Stroke

ORIGINAL CONTRIBUTION

Health Screening Program to Enhance Enrollment of Women and Minorities in CREST-2

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BACKGROUND AND PURPOSE: The CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial) consists of 2 parallel randomized stroke prevention trials in patients with asymptomatic high-grade stenosis of the cervical carotid artery. The purpose of this report is to detail the outcomes of a health screening effort to increase trial enrollment of women and minorities.

METHODS: Life Line screening (LLS) conducts nationwide screening for vascular disease. Screenings within a 50-mile radius of each CREST-2 center were identified for participation in a joint CREST-LLS program over the course of one year (November 2018 to October 2019) whereby patients with an abnormal carotid ultrasound were referred to the local CREST-2 center for further workup, management, and potential consideration for trial enrollment.

RESULTS: LLS completed the screening of 588 198 individuals in 29 732 zip codes across the United States. Of those, 230 021 individuals were screened at events occurring near a CREST-2 clinical center and 646 (0.3%) were found to have abnormal carotid ultrasound findings. Each of the 646 individuals was contacted by CREST-LLS program staff for permission to be referred to their local CREST-2 center; 200 (31%) consented to be contacted by CREST-2. Of those, 39 (19.5%) agreed to be, and were, evaluated at their local CREST-2 center. High-grade stenosis was confirmed in 27 patients. A total of 3 patients were eligible for the trial and were enrolled, one woman but no racial/ethnic minorities.

CONCLUSIONS: The LLS program appears to identify community-living individuals with high-grade carotid stenosis through ultrasonography. However, the prevalence of abnormal carotid findings was low. In addition, screening and offering participation into the CREST-2 trial had no substantial impact on the proportion of women and minorities enrolled in the trial. Additional innovative strategies are needed to promote enrollment of diverse patients with carotid stenosis into stroke prevention trials.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: carotid arteries ■ carotid endarterectomy ■ carotid stenosis ■ prevalence ■ ultrasonography

Despite major efforts to bolster recruitment of women and minority patients, the percent of women and Black patients has remained low in National Institutes of Health-funded trials related to asymptomatic carotid disease.[1] Similarly, trials pertaining to carotid disease have also historically enrolled far fewer women than men, and proportionately fewer women and minorities than represented in the general population. The Asymptomatic Carotid Atherosclerosis Study enrolled 34% women and 3% Black patients, while the North American Symptomatic Carotid Endarterectomy Trial Collaborators enrolled 31% women and 4% Black patients.[2,3] Barriers to recruitment of a diverse population can exist at multiple levels including sex and racial/ethnic differences in disease prevalence, identification of disease, access to health care and to clinical trials, patient perceptions, and physician/hospital related issues.

The CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial) has striven to address those barriers to enrollment

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Nonstandard Abbreviations and Acronyms	
CAS	carotid artery stenting
CREST-2	Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial
LLS	Life Line Screening

diversity. CREST-2 consists of 2 parallel randomized trials in patients with asymptomatic high-grade stenosis of the cervical carotid artery. The trials compare Intensive Medical Management with or without carotid revascularization by carotid endarterectomy and carotid artery stenting (CAS).[4] As of March 2020, 39.8% of participants are women, 7.2% are Black patients, and 4.3% are Hispanic. These represent the highest rates of women and minorities enrolled in any randomized trial for carotid disease, yet the rates are below the proportion of these groups in the United States population. Hence, with support from the National Institute for Neurological Disorders and Stroke National Institutes of Health, CREST-2 partnered with a private health screening organization to design a nationwide screening program to enhance the diversity of CREST-2 enrollments.

Life Line Screening (LLS) is the nation's largest screening provider identifying asymptomatic adults at risk for serious vascular diseases. Their mobile resources conduct screening events in local communities for over five hundred thousand people across the United States each year. LLS screens in multiple locations across 49 states in the United States. They do not specifically target women or minorities. However, the CREST-LLS program was designed to receive referrals from LLS screenings occurring in a 50-mile radius of actively enrolling CREST-2 centers. A large proportion of CREST-2 centers are located in urban areas with relatively large minority populations. In addition, historically, more women have volunteered to be screened in an LLS screening event than men. Through the CREST-LLS partnership, we hoped to communicate with these screenees and offer them an opportunity to participate in the CREST-2 trial. To the best of our knowledge, this was a unique program without prior precedence. The CREST-2 Executive Committee, therefore, posited that the infrastructure, marketing strategies and geographic reach of LLS could enhance identification of asymptomatic carotid stenosis among women and minorities in the community. CREST-2 centers are recognized leaders in the management of carotid disease. These centers agreed to receive and manage any case of carotid disease identified by the screening program to enhance and expedite access to high-quality care for these patients. The purpose of this report is to detail the outcomes of this national health screening partnership.

METHODS

The authors declare that all supporting data are available within the article. The protocol was reviewed and approved by the Central Institutional Review Board of CREST-2 at the University of Cincinnati and waived the need for patient consent. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and Racial and Ethnic Disparities Reporting guidelines were used to prepare this report (Supplemental Material).[5,6] The LLS screening program involves the conduct of recurring predetermined screening events at multiple locations within local communities across the country. The screenings are performed by rotation whereby the entire country is covered over a 3 to 5 year period before repeating the cycle. Each screening event is preceded by a communications/marketing engagement conducted by the LLS including targeted advertisements by email, local television channels, local radio channels, direct mail, and local newspapers. Each event evaluates 25 to 100 individuals and offers a broad spectrum of screening options for vascular disease including blood pressure measurements, ankle-brachial index measurements, electrocardiography, and blood lipid level assessments. The primary assessment is a duplex ultrasound of the carotid arteries performed on participants that are ≥50 years of age with at least 2 vascular risk factors. Since the screening is voluntary, some patients may return though the vast majority are new screenees. The cost of screening is borne by the participant, by prearranged sponsorships from local businesses or employers, or through coverage provided by union health plans. The cost ranges from $60 to $149, depending on the assessments selected by the participants. Ultrasound screening is performed by trained and certified vascular ultrasound technologists using a standardized protocol and interpreted centrally at LLS by qualified physicians.[7,8] Quality control mechanisms include random and planned audits by LLS sonographers and physicians, monthly reviews, and an annual assessment of competencies by LLS auditors. Participants with a screening ultrasound peak systolic velocity of ≥230 cm/s in the carotid artery are considered to have a suspected high-grade stenosis. Logistics of the study precluded systematic comparisons between screening procedures in the community versus more detailed diagnostic ultrasounds in an academic center. These individuals are provided a note with the screening findings and advised to contact their physician of choice for further confirmation of the diagnosis and appropriate treatment. CREST-2 did not pay for or participate in the communications program, conduct of the screening events, or audits of the program.

The locations of these screening events were geo-coded and mapped onto existing CREST-2 enrolling centers. All LLS screening events occurring within a 50-mile radius of each CREST-2 center (CREST-LLS target sites) were identified for participation in the CREST-LLS program over the course of 1 year (November 2018 to October 2019). The program was piloted with 20 screening events around 10 selected CREST-2 clinical centers (a total of 420 events), and about 12 600 individuals were screened over the first 3 months. The program was then implemented in the remaining CREST-2 centers over the following 9 months.

The aim of the program was to identify potential new carotid disease in the community and to also improve access to care for these individuals. Once an individual was found to have a suspected high-grade stenosis at a screening event, they were

provided the findings and informed about the opportunity to be evaluated at the nearest CREST-2 clinical center. They were requested to provide permission to be contacted by the local CREST-2 center. Participation of screenees was voluntary as was the participation of CREST-2 clinical centers. If a screenee agreed to participate in the program, they were contacted by staff from the local CREST-2 center to set up an appointment in their clinic. They were informed that at this appointment, the primary goal would be further workup to establish a diagnosis and quantify the severity of carotid stenosis. The evaluation could identify disease-severity that warranted medical management alone, or a combination of medical management and revascularization. The evaluation could also result in recommendations for vascular risk-factor management addressing diabetes, hypertension, hypercholesterolemia, weight control, exercise, and smoking-cessation programs. For those participants, that were confirmed to have a high-grade stenosis, the appointment would also afford the physician an opportunity to discuss the opportunity to participate in CREST-2.

χ^2 tests were used to compare the positivity rate of stenosis between sexes, race/ethnicity categories, and their combinations, where males, White patients and White males were the reference categories as appropriate. Fisher exact tests were used if there were cell values of 5 or less. These tests were run in R version 3.6.2 (R Core Team; Vienna, Austria, 2019).

RESULTS

LLS Participants Overall

During a 12-month study period (November 2018 to October 2019), the CREST-LLS program completed the screening of 588 198 unique individuals across 29 732 zip codes in the United States (Figure). Of these, 7500 zip codes were geo-coded to be located within a 50-mile radius of a CREST-2 clinical center participating in the CREST-LLS program (n=101 centers). Across all race/ethnic categories, more women arrived for screening (60.3%, n=138 679) than men (Table 1). Of the 230 021 individuals screened, more White patients were screened than other race/ethnic categories; 78.4% were White patients (n=180 395) and 10.0% were Black patients (n=23 114). The overall rates of abnormal carotid ultrasound findings were <1%, ranging from 0.15% to 0.76%, and varied by race and by sex. The rate for White patients was 0.29%. Compared with White patients, lower rates of stenosis were found for Hispanic (0.20%, *P*=0.08), Black (0.19%, *P*=0.01), and Asian (0.15%, *P*=0.05) patients. Native Americans had the highest rate (0.76%) which was significantly higher than the rate for White patients (*P*=0.01). Fewer women had abnormal carotid ultrasounds (0.23%, *P*<0.001) than men (0.36%). Race/ethnic trends were maintained within sex categories, with Asian women showing the lowest rates overall. The rate of high-grade carotid stenosis for White males was 0.37%. Compared with White males, lower rates were found for Black males (0.21%, *P*=0.03), White women (0.24%, *P*<0.001), Black women (0.19%, *P*<0.001), Hispanic women (0.14%, *P*=0.002), and Asian women (0.11%, *P*=0.005). Native American males had the highest rates of stenosis (1.15%, *P*=0.03) which was significantly higher than the rate for White males (*P*=0.03).

Participants Suspected of High-Grade Stenosis

A total of 230 021 individuals were screened at events conducted by LLS in these selected zip codes and 646 were found to have carotid ultrasound findings consistent with a suspected high-grade stenosis (peak systolic velocity ≥230 cm/s). Each of these individuals was contacted by CREST-LLS program staff for permission to be referred to their local CREST-2 clinical center and 200 (31.0%) consented (Figure). On being contacted by the local CREST-2 center, 51 of the 200 did not respond despite 3 attempts (2 by telephone and 1 by mail) and 110 decided to meet with their own physician. The main reasons for this decision were preference to go to their own physician (n=87), or the location of their own physician was closer than the CREST-2 center (n=23).

Evaluation at Local CREST-2 Center

The 200 individuals with who consented for potential participation in the CREST-2 screening program varied by race and sex (Table 2); 90.5% were White (n=181), 5% were Black (n=10), and 52.0% were women (n=104). Only 39 agreed to participate in the CREST-LLS program and came to a CREST-2 center for evaluation. Each of these was a newly diagnosed carotid stenosis. Those evaluated included 33.3% women, 87.2% White, and 7.7% Black patients.

A total of 39 individuals agreed to be evaluated at the local CREST-2 center and followed through with an evaluation. Of those, 12 were found to have a carotid artery stenosis <70%; appropriate management was recommended, incorporating pharmacological, risk-factor, and lifestyle interventions. The remaining 27 were diagnosed with a carotid stenosis ≥70% and were evaluated for potential participation in CREST-2. Of these, 22 elected to continue their medical care with a vascular specialist recommended by their primary care physician and subsequently underwent carotid artery revascularization (n=7 carotid endarterectomy, n=10 CAS, and n=1 modality not known) or nonoperative management (n=4). In addition, 2 patients were found to be ineligible for participation in the trial (n=1 prior radiation to the neck and n=1 atrial fibrillation). The remaining 3 patients were found to be eligible for the trial (Figure), were successfully enrolled and randomized (n=2 to the CAS trial and n=1 to the carotid endarterectomy trial), and continue to be followed in the trial. One of these patients was a woman, and none were racial/ethnic minorities.

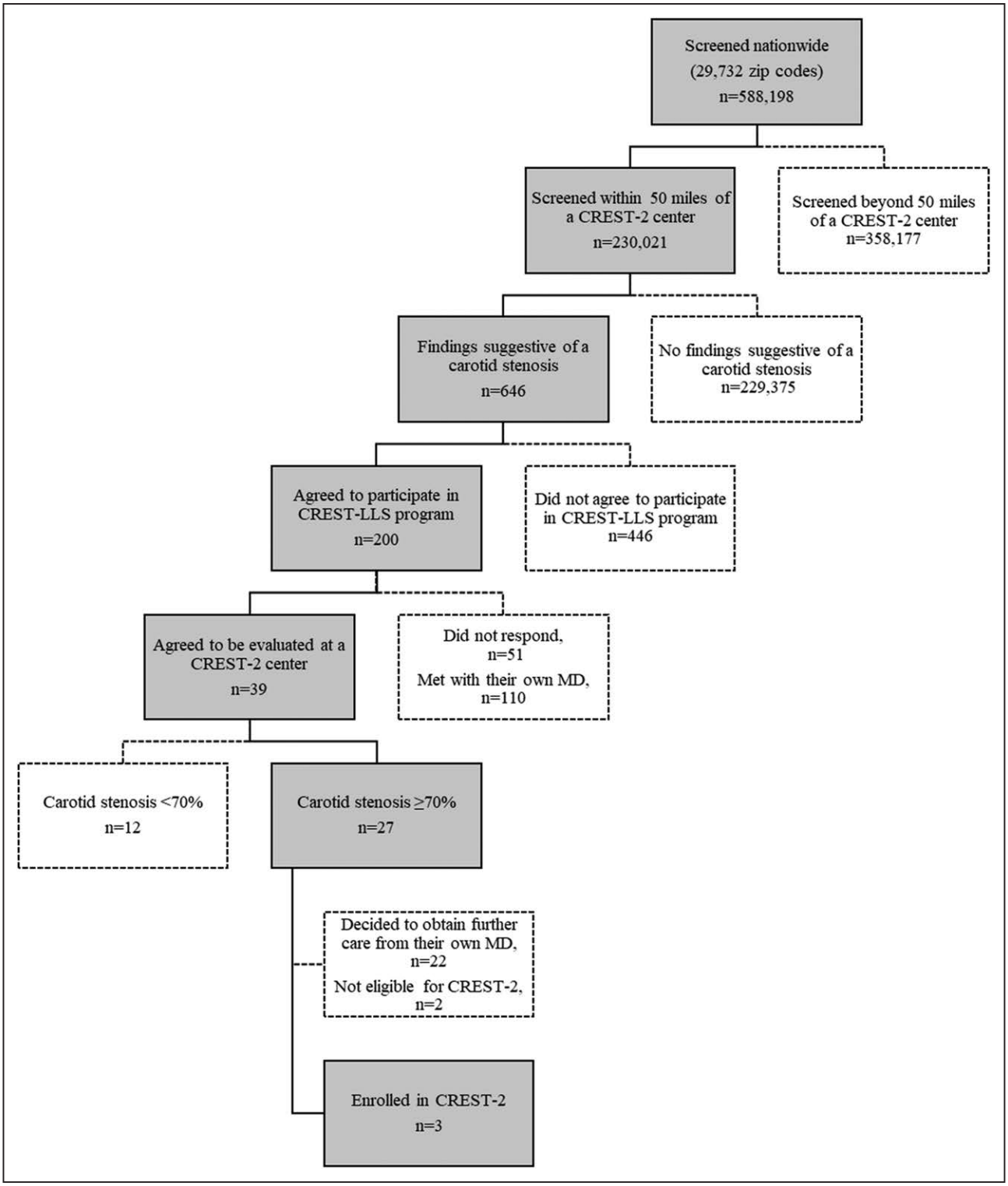

Figure. Flow diagram for patients screened in the CREST (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial)-Life Line Screening (LLS) program.

DISCUSSION

The CREST-LLS program was successful in identifying undiagnosed carotid stenosis in the community though the prevalence was low. After screening 230 021 individuals over 1 year, 646 unique new individuals with suspected carotid stenosis were identified because of the screening program. However, the CREST-LLS program did not substantively enhance enrollment of participants into CREST-2 overall and did not result in a substantive change in the proportion of women or racial/ethnic minorities enrolled into the trial. Ultimately, only

Table 1. Screening Results of All Participants Stratified by Race/Ethnic Category and Sex

Race/ethnic category	No. of carotid screenings	% positive	Sex					
			Male			Female		
			No. of carotid screenings	No. of positive findings	% positive	No. of carotid screenings	No. of positive findings	% positive
White	180 395	0.29%	72 674	272	0.37%	107 721	256	0.24%
Black	23 114	0.19%	8086	17	0.21%	15 028	28	0.19%
Hispanic	11 996	0.20%	4683	14	0.30%	7313	10	0.14%
Asian	6182	0.15%	2511	5	0.20%	3671	4	0.11%
Native American	1059	0.76%	434	5	1.15%	625	3	0.48%
Other	7275	0.44%	2954	14	0.47%	4321	18	0.42%
Total	230 021	0.28%	91 342	327	0.36%	138 679	319	0.23%

3 patients were successfully enrolled into the trial. All enrollees were White, and only 1 was a woman.

The fact that we were trying to enhance recruitment into a trial that tests the utility of an invasive procedure (either stenting or endarterectomy), may have had some bearing on the low yield of the partnership with LLS in terms of generating new trial enrollees. Patients who self-refer for screening for carotid atherosclerosis may be more focused on prevention through diet and exercise rather than through invasive procedures. Referral of newly identified patients with carotid stenosis from LLS to a trial with no interventional arm may be more fruitful.

Interventions to improve enrollment of women and minorities into clinical trials have primarily focused on expanding access to patients with known disease.[9] Efforts have mainly concentrated on identifying and enlarging referring physician pools to facilitate the transfer of patients with known disease to an appropriate specialist who could then introduce the option of trial participation. There are, however, limited opportunities to expand the actual pool of patients by identifying undiagnosed disease, and this remains an unmet need. The preexisting LLS infrastructure and its ongoing screening program had the potential to identify new cases of carotid stenosis and thereby expand the pool of patients. The CREST-LLS program was indeed instrumental in identifying 646 unique new individuals with suspected carotid stenosis, though it was unsuccessful in convincing them to enroll in the randomized trial.

Access to health care remains a key challenge for racial/ethnic minorities.[10] Limited access is a barrier to delivering appropriate medical care. This barrier also limits participation of minorities in high-quality clinical trials. The CREST-LLS partnership was formulated as an attempt to overcome this barrier by offering direct referrals and access to physicians with expertise in the management of carotid disease who could then offer an opportunity to participate in CREST-2. The first step in this process was to obtain permission from each individual, so they could be contacted by the local CREST-2 center. All 646 screenees were approached, but only 31.0% (200/646) agreed to be contacted. The contacts were made by well-trained nonmedical LLS staff telephone operators with a scripted communication, with language modification for the lay public, but medical staff from CREST-2 centers may have met with better success because of their ability to answer clinical questions. However, Health Insurance Portability and Accountability restrictions precluded sharing of screenee contact information without their permission, so these contacts could only be made by LLS staff. This represents an interesting and challenging tension between 2 social goals: personal privacy and equity of access. Since the cost of the ongoing screening activities could not be defrayed by the trial administration, it is possible that this also contributed to

Table 2. Response Counts Stratified by Race/Ethnic Category and Sex

Race/ethnic category	No. positive findings suggestive of stenosis		No. agreed to be contacted		No. agreed to participate and arrived for evaluation		No. with high-grade carotid stenosis		No. enrolled	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
White	272	256	88	93	23	11	17	7	2	1
Black	17	28	4	6	2	1	1	0	0	0
Hispanic	14	10	0	2	0	1	0	1	0	0
Asian	5	4	1	0	1	0	1	0	0	0
Native American	5	3	1	1	0	0	0	0	0	0
Other	14	18	2	2	0	0	0	0	0	0
Total	327	319	96	104	26	13	19	8	2	1

the exclusion of several patients, especially those with a worse socioeconomic situation.

Research coordinators are on the front lines of site level recruitment, giving them significant influence on the patient composition of clinical trials.[11–13] They, therefore, represent a critical element in trial recruitment. Once screenees agreed to be contacted by the local CREST-2 center, research coordinators and physicians reached out to them to establish a relationship and invite them to come in for an evaluation in their clinic. Less than 20% of LLS screenees that were contacted agreed to come to the local CREST-2 center (39/200). Most elected to be evaluated and treated by their own primary care physician. Once diagnosed with a high-grade stenosis, most of those patients also elected to pursue subsequent care with their own specialty physician. This reflects the power that a preexisting therapeutic relationship has in guiding patient preferences. With these physicians being numerous and spread over a large geographic area, it was logistically impractical and, therefore, impossible for the CREST-LLS program to reach out to each one individually. In addition, travel expenses were not supported for participants, and it is possible that this also incentivized them to pursue their care with local physicians.

The CREST-2 LLS partnership highlighted different recruitment challenges for women versus minorities. More women attended LLS screening events than men (138 679 versus 91 342, Table 1), and more women agreed to be contacted by telephone than men (93 versus 88, Table 2). However, once identified with suspected disease, fewer women agreed to participate in the CREST-LLS program and came in to be evaluated at a CREST-2 center (11 versus 23). Studies indicate that more women are the primary caregivers in a household, and this may contribute to difficulties in finding the time to participate in clinical trials.[14] Despite this, the same proportion of women finally agreed to enroll as men (1 of 7 versus 2 of 17). Ultimately, the program was not persuasive to either women or to men. Participation of racial/ethnic minorities was most affected between the time their screening results were shared with them and their agreement to be contacted for further care at a CREST-2 center. Collectively, the probability of non-White patients agreeing to be contacted was only half that of White patients even when given the opportunity. Even with a national screening program, it was difficult to represent minority populations at every stage of the process down to trial enrollment. This highlights the need to rethink the approach to trial recruitment. It is essential to identify reasons that non-White patients opt out and could include distrust of research, personal, social, financial, or a combination of factors. It is imperative that future trials take their protocols directly to the communities and seek community involvement to set priorities and get buy-in.[15] Another approach would be to favor selection of trial performance sites that have a record of successfully recruiting women and minorities into randomized trials, particularly trials of the same or similar condition and trials of similar interventions (invasive versus noninvasive).

Health Insurance Portability and Accountability restrictions prevented the CREST-LLS team from initiating the first contact with the 646 screenees with abnormal ultrasound findings. We were, therefore, not able to determine specific reasons why 446 of these individuals did not consent to participate in the program. For the 200 individuals who agreed to be contacted by the CREST team, we were able to determine reasons from those not agreeing to visit a CREST-2 center for their care (preferred their own physician or CREST-2 center located too far). Additionally, more men and White patients agreed to come in for evaluation. In retrospect, our questions were not specific enough to determine the reasons underlying differences in acceptance rates between sex and race/ethnic categories. Several additional variables would have enriched this analysis and informed us of factors favoring or preventing participation, but could not be collected due to regulatory limitations. These included sex, race, ethnicity, education level, urban versus rural location, mean income, and marital status.

CONCLUSIONS

The National Institutes of Health clinical trial guidelines require that enrollment of racial/ethnic minorities and of women be sufficient such that the results can provide valid comparison of treatment effect among the groups. A carotid ultrasound screening program did identify undiagnosed disease within the community. Unfortunately, the program did not enhance enrollment of racial/ethnic minorities or women, and most patients elected to pursue medical care within their own health care networks.

ARTICLE INFORMATION

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Disclosures

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