
Protocol planning for endpoint selection (pre-submission phase)

Multiple considerations and perspectives were considered in defining the primary endpoint for the RECHARGE trial program that necessitated novel data collection prior to grant submission.

Patient perspectives

A major design goal of RECHARGE was to design a study with a primary endpoint that would be fundamentally meaningful to patients. Prior to grant submission, a Patient Stakeholder Advisory Board (PSAB) was constituted to work closely with the RECHARGE leadership to identify and address the expected challenges of enrolling traditionally under-represented patient groups and informing the trial endpoints to meaningfully address the outcomes that matter most to our patients (Supplementary Table 1). The PSAB is chaired by a woman (RM) who has undergone both CABG and PCI and co-chaired by a pastor (PG) committed to engaging the Black community and other under-represented minority groups in clinical research. Other members of the PSAB include patient advocacy leaders and ethics experts, hospital administrators and industry representatives, as well as noninvasive and invasive cardiologists and cardiac surgeons with expertise in research involving women and minority group patients. With their support and guidance, more than 40 focus group sessions and individual interviews were held with patients who had previously undergone coronary revascularization, as well as community leaders committed to engaging women and minorities in research.[55] The clear consensus from these inquiries was that the most important concerns facing patients considering CABG or PCI were their survival and QOL. When queried about whether the primary outcome should be disease-specific (given that treatment is directed at coronary disease and no other comorbidities) or overall health status, the latter was of primary importance. Congruent with prior studies,[56] traditional clinical events, including myocardial infarctions [MIs], repeat procedures, etc., were less im-

Figure 1. Key elements of the RECHARGE trial program. Patients who are women, Black or Hispanic, and have left main or multivessel coronary artery disease but otherwise are not randomized either because of not meeting all other entry criteria or refusal to consent by patient or physician are enrolled in a screening registry (not represented in this figure). CABG, coronary artery bypass grafting; CAD, coronary artery disease; LM, left main (coronary) disease; MCS, mental component summary (score of SF–12v2); MVD, multivessel disease; PCI, percutaneous coronary intervention; PCS, physical component summary (score of SF–12v2); QOL, quality of life; RECHARGE, REvascularization CHoices Among Under-Represented Groups Evaluation; SF–12v2, 12–Item Short Form Health Survey, version 2.



portant from the patient's perspective than survival and QOL.

Scientific perspectives

Based on patients' priorities, the trial's principal investigators adopted a novel primary outcome instead of the traditional major adverse cardiovascular events (MACE) endpoint, to both honor patients' perspectives and to address the known limitations of MACE as an endpoint.[57-63] For example, traditional MACE outcomes do not weight the individual components of the composite based on clinical relevance, leading to more frequent and potentially less clinically relevant events (eg, small procedural myocardial infarctions [MIs] or repeat revascularizations), dominating the study results and diluting the influence of more clinically relevant but less common events (eg, death or stroke). In addition, a less severe MACE (eg, repeat revascularization) that occurs early is given priority over a more serious event (eg, death or stroke) that occurs later but is ignored entirely in standard time-to-first event analysis. Similarly, recurrent adverse events of the same or different type are disregarded after the first event is counted. Finally, the typical 4-component composite MACE outcome (death, stroke, MI, or repeat revascularization) only captures select cardiovascular events and fails to account for other cardiovascular outcomes associated with treatment strategy (eg, heart failure, arrhythmias, angina, urgent care visits, and repeat hospitalizations, etc.), let alone non-cardiovascular outcomes (eg, renal failure, bleeding and vascular complications, infections, depression, time to recovery, musculoskeletal chest pain, fatigue and more) that may be as or more important to patients than the traditional MACE components.

Primary and secondary outcomes of RECHARGE

Those key considerations informed by direct patient interactions led to the choice of a hierarchical composite outcome that includes only mortality and generic health status over time as the primary outcome for RECHARGE. This novel measure captures the totality of the effect of the tested interventions on survival and patient well-being and provides the data that are most meaningful to patients, while also overcoming the methodological and clinical limitations of classic MACE endpoints. The rationale for the choice of this novel composite outcome, instead of the traditional MACE composite outcome used in all previous coronary revascularization trials, has been discussed in detail previously.[64,65]

Specifically, for both RECHARGE:Women and RECHARGE:Minorities, the primary powered endpoint is a hierarchical composite of all-cause death and the time-averaged change from baseline in the physical and mental component summary scores of the 12-item Short Form Survey[66] assessed through 5-year follow-up when the last enrolled patient reaches 3-year follow-up, analyzed by the win ratio. The powered key secondary endpoint is the time-averaged change in disease-specific health status, as measured by the Seattle Angina Questionnaire.[67-69] In addition, over 20 clinical events (including MI, stroke, repeat revascularization, rehospitalization, heart failure, arrhythmias, vascular and bleeding complications, and others) are collected and adjudicated, and data from 11 QOL instruments will be reported.[64,65,70-76]

The decision to use QOL as a central component of the primary outcome had important consequences on the trial's design. To reduce heterogeneity in assessment and investigator bias, a centralized follow-up core lab, blinded to treatment allocation and separate from the enrolling sites, was established. In addition, to reduce language selection bias, translation was obtained not only for informed patient consent but also for all QOL questionnaires in 15 languages. These decisions, although critically important from a clinical and methodological perspective, added substantial financial cost and logistical complexity.

There are some limitations of using the win ratio for hierarchical endpoint analysis and reporting. One challenge is interpretability for both clinicians and patients, as valuing the treatment effect size of the win ratio (the ratio of patient-pair wins divided by losses) is less intuitive than absolute risk differences or hazard ratios from time-to-first event analysis. However, conventional effect measures for time-to-first MACE composites are also challenging to interpret when the component events differ substantially in clinical importance, frequency, timing, and treatment effect. A hazard ratio or relative risk for MACE may be driven by less severe but more frequent events, or by early nonfatal events that mask later, more consequential outcomes. In contrast, the win ratio enables hierarchical ranking of outcomes according to their clinical importance. The RECHARGE primary endpoint addresses an explicitly patient-centered question: which revascularization strategy results in better survival (the first comparison) and among survivors, better overall health status during 3-year to 5-year follow-up (the second comparison)? Survival is prioritized over QOL, as QOL only resolves differences when participants have survived. We acknowledge that this hierarchy may not reflect the preferences of all patients, particularly older or frail individuals who may value QOL over survival. To aid clinical interpretation and preserve comparability with prior revascularization trials, the primary win ratio will be reported together with the win difference (the absolute difference between the proportions of wins and losses), absolute survival rates, time-averaged differences in generic and disease-specific QOL, and treatment effects for conventional clinical outcomes, including death, MI, stroke, repeat revascularization, hospitalization, and other adverse events. This approach allows the primary patient-centered endpoint to be interpreted alongside fa-

Table 1. Lessons learned recruiting women and under-represented groups

Recruitment and retention strategy	RECHARGE feasibility phase observations	Actionable tactics for investigators
Communication and trust-building with potential participants	1. Focus groups identified concerns regarding mistreatment of women, Black and Hispanic patients, in medical research 2. Patients required extended time and tailored communication materials with inclusion of significant others in research participation discussions	A. Engage a diverse group of patient stakeholders to co-develop enrollment support B. Develop effective and culturally sensitive communication materials addressing the why, what, and how of clinical trials C. Take definitive steps to restore trust; begin by listening; build networks of trusted individuals D. Explore concise project and consent summaries to counter extensive legal language; allow patients to "see themselves"; use multimedia tools (eg, videos); invite extended discussion with family and friends
Site-level infrastructure at non-academic centers	1. RECHARGE-targeted populations are often treated at non-academic research-naïve centers that emphasize clinical care and do not hold research infrastructure 2. Certain populations hold naivete regarding global benefits of human research	A. Anticipate that many potential participants receive care at non-academic centers with limited research infrastructure. B. Enable participation via initial financial investment, perhaps substantial with ROI for future clinical trial enrollment C. Develop on site education, and at the ready operational support
Entrenched practice patterns and lack of equipoise	1. Physicians rely on inferences and empiricism when treating under-represented groups 2. Absence of equipoise is a substantial recruitment/enrollment challenge	A. Highlight evidence gaps and reinforce clinical equipoise through ongoing, multi-domain structured engagement across sites B. Own and normalize uncertainty; promote collective responsibility for evidence generation
Site activation timelines, costs, and network expansion	1. The mean enrollment rate was substantially lower than that reported in previous PCI vs CABG trials 2. Site start-up fees were generally higher than expected and materially affected the budget	A. Budget accordingly for more "boots-on-the-ground" recruitment efforts B. Leverage within focused community liaisons C. Allocate more funds per site at centers hosting historically under-represented populations
Physician and patient treatment preferences	1. Over two-thirds of otherwise eligible patients declined enrollment because of strong treatment preferences 2. Physicians strongly suggested treatment biases 3. Patients were heavily persuaded by physicians' opinions 4. Once strong preferences for treatment were embedded, willingness to be randomized declined precipitously	A. Consider introducing trials earlier in the care pathway (eg, prior to or immediately after angiography) and, when feasible, presenting the study jointly across disciplines (both surgeon and interventionalist present) B. Develop coordinated messaging informing both physicians of record and patients/caregivers that emphasize safety, equity, and the value of randomization C. Seek novel ways at the community level to maintain receptivity to enrollment before preferences solidify
Social determinants of health data	1. Baseline social determinants of health information revealed potential participation barriers such as transportation challenges and language barriers	A. Collect social determinants of health data early in a trial and identify structural barriers to participation B. Accommodate enrollment barriers in clinical trial planning
Public/professional communication and awareness-building	1. Skepticism emerged among some investigators and trialists regarding the feasibility of enrolling historically under-represented populations 2. Construct of a novel primary outcome required open and honest debate	A. Engage all parties transparently B. Disseminate trial rationale and design through professional forums, institutional education, peer-reviewed literature, and public-facing media C. Improve acceptability, support site recruitment, and enhance patient and caregiver awareness

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; RECHARGE, REvascularization CHoices Among Under-Represented Groups Evaluation; ROI, return on investment.

miliar event-based outcomes to support clinical decision-making and inform future guidelines without relying on the win ratio alone.[77]

The pilot phase

The PCORI pilot phase for RECHARGE was designed to achieve several main goals (Table 1):

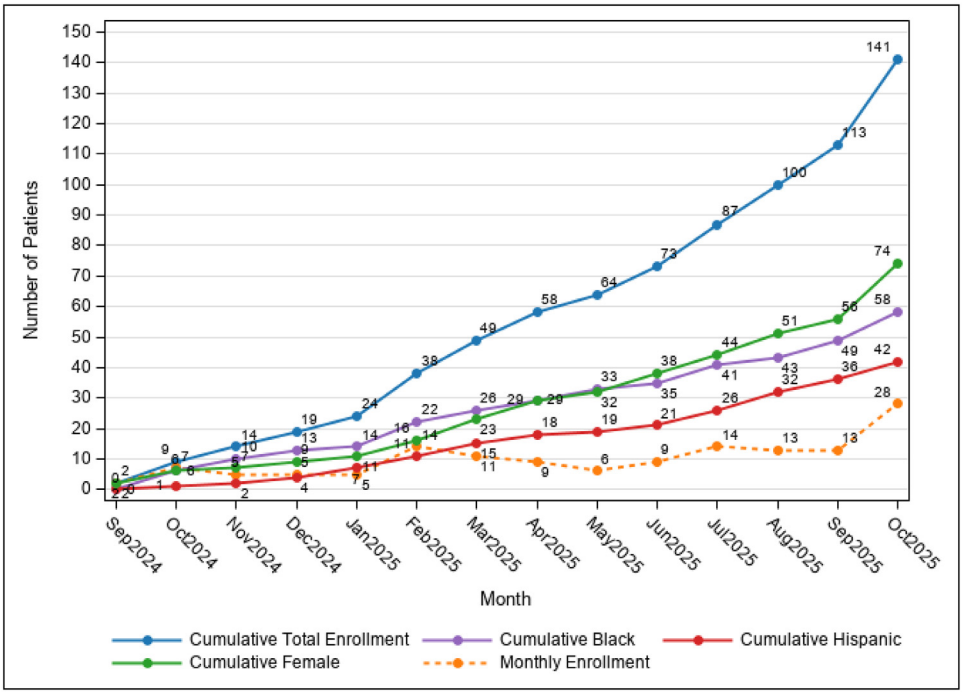
1. To confirm the feasibility of enrolling the target population and assessing the rate of patient recruitment. Due to the absence of solid data on enrollment rates in coronary revascularization trials for women, Black and Hispanic patients, the pilot phase assessed recruitment across 60 centers. From this process, it was learned that baseline data, which included information on social determinants of health, could be leveraged to identify potential participation barriers, such as transportation difficulties and language barriers, which could be proactively addressed to support enrollment.

2. To evaluate patients' willingness to be randomized to PCI vs CABG. The investigators evaluated the attitudes and concerns of women, Black and Hispanic patients, toward randomization through interviews and focus groups with people having lived experiences with coronary revascularization, including sessions conducted in Spanish.[55] Lessons learned were central to formulating supportive patient-facing materials and site training. Key examples include highlighting the current gap in knowledge about the best treatment for patients like them; the altruistic benefit of informing future practice; giving potential participants time to discuss the opportunity with their friends and family; emphasizing that both treatments are standard, state-of-the-art care; and the value of having the interventionalists and cardiac surgeons, ideally together, introduce the trial to potential participants.
3. To optimize communication and patient engagement. Given concerns of past mistreatment of Black patients and women in medical research, the PSAB was challenged to develop strategies to best explain and reassure potential participants about enrolling in RECHARGE. These insights represent another key benefit of having conducted focus groups with patients similar to the target population to understand barriers and facilitators to participation.[57-59,78-80] After reflecting on the lessons learned from the focus groups, the PSAB developed several aids to support enrollment. The first was an introductory brochure that directly addressed the need for RECHARGE, what a clinical trial is, how treatment is assigned, the historic mistrust of medical research, and encouragement to learn more about the trial. The second document was a one-page summary of the informed consent document to condense the extensive legal language used in current consent forms. Finally, YouTube videos[81] were created by the RECHARGE principal investigators, steering committee, and PSAB members discussing different aspects of RECHARGE to better acquaint potential participants with the trial. Substantial effort was made so the qualifying patient population would "see themselves" in these materials. In addition, the PSAB provided important insights into how best to approach potential participants. Most importantly, the focus groups identified that patients need time to discuss trial participation with their family and friends, which was communicated to sites during the activation process.
4. To build an efficient trial infrastructure. The pilot phase included time for finalizing legal agreements, obtaining regulatory approvals, and piloting data collection systems. Selected sites tested workflows for reducing implicit bias in screening, randomization, data collection, and follow-up, from which improved study procedures and protocol refinement occurred.
5. To finalize case report forms. Recognizing that a myriad of outcomes might be important to patients and that a number of social determinants of health could influence these outcomes, an extensive review of the data collection forms assessing participants' socio-demographic characteristics and patient-reported outcomes was done with the PSAB. This enabled the study to collect potentially sensitive information (eg, economic status, drug use, food or transportation insecurity) in a culturally acceptable manner. Moreover, additional QOL instruments were endorsed as being important in understanding the risks and benefits of CABG and PCI.[64,65,70-76] The final case report forms were heavily influenced by PSAB input.
6. To "spread the word" across the clinical and academic community. To generate knowledge of the trial, recruit new interested sites, and assess acceptability of the novel primary endpoint (improvement in survival and QOL), numerous talks were delivered by the investigators at major cardiology and surgical societal congresses, as well as at specialty meetings. In addition, the principal investigators presented dozens of grand rounds at individual hospitals to support broader awareness, motivate enrollment, and to proactively address questions from the providers. Conventional media (coverage by Good Morning America and the New York Times) and social media (X [formerly Twitter], Instagram, YouTube) were used to provide information about the trial to patients and caregivers and to assess interest for participation. Articles were published in peer-reviewed literature to describe the novel challenges addressed and solutions developed for the RECHARGE clinical trial program.[57-63]
7. Live testing of the protocol and identifying barriers to enrollment. Many physicians had expressed doubts as to whether exclusively enrolling women, Black and Hispanic patients, into a dedicated trial was possible. Modest enrollment goals were established in collaboration with the trial principal investigators and PCORI in the pilot phase to live test the feasibility of enrollment within an acceptable time frame and to identify clinical and social/societal barriers to enrollment that might be overcome through process adjustments or protocol amendment during enrollment in the full phase.

Activities during the pilot phase

The 2-year feasibility phase supported start-up activities, including protocol approval by the central IRB, or local IRBs when required, contracting, and pilot phase enrollment. Over the course of 2 years, 91 US and 17

Figure 2. Cumulative enrollment during the RECHARGE pilot phase. Note that because patients can belong to more than one subgroup (eg, a participant may be both female and Black and/or Hispanic), the subgroup totals are different than the overall cumulative enrollment.



Canadian sites were selected to participate, of which 65 (61 US, 4 Canada) were activated by the end of the pilot phase, with 43 more in process. Median activation time (defined as the time from receipt of the start-up package to formal activation) was 10.8 (Interquartile range [IQR] 9.1-13.6) months.

In RECHARGE, sites have the option to use a central IRB (Biomedical Research Alliance of New York [BRANY]) or their local IRB; the median activation time was 10.7 (IQR 8.5-13.5) months for sites using the central IRB and 11.3 (IQR 9.7-13.5) months for sites using their local IRB ($P = .38$). These times were longer than expected and were principally attributable to delays in hospital contracting and IRB approval, whereas site activation generally occurred within several weeks after these prior activities were complete. Site start-up fees were, in general, also higher than expected and had a major impact on the trial budget. The median start-up cost (defined as all costs needed for activation) was $9,500 (IQR $9,500-$12,500; range $5,000-$17,000); a few centers with substantially higher start-up costs were rejected from participation.

To establish feasibility for the full trial, the pilot phase enrollment goal was 60 patients (5% of the maximum expected sample size) within 2 years (including all start-up activities). This goal was substantially exceeded, with 141 patients (74 women, 58 Black and 42 Hispanic) randomized within 13 months (Figure 2). The mean enrollment rate per site was 2 patients over the study period or 0.27 ± 0.44 patients/month (ranging across sites from 0 to 2.92 patients/month). This mean rate was substantially lower than that reported in previous PCI vs CABG trials that recruited mostly White men. Based on this consideration, the number of participating sites was increased from 60 to a maximum of 150, and it was decided to include select European sites (for enrollment in RECHARGE:Women only).

Finally, seven peer-reviewed articles were published describing the novelty, scientific rationale for and objectives of RECHARGE,[57-63] and a protocol amendment has been prepared to clarify several of the inclusion and exclusion criteria (including the definition of "equipoise"), to better define the RECHARGE registry (patients who are women, Black or Hispanic and have left main or multivessel disease but are otherwise not randomized), and to further define the statistical methods. However, the core goals and design elements of the original protocol remain unchanged.

Lessons learned, challenges, and ongoing activities

Despite the preliminary work done in the design stage, several enrollment barriers became evident during the

pilot phase, which are being addressed during the full phase of the trial recruitment.

Concerns regarding enrollment feasibility and endpoints

After PCORI funding was publicly announced, several trialists and investigators (even some who agreed to participate) raised concerns about the inclusion and exclusion criteria, being skeptical about the feasibility of enrolling patient groups that have been traditionally difficult to engage. Others were concerned about the study's primary outcome, as compared with the traditional MACE endpoint of prior PCI vs CABG trials. To directly address these preconceived issues and biases, a systematic process of engaging detractors to better understand their concerns was undertaken. These efforts not only reassured the investigators but also contributed to the development of the broader professional education efforts described above. These activities will be continued during the full phase.

Site selection and eligibility issues

To enhance generalizability and equity, RECHARGE implemented strategies to enroll a broadly representative population, including: (1) recruiting from both urban academic medical centers and community, rural, and safety-net hospitals; (2) including sites that serve patients who are Medicaid-insured, uninsured, or non-English-speaking; (3) designing the trial with few exclusion criteria to maximize eligibility; and (4) collecting detailed data on social determinants of health to enable rigorous assessment of representativeness.

Site-level infrastructure challenges to enrollment

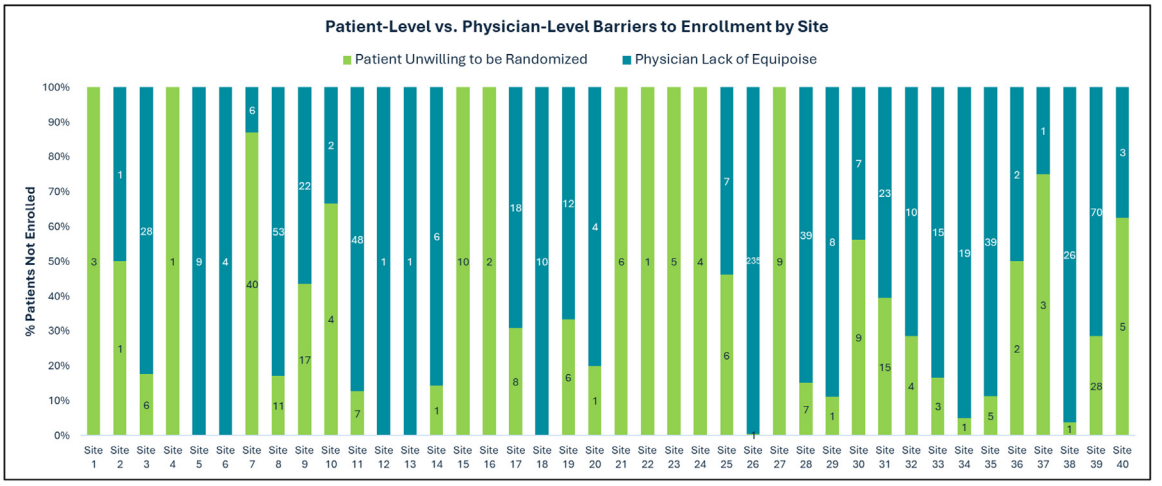
The patient populations targeted by RECHARGE are often treated at non-academic medical centers that emphasize clinical care but often do not participate in academic research and frequently lack a robust research infrastructure. While including those sites was critical to assuring enrollment and generalizability, they required more financial and educational support than larger, more experienced, academic medical centers. To support these sites and maintain consistent study performance, the coordinating center uses centralized monitoring procedures, including routine review of missing visits and incomplete case report forms through an internal study dashboard, as well as regular reports from the centralized follow-up center on visit completion and follow-up status. These processes have helped identify operational gaps early and direct additional support across heterogeneous sites. Future clinical trials recruiting diverse populations should consider the additional costs and logistical support required to support practices that are less experienced in clinical research.

Another key revelation was the way in which revascularization strategies are often selected in routine clinical care for patients with chronic stable coronary disease. While most sites have structured multidisciplinary Heart Teams including surgeons, interventionalists, and general cardiologists for valvular heart disease, formal Heart Teams for coronary artery disease rarely exist (at least in the United States), despite contemporary guidelines emphasizing their importance.[82] Emphasizing the lack of prior clinical trial evidence leading to equipoise in selecting between PCI and CABG in many women, Black and Hispanic patients, a key effort in RECHARGE has been to encourage sites to develop better processes for constituting Heart Teams to collaboratively review coronary cases. This effort was met in some cases with resistance due to substantial logistical challenges in changing "the way things are done." Encouragingly, however, feedback from some sites has indicated that instituting these recommendations has led to better interdisciplinary interaction and improved communication (beyond RECHARGE cases) in managing complex coronary disease. The RECHARGE trial leadership continues to reinforce the rationale and benefits of multidisciplinary care and communication.

Physician-level challenges to enrollment

Given the paucity of dedicated comparative outcome data in women, Black and Hispanic patients, physicians have spent the last several decades applying evidence generated from trials that largely enrolled White men to these under-represented groups. Breaking this entrenched practice has proven to be the greatest challenge to patient recruitment, as reliance on common clinical characteristics (eg, diabetes, ejection fraction, angiographic severity [the SYNTAX score], etc.) that have been shown to differentiate PCI vs CABG outcomes in White men has led to an intuitive sense of how best to treat women, Black and Hispanic patients, even without comparative data from these populations that are known to have worse outcomes with both PCI and CABG. Even less is known as to which revascularization procedure in these under-represented groups might optimize improvement in QOL. Thus, a major initiative of the RECHARGE team has been to highlight this lack of evidence and that equipoise may be present in most RECHARGE-eligible patients with left main or multivessel disease (although ultimately it is up to the local Heart Team to decide whether equipoise is present for each potential individual participant). Regular calls (monthly or bi-monthly) are hosted by the RECHARGE principal investigators and PSAB for all principal investigators and their study teams, regardless of enrollment. During these calls, the nuances of equipoise, logistics, patient communication, and opportunities for improvement are discussed. Strategies for recruitment success that have been effective at the top enrolling centers are shared. Our collective professional responsibility of learning how to best treat such patients in the future has been emphasized, acknowledging the mis-

Figure 3. Site variability in patient vs physician refusal to randomize. The numbers of patients who met all entry criteria but were not enrolled due to patient unwillingness to be randomized (patient-level barrier) vs physician lack of equipoise (physician-level barrier) at each site are demonstrated, the 2 most common reasons for lack of eligible patient participation. Twenty additional sites with no patients who were not enrolled for either of these reasons are not shown.



alignment of economic incentives (procedural-based reimbursement) in some health systems. Collaborative involvement of both interventional cardiologists and cardiac surgeons (each identifying patients that might be sent to the other proceduralist) has been crucial to overcome this issue. A unique and major strength of RECHARGE is the diversity of the investigators both in the leadership committees and at the participating centers. A diverse and motivated team at each site (including both a cardiac surgeon and an interventional cardiologist serving as co-principal investigators) appears to be the single most important determinant of recruitment success.

Patient preference for one or another intervention

Patients often have a strong preference for one or the other tested intervention; during the pilot phase over two-thirds of otherwise eligible patients declined enrollment because of strong treatment preferences, although (perhaps surprisingly) similar proportions preferred CABG (39%) and PCI (42%). Feedback from site calls indicated that these preferences were often established only after patient interactions with referring physicians, interventionalists, or surgeons who strongly suggested one of the procedures. At many sites the most convenient point to identify potentially eligible patients was the initial consultation with a revascularization specialist (interventionalist or surgeon), which may have inadvertently reinforced an expectation, by both patient and clinician, that a specific approach would be pursued. Once the patient and their family had gone through the intellectual and emotional adjustment of accepting one or the other procedure, the willingness to be randomized declined precipitously. This experience illustrates the importance of anticipating treatment preferences in trials of interventions that differ markedly in invasiveness, recovery, and perceived long-term durability. In RECHARGE, the observation that preferences often arose after exposure to a single procedural perspective highlights the importance of the timing and framing of trial discussion as an opportunity to improve enrollment. More broadly, systematically considering treatment preferences may increase enrollment by informing how and when the opportunity to participate in a study is introduced to the patient and by identifying the reasons that otherwise eligible patients decline randomization.[83] Accelerating the timing of discussing potential RECHARGE participation to prior to or immediately after angiography, and having both surgeons and interventionalists presenting the trial together (when possible), have proven to be effective in communicating the equity, safety, and benefits of enrolling.

Figure 3 shows the varying impact of the 2 most important barriers to enrollment at 40 different sites among patients who otherwise met all entry criteria—patient unwillingness to be randomized (patient-level barrier) and physician lack of equipoise (physician-level barrier). The number of otherwise eligible patients not enrolled because of patient unwillingness to be randomized ranged from 0 to 40 per site, whereas the number not enrolled because of physician lack of equipoise ranged from 0 to 235 per site. Non-enrollment at 14 sites was mainly attributable to one of these 2 major barriers, whereas at 26 sites both barriers affected recruitment. These data demonstrate the necessity for center-specific patient (and physician) engage-

ment strategies based on the needs of each participating site.

Despite the extensive preparatory work in launching RECHARGE and the lessons learned to date, the RECHARGE leadership is continuing to discover the best approaches to enroll under-represented patients in clinical trials. Across the sites, the number of otherwise eligible patients who refused to participate in the pilot phase has ranged from 0 to 60. While the initial focus groups interviewed patients who had previously been treated with coronary revascularization, few of these participants had actually faced a decision to be randomized in a clinical trial, especially to such disparate therapies as PCI and CABG. To understand these issues, the PSAB is continuing to work with selected sites to interview otherwise eligible patients who did vs did not choose to enroll. These findings will guide the RECHARGE leadership in further refining its patient-facing materials and to inform sites on how to best approach such patients going forward.

Conclusions

It has long been recognized that certain patient populations are under-represented in clinical trials.[84–86] The traditional reaction to this issue has been to declare that enrollment of these patient groups is a priority. This strategy, while well-intentioned, has typically failed to enhance representation of women and minority group patients in trials that have historically been dominated by White men. As shown in the Graphical Abstract, the RECHARGE trial program has taken a different approach, conducting 2 integrated trials dedicated solely to women and Black or Hispanic patients. With this strategy, characteristics of the trial design and the engagement activities can be more efficiently tailored to the target populations. The resulting trial findings can directly inform culturally-sensitive, evidence-based revascularization choices for women, Black and Hispanic patients, supporting patient-centered clinical decision-making.

As proof of the effectiveness of this approach, ROMA:Women, a CABG trial including only women led by the same trials team, completed enrollment of 2000 participants in 31 months, half the time originally estimated.[87] To date, RECHARGE is ahead of its enrollment goals, and has randomized approximately equal numbers of minority patients and women, a notable achievement given the difficulty of recruiting under-represented minority group patients in prior revascularization trials. While more data and the completion of the full phase of RECHARGE are needed to draw final conclusions, designing trials dedicated to under-represented patient groups, rather than trying to include them in all-comers trials, may be the key to finally providing robust and informative data for these populations. However, as appreciated from the description of the trial activities herein, this has not just "happened," but has required the dedicated efforts of diverse, experienced, and highly motivated leadership and stakeholder groups, entailing substantial time and resource commitments. But the message is "it can be done," and hopefully the realization of RECHARGE will provide much-needed evidence to inform future patients with extensive coronary artery disease (and their caregivers) who have traditionally been under-represented in mainstream clinical research in selecting the optimal revascularization approach to meet their life objectives.

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Conflict of Interest

GWS has served as a consultant to Occlutech, Oxitope, Elixir, Impulse Dynamics, Asceneuron, Myochron, Vesalio, HeartFlow, Colibri, Bioventrix, Abbott, Aria, Adona Medical, Curie Bio, Cardiac Success, Remote Cardiac Enablement, Valfix, Zoll, Shockwave, HighLife, Elucid Bio, Alleviant, FBR Medical, MedHub, Biotyx Medical, Ablative Solutions; and has equity/options from Cardiac Success, Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Valfix, Xenter, Vascentis. GWS's employer, Mount Sinai Hospital, receives research grants from Shockwave, Biosense-Webster, Bioventrix, Abbott, Abiomed, Cardiovascular Systems Inc, Phillips, Pulnovo, V-wave and PCORI (via Weill Cornell Medical Center). DLB discloses the following relationships - Advisory Board: Angiowave, Antlia Bioscience, Bayer, Boehringer Ingelheim, CellProthera, Cereno Scientific, E-Star Biotech, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, NirvaMed, Novo Nordisk, Repair Biotechnologies, Stasys, SandboxAQ (stock options), Tourmaline Bio, Viatris; Board of Directors: American Heart Association New York City, Angiowave (stock options), Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock); Consultant: Alnylam, Altimmune, Broadview Ventures, Corcept Therapeutics, Corsera, GlaxoSmithKline, Hims, SERB, SFJ, Summa Therapeutics, Worldwide Clinical Trials; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research, Boston Scientific (Chair, PEITHO trial), Cleveland Clinic, Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ABILITY-DM trial, funded by Concept Medical; for ALLAY-HF, funded by Alleviant Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials

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Supplementary materials

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