Increasing Diversity in Clinical Trials: Overcoming Critical Barriers

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Abstract: Clinical trial results provide the critical evidence base for evaluating the safety and efficacy of new medicines and medical products. Efficacy and safety may differ among population subgroups depending on intrinsic/extrinsic factors, including sex, age, race, ethnicity, lifestyle, and genetic background. Racial and ethnic minorities continue to be underrepresented in cardiovascular and other clinical trials. Although barriers to diversity in trials are well recognized, sustainable solutions for overcoming them have proved elusive. We investigated barriers impacting minority patients' willingness to participate in trials and—based on literature review and evaluation, and input from key stakeholders, including minority patients, referring physicians, investigators who were minority-serving physicians, and trial coordinators—

The name of the institution where the work reported was done: Merck & Co., Inc.; Association of Black Cardiologists, Inc.; Albert Einstein College of Medicine/Montefiore Medical Center; Queens Heart Institute; National Black Nurses Association; Duke School of Medicine, Center on Biobehavioral Health Disparities; Society for Clinical Research Sites; and National Minority Quality Forum, Washington, DC.

Grant support: Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

Declaration of conflicting interests: LTC, ME and ABP report other disclosures from Merck & Co., Inc outside the submitted work (employees). IP, OA, BJ, LW, MG, CM, CP, GP and JMR have nothing to disclose.

Curr Probl Cardiol 2019;44:148–172.
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2018.11.002

formulated potential solutions and tested them across stakeholder groups. We identified key themes from solutions that resonated with stakeholders using a transtheoretical model of behavior change and created a communications message map to support a multistakeholder approach for overcoming critical participant barriers. (Curr Probl Cardiol 2019;44:148−172.)

Introduction

Clinical research is necessary to generate evidence for the efficacy and safety of new therapies. Some subgroups of patients may respond differently to medical therapies; for example, women may respond differently than men, and members from one racial or ethnic group may respond differently than those from another.[1-3] Therefore, diversity of clinical trial participants is needed to help ensure that the trial population is representative of the patients who will use the medicine or medicinal product and ensure that the results are generalizable. According to a review of 167 new molecular entities approved by the Food and Drug Administration (FDA) between 2008 and 2013, approximately 1 in 5 had differences in exposure, response across racial or ethnic groups, or both.[4] Racial and ethnic minorities have historically been underrepresented in clinical trials,[5] a shortcoming that persists in modern trials. For example, as reported in 2011, African Americans and Hispanics comprised 12% and 16% of the US population, respectively, but only 5% and 1% of trial participants were African Americans and Hispanics, respectively.[6] By 2016, the US population included approximately 13% and 18% of African Americans and Hispanics, respectively.[7] Furthermore, because of changing demographics, more than 50% of the US population is projected to be other than non-Hispanic white by 2045.[7]

Lack of diversity in clinical trials is a moral, scientific, and medical issue.[8] When trial participants are homogenous (eg, primarily 1 gender, race/ethnicity, or age group), findings may be skewed and result in a body of clinical knowledge that is not generalizable. Cardiovascular health and outcomes vary among racial and ethnic groups.[9-11] However, while general scientific knowledge and medical care have advanced substantially in recent years, African Americans, Hispanics, and other US minority groups have benefited less from those advances than their white counterparts.[9-11] Inclusion of diverse participants in clinical research may lead to more robust and complete data that broadens the understanding of racial and ethnic differences in treatment responses[1,2,12] that, in turn, may contribute to reduced disparities in outcomes. However, despite major efforts, including those from the US FDA and the Revitalization Act of 1993, which required that clinical trials funded by the National Institutes of Health include women and minority participants,[13,14] diversity in clinical trials has not substantially improved.[15,16]

Increasing clinical trial diversity in an effective, sustainable, and scalable manner remains a mutual challenge for the pharmaceutical industry, academic institutions, and clinical research overall. Accordingly, we conducted a collaborative study involving members of the Association of Black Cardiologists, individuals from a large research-intensive biopharmaceutical company, clinical trial experts, and other key stakeholders to investigate barriers to minority participation in US clinical trials and to identify potential solutions with respect to implementation and communication. We specifically focused on minority patients, referring physicians, investigators who were minority-serving physicians, and trial coordinators. Our overall goal was to develop potentially sustainable solutions that would benefit all key stakeholders and lead to making diversity in clinical trials a standard part of the clinical research model.

Methods and Results

Study Design and Participants

The study involved an 8-step process. Steps 1-5 (literature review and evaluation, expert interviews, and development of stimuli to address barriers and find solutions) formed the foundation for steps 6-8 (testing the solutions; Table 1). Study participants belonged to 1 of 4 key stakeholder groups: patients, referring physicians, investigators, and clinical trial coordinators. Patients were 35-80 years old with a cardiometabolic condition who belonged to 1 of 3 groups: those who participated in at least 1 cardiometabolic clinical trial, those who were asked to participate but declined, and those who were eligible for clinical trial participation but were not asked to participate. Referring physicians were physicians who referred patients to participate in cardiometabolic trials conducted by others. Investigators were minority-serving physicians who led cardiometabolic trials, and trial coordinators worked with investigators and had cardiometabolic clinical trial recruiting experience (Table 1).

The study was considered minimal risk research. Participants provided informed consent before study participation.

TABLE 1. Description of study steps.

Step	Description of step	Study participants
1. In-depth literature review	Reviewed primary research studies, descriptive studies, review articles, and industry or sponsored projects	na
2. Gap analysis	Identified barriers to recruitment/enrollment, strategies to overcome these barriers, and any respective knowledge gaps	na
3. Expert interviews	Conducted in parallel with steps 1 and 2 to gain further insights	Patients: 9 (3 participated[*], 3 declined[†], 3 eligible[‡]) 4 African-American 3 Hispanic 2 Asian Referring physicians: 2 Investigators: 2 Study coordinators: 2
4. In-depth review and analysis based on Steps 1-3	Reviewed baseline data, prioritized identified barriers, and developed potential communication solutions	na
5. Stimuli development	Stimuli—with respective barriers and potential solutions—were developed for testing with key stakeholders. All stimuli were reviewed for consistency with principles of health literacy	7na
6. Pilot IIR interviews	Stimuli were tested among 6 patients	Patients: 6 (2 participated[*], 2 declined[†], 2 eligible[‡]) 2 African-American 3 Hispanic 1 Asian Referring physicians: 2 Investigators: 2 Study coordinators: 2
7. Field testing IIR interviews	Pilot learnings served as a foundation for optimizing and finalizing the stimuli for field-testing among 30 patients	Patients: 30 (11 participated[*], 7 declined[†], 12 eligible[‡]) 14 African-American

(continued)

TABLE 1 (*Continued*)

Step	Description of step	Study participants
		11 Hispanic 5 Asian (3 aged ≥73 years) Referring physicians: 5 Investigators: 5 Study coordinators: 5
8. In-person patient session	Optimization resulted in use of a more active training video and rotating message order, and grounding of participants in their specific role throughout discussions. Further-optimized stimuli were tested among a single, in-person focus group of 9 patients	Patients: 9 (all eligible[‡]) 4 African-American; age range, 43-73 years 4 Hispanic; age range, 35-72 years 1 Asian: age 46 years
Total (Steps 6-8)		Patients: 45 (13 participated[*], 9 declined[†], 23 eligible[‡]) Referring physicians: 7 Investigators: 7 Study coordinators: 7

IIR, individual instant response; na, not applicable.

[*] Participated in 1 or more cardiometabolic clinical trials.

[†] Asked but declined participation in 1 or more cardiometabolic clinical trials.

[‡] Eligible but not asked to participate in any cardiometabolic clinical trials.

Identification of Critical Barriers to Minority Participation in Clinical Trials (Steps 1-5)

Results were summarized for 3 main audiences (patients, referring physicians/investigators/coordinators, and community) and 2 main areas (barriers to recruitment and enrollment, and strategies [ie, possible solutions] to overcome these barriers).

Based on steps 1-5, we identified 5 critical barrier categories (Fig. 1): (1) *mistrust*: lack of understanding the value, fear, stigma of participating, and communication style of investigator/staff; (2) *lack of comfort with the clinical trial process*: mistrust of process, fear, family members' opinions, and information; (3) *lack of information about clinical trials*: fear and stigma of participating; (4) *time and resource constraints associated*

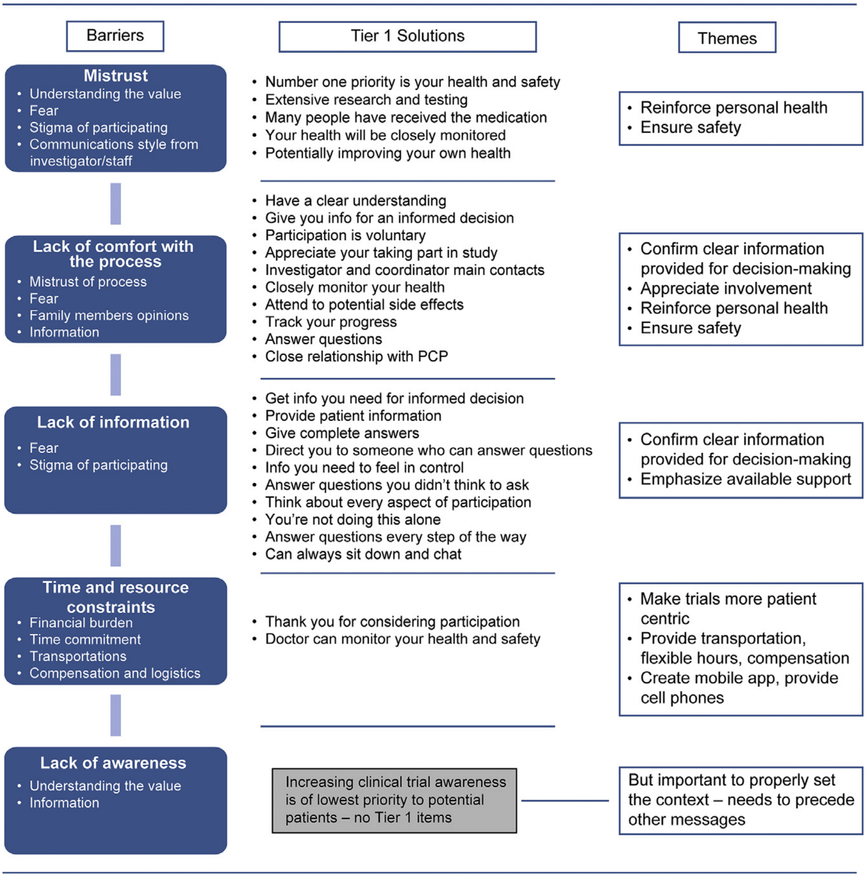


FIG. 1. Patient barriers and corresponding solutions used to identify major themes. PCP, primary care physician.

with clinical trial participation: financial burden, time commitment, transportation, and compensation and logistics; and (5) *lack of clinical trial awareness*: understanding the value and information (lack of awareness about the existence and importance of clinical trials). Detailed results from steps 1 to 5 are provided in the Appendix and Table S1.

Solutions for Critical Barriers to Clinical Trial Participation (Steps 6-8)

During the pilot phase (step 6), stimuli were tested among 6 patients, and learnings from this phase served as a foundation for optimizing and finalizing the stimuli for field testing among 30 patients (step 7).

Optimization resulted in use of a more active training video and rotating message order, and grounding of participants in their specific role throughout discussions. Further-optimized stimuli were tested in a single, in-person focus group of nine patients (step 8) using the dial methodology, where dials displayed a second-by-second, word-by-word measurement of patients' reactions (details provided below).

Testing Processes. Combinations of dial reactions (from pilot and field testing individual instant response [IIR, online] sessions and instant response [IR, in-person] sessions) were used to identify which solutions resonated and which did not, and in-depth discussions were conducted to understand why certain solutions resonated while others did not. The IIR and IR sessions were designed to test a wide range of approaches and identify those that elicited positive emotional responses.

Interviews and Discussions. After initial introduction to the IIR technology, patients received a web link directing them to interview videos, beginning with a short test video about how to use the dial (slider) to indicate their responses. Using discussion guides to help facilitate conversations, moderators then conducted 45- to 60-minute telephone conversations with patients, during which they gathered quantitative feedback through the IIR technology and in-depth qualitative feedback through conversation. Follow-up discussion after each video was influenced by each patient's dial reactions. Moderators allowed unaided responses, and then probed, as appropriate, on specific barriers/solutions identified. For patients who did not have computers, moderators read each stimulus during the discussion. All patients then participated in in-person sessions using IR in a focus-group setting, wherein further-optimized stimuli were tested using dial methodology followed by candid discussions.

Stimulus Development and Testing: Tier Assignments. In steps 6-8, stimuli (potential solutions) were built on the knowledge attained during the previous steps, and further tested and optimized at every step based on a 3-tier response (Table 2) per participants' feedback on each solution within each stimulus. For example, in the field-testing phase, investigators expressed concerns about time constraints and implementation issues, and their feedback was incorporated to optimize the stimuli.

A Clinical Trials Roadmap to Success. Following the analyses described above, we conducted an in-depth qualitative assessment of the

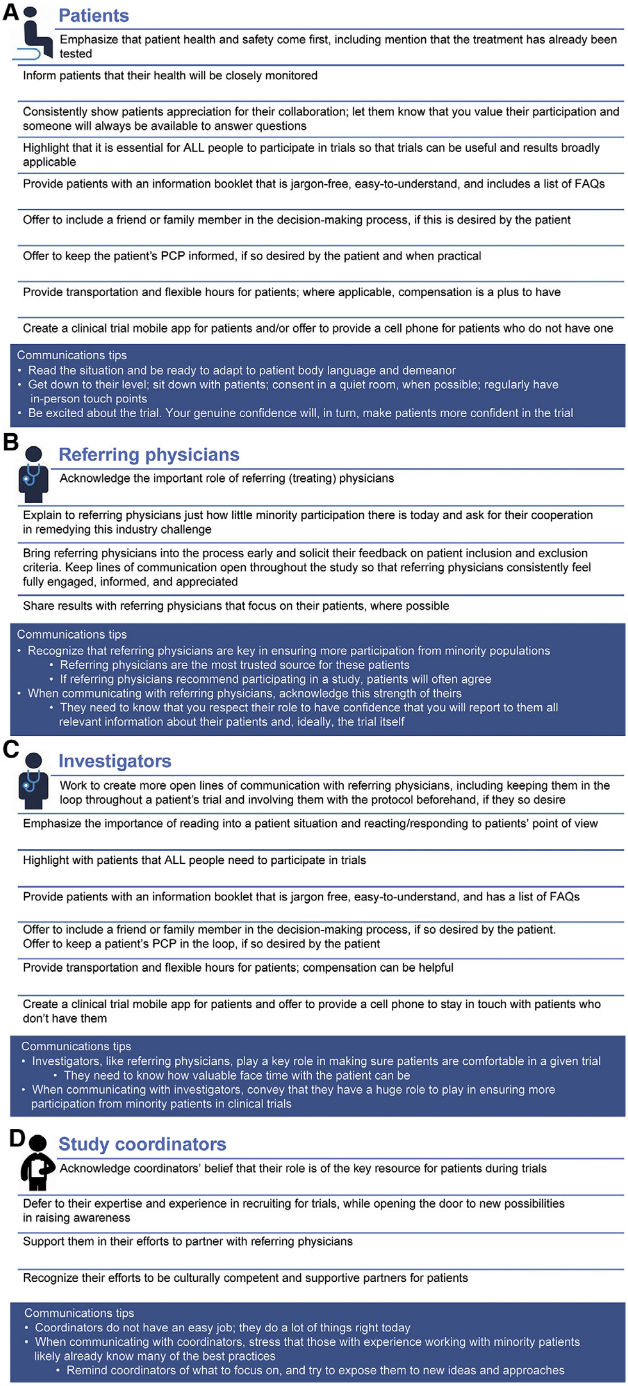
TABLE 2. Tier assignment of stimuli in steps 6-8.

	Positive response	Dial response	Participant recall	Participant alienation
Tier 1	Near uniform	Consistently positive	Consistently high positive	Low/no
Tier 2	Among majority of participants	Consistently positive	Consistently high positive	Low/no
Tier 3	Generally positive reaction	Less positive	Generally positive	Limited

research findings to refine the solutions initially identified. Using a multistep process, we sought to comprehensively analyze patient results for each stakeholder group, develop more specific and nuanced communications, identify segment-specific messages, and guide the flow and staging of the messages. First, each of the barriers initially identified was matched to the corresponding solutions (messages) that consistently resonated across all participants (ie, tier-one solutions; Fig. 1). Next, broad themes were identified among tier-one solutions. Two coders independently determined the themes, and then worked together to achieve consensus on the themes that accurately and comprehensively captured the tier-one solutions. Five themes were identified: reinforce personal health, ensure safety, confirm clear information is provided for decision-making, appreciate involvement, and emphasize available support. Increasing awareness of research studies is needed to set the context for patients and should precede other messages, though increased awareness of trials was of lower priority (not tier one) for potential patients. Overall solutions that resonated well across stakeholder groups and corresponding communication tips are shown in Fig. 2. Segment-specific stimuli testing results are provided in the Appendix.

Following this step, we applied a "message-mapping" technique that is used frequently in the public health sector[17] to the themes and solutions. Message mapping provides a clear, evidence-based script for addressing target audiences about a specific issue. Message mapping also provides a concise template for communication that is constructed with the literacy capability of the audience in mind, is easy to follow (provides sufficient information without overwhelming), and can be applied to various dissemination methods (eg, one-on-one discussion, videos, and brochures). Typically, message mapping presents the key messages, along with 3-5 supporting and specific facts.

In the present application, the key messages were the themes identified, and the specific facts were the tier-one solutions. The original solutions were modified to be at a sixth-grade reading level (using Flesch



A

Patients

Emphasize that patient health and safety come first, including mention that the treatment has already been tested

Inform patients that their health will be closely monitored

Consistently show patients appreciation for their collaboration; let them know that you value their participation and someone will always be available to answer questions

Highlight that it is essential for ALL people to participate in trials so that trials can be useful and results broadly applicable

Provide patients with an information booklet that is jargon-free, easy-to-understand, and includes a list of FAQs

Offer to include a friend or family member in the decision-making process, if this is desired by the patient

Offer to keep the patient’s PCP informed, if so desired by the patient and when practical

Provide transportation and flexible hours for patients; where applicable, compensation is a plus to have

Create a clinical trial mobile app for patients and/or offer to provide a cell phone for patients who do not have one

Communications tips
- Read the situation and be ready to adapt to patient body language and demeanor
- Get down to their level; sit down with patients; consent in a quiet room, when possible; regularly have in-person touch points
- Be excited about the trial. Your genuine confidence will, in turn, make patients more confident in the trial

B

Referring physicians

Acknowledge the important role of referring (treating) physicians

Explain to referring physicians just how little minority participation there is today and ask for their cooperation in remedying this industry challenge

Bring referring physicians into the process early and solicit their feedback on patient inclusion and exclusion criteria. Keep lines of communication open throughout the study so that referring physicians consistently feel fully engaged, informed, and appreciated

Share results with referring physicians that focus on their patients, where possible

Communications tips
- Recognize that referring physicians are key in ensuring more participation from minority populations
  - Referring physicians are the most trusted source for these patients
  - If referring physicians recommend participating in a study, patients will often agree
- When communicating with referring physicians, acknowledge this strength of theirs
  - They need to know that you respect their role to have confidence that you will report to them all relevant information about their patients and, ideally, the trial itself

C

Investigators

Work to create more open lines of communication with referring physicians, including keeping them in the loop throughout a patient’s trial and involving them with the protocol beforehand, if they so desire

Emphasize the importance of reading into a patient situation and reacting/responding to patients’ point of view

Highlight with patients that ALL people need to participate in trials

Provide patients with an information booklet that is jargon free, easy-to-understand, and has a list of FAQs

Offer to include a friend or family member in the decision-making process, if so desired by the patient.
Offer to keep a patient’s PCP in the loop, if so desired by the patient

Provide transportation and flexible hours for patients; compensation can be helpful

Create a clinical trial mobile app for patients and offer to provide a cell phone to stay in touch with patients who don’t have them

Communications tips
- Investigators, like referring physicians, play a key role in making sure patients are comfortable in a given trial
  - They need to know how valuable face time with the patient can be
- When communicating with investigators, convey that they have a huge role to play in ensuring more participation from minority patients in clinical trials

D

Study coordinators

Acknowledge coordinators’ belief that their role is of the key resource for patients during trials

Defer to their expertise and experience in recruiting for trials, while opening the door to new possibilities in raising awareness

Support them in their efforts to partner with referring physicians

Recognize their efforts to be culturally competent and supportive partners for patients

Communications tips
- Coordinators do not have an easy job; they do a lot of things right today
- When communicating with coordinators, stress that those with experience working with minority patients likely already know many of the best practices
  - Remind coordinators of what to focus on, and try to expose them to new ideas and approaches

reading ease formula[18]) rather than a 10th- to 12th-grade level, which is where many of the initial solutions scored. Two coders worked collaboratively to simplify the messages until reaching a consensus. The simplified messages in each theme in the message map represented the breadth of ideas in the tier-one solutions. The message map for the core messages appropriate for all patients is shown in Table 3.

After isolating the core messages, we identified secondary messages that did not resonate consistently among participants. These messages can be relayed to provide further reinforcement after the core messages have been delivered and understood. Additionally, we identified messages that resonated with specific patient segments, including race, age, and education, which can further reinforce the core messages among specific target groups.

The last step in the process was to determine the optimal cadence in which to deliver the messages. This step was considered essential based on the patient perspective that too many messages could be overwhelming and because each theme may not apply to every individual based on participation readiness. Therefore, the message burden on the health care professional (physician, investigator, or coordinator) recruiting for clinical trials should be limited. We used the transtheoretical model (TTM) of behavior change, which is a model of behavior change readiness first developed during smoking cessation research,[19] to guide this step. The TTM focuses on individual decision-making and models intentional change on the assumption that change in behavior does not happen quickly and decisively but occurs continuously through a cyclical process of readiness. Five stages of behavior change are precontemplation, contemplation, preparation, action, and maintenance, and for each stage of change, different intervention strategies or communications are most effective at moving a person to the next stage.[20] The TTM has been successfully used to address a wide array of healthcare applications.

After completion of this phase of research, we aligned the themes and messages with the stages of change (Fig. 3). For example, in the precontemplation stage, the patient needs to hear about context; that is, basic information about a clinical trial. Only then can patients be receptive to the core messages of reinforcing personal health and ensuring safety. In the contemplation stage, the patient knows basic information about a clinical trial but may need reinforcement about the themes of personal health

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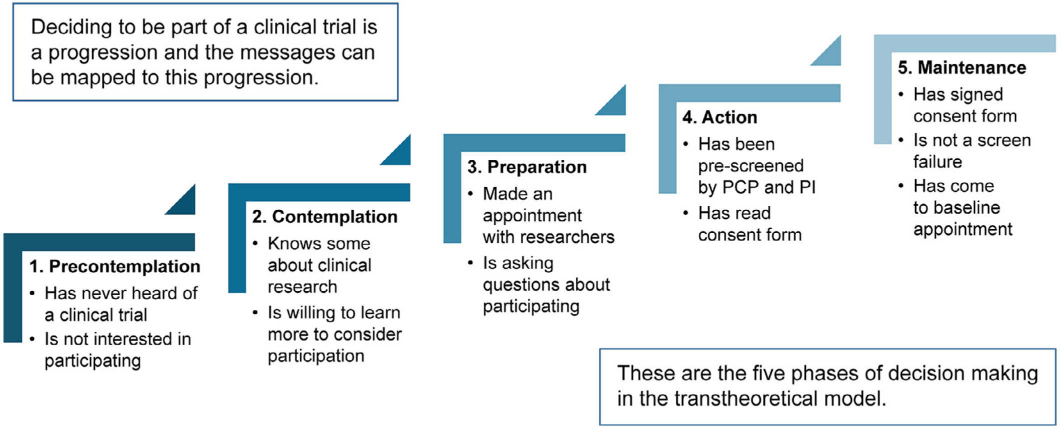
FIG. 2. Solutions that resonated among racial and ethnic minority patients (A), referring physicians (B), investigators (C), and trial coordinators (D).

FAQ, frequently asked question; PCP, primary care physician.

TABLE 3. Core message map.

Explain research studies	Reinforce personal health	Ensure safety	Confirm clear information is provided for decision-making	Show appreciation for involvement	Emphasize available support
Research studies are why we have the medicines we use today	Your health and safety is most important during the study	The medications in this study have already been tested in animals and some people to make sure they are safe	We want you to have all the information you need to make a good decision about being in the study	We thank you for considering taking part in this study	During the study, the study doctor and research staff will be the people you see and call
Your chart shows you would be a very good fit for the study and this study could benefit you	We will watch your health very closely	We will be paying close attention to any side effects that you may have	Your participation is voluntary and you can stop at any time	We will watch how well you are doing in the study and share this with you as we go	We are here to answer your questions and listen to your concerns every step of the way
All types of people need to join studies so that we can know how the medicine works in different people—all ages, all races, men, and women	You may see the study doctor more often than usual so that we can track how well you are doing		You will always get honest answers to any questions	You will know what to expect at all times so you feel in control	Whether you want to sit down and chat in person or over the phone, you'll always have a familiar face to turn to



Deciding to be part of a clinical trial is a progression and the messages can be mapped to this progression.

1. Precontemplation
- Has never heard of a clinical trial
- Is not interested in participating

2. Contemplation
- Knows some about clinical research
- Is willing to learn more to consider participation

3. Preparation
- Made an appointment with researchers
- Is asking questions about participating

4. Action
- Has been pre-screened by PCP and PI
- Has read consent form

5. Maintenance
- Has signed consent form
- Is not a screen failure
- Has come to baseline appointment

These are the five phases of decision making in the transtheoretical model.

FIG. 3. Aligning the messages with the transtheoretical model. PCP, primary care physician; PI, principal investigator.

and safety followed by messages that relay clear information for decision-making. As the patient moves along the continuum of stages of behavior change, other themes can be brought in, the messages can be targeted based on segment, and the secondary messages can be used as needed. For example, a patient may not need to know about transportation arrangements in the precontemplation stage, but this aspect of trial participation becomes important in the preparation or action stage, as they are closer to considering enrollment.

Approaches to Mitigating Potential Errors. In any research setting, an aim is to create an environment as close to reality as possible. Potential errors and corresponding mitigation strategies to minimize the impact on outcomes were identified (Table S2).

Discussion

In this study, we reaffirmed well-known critical barriers impacting the willingness of minority patients to participate in clinical trials, identified solutions for overcoming the barriers by direct testing with key stakeholders, and developed a multistakeholder roadmap designed to enhance sustainable success.

Barriers

Using a multistep approach that included an in-depth literature review, gap analysis, and expert interviews, we identified 5 critical barriers to participation of racially and ethnically diverse patients: mistrust, lack of comfort with the clinical trial process, lack of information about clinical trials, time and resource constraints associated with participation, and lack of awareness about the existence and importance of clinical trials. Identification of solutions for overcoming barriers that resonated with key stakeholders (Fig. 2) was a crucial aspect of the study because effective communication requires not only an understanding of research and the importance of research but also the perspectives, values, and preferences of key stakeholders. Solutions that best resonated with patients and other key stakeholders were broadly characterized as fitting into 1 of 3 broad categories: (1) mistrust, including lack of information about and comfort with the research process; (2) logistical barriers such as time and resource constraints; and (3) limited clinical trial awareness.

Trust, Mistrust, and Trustworthiness. In the present study, as in other published studies,[21-25] lack of trust in research and the research community and fear of being a "guinea pig" were major barriers to clinical trial participation. Trust and trustworthiness of the profession, professionals, and system are important considerations during communications and collaborations between researchers and minority groups.[26] Communications and partnerships with trusted individuals and community groups (eg, providers, community leaders, and faith-based community) in a manner that is effective, transparent, and culturally appropriate helps build trust.

The ultimate decision regarding clinical trial participation rests with the patient, and our findings indicate that while a number of factors are important considerations, patients are most concerned with obtaining the best treatment for their disease. In addition, the decision about whether to participate may also be influenced by family and close friends. Therefore, reassuring patients about the importance of their health and safety, reinforcing that their health will be closely monitored, and including family members in decision-making should increase comfort with the clinical trial process (Fig. 2). These results reinforce the recommendations in a recent report from the American Cancer Society,[27] which emphasized the importance of efforts to increase trust by using input from patients to help design and conduct clinical trials that are more patient centric, and engaging and partnering with community leaders and community-based organizations to effectively disseminate information about clinical trials and the importance of research participation. The issues of trustworthiness and trust/mistrust are critical and pivotal aspects of developing and restoring effective communication and collaboration with minority populations.[26]

Logistics, Time, and Resource Constraints. In addition to the aforementioned factors, logistical and financial considerations influence a patient's decision to participate in clinical research. The significance of these constraints as important participant barriers was affirmed in the current study. Patients are often concerned about the cost of research participation even though sponsors and/or insurers usually cover costs. In 1 review, cost concerns were identified as the second most frequent reason for not participating in clinical trials.[28]

Solutions related to logistical considerations that resonated with patients and investigators (Fig. 2) included providing transportation, flexible hours for patients, appropriate compensation, and mobile technology support such as an app for patients and cell phones for those who do not have one. Identification of the benefits of technology reinforces current trends and opportunities provided by the increasing use of mobile technology and social media platforms (eg, improved communication between researchers and trial participants).[29]

Addressing patients' logistical and financial challenges may not only increase the likelihood of participation but also may increase satisfaction and improve the overall experience of research participation. Collecting and incorporating input from patients—a unique feature of this study—and focusing on their needs and priorities will help make research more patient centric and contribute to overcoming one of the critical barriers to participant diversity.

Clinical Trial Awareness. Lack of clinical trial awareness and information, as well as appreciation of their value, are key critical barriers to minority participation. Results of our research affirm and amplify the importance of effectively communicating and providing information that ensures potential participants understand the importance of the research and the research process. All key stakeholders involved in the clinical trial process, particularly the patients' treating physicians—often key gateways to participation—should understand and be comfortable with the clinical research process and be able to effectively communicate that process to potential participants. Increasing awareness during the precontemplation and contemplation stages of behavioral change helps set the context for further stages of change and likely will increase clinical trial participation.

Roles of Key Stakeholders

Referring Physicians. The results of our study reinforce the findings of others and of national surveys that physicians are consistently rated as the most trusted source of information for patients[30,31] and, therefore, represent a key path to communicating with them and recruiting them for participation in clinical trials. Patients who are advised by their providers to participate in a clinical trial are considerably more likely to enroll than those who are not.[30] However, physicians may lack incentives or face their own barriers to referring patients for trial enrollment, including practical considerations such as lack of the time required to explain clinical trials to their patients, concerns that clinical trial participation may interfere with the physician-patient relationship, and lack of comfort with obtaining informed consent and/or explaining clinical trials to their patients.[32] Physicians are "trusted voices" for patients; therefore, they should be knowledgeable about, comfortable with, and able to effectively communicate the importance of considering participation in clinical research and describe the clinical trial process. The solutions, messaging, and roadmap developed as part of this study highlight the importance of referring physicians (Fig. 2) and provide a structured, understandable guide to support recruitment and enrollment of diverse trial participants.

Investigators. Investigators are key stakeholders in the clinical trial process and can be meaningful contributors to increasing diversity. As a result of our findings, we suggest that investigators and all stakeholders involved in the clinical trial process incorporate an Inclusive Clinical Trials Implementation Checklist (Table 4) to address the barriers to minority participation in clinical trials at a local and national level. This checklist mirrors several core recommendations from the cancer clinical trial stakeholder community.[27]

Coordinators and Clinical Trial Teams. Clinical trial coordinators play a critical role in the clinical trial process. Referred by some as the "invisible hand,"[33] they perform dozens of activities, including assistance with recruiting, explaining the study, obtaining participant consent, maintaining the clinical data, and coordinating with clinical facilities (hospitals, clinics, laboratories). Importantly, they also serve as the main contact person for participants. Trial coordinators and their site teams, from the patients' perspective, represent the "face of the trial" and are vital for recruitment, enrollment, and retention, as well as the participants' overall clinical trial experience. Lack of cultural competency by principal investigators, coordinators, or site staff was identified as an important barrier to minority participation in our study. In addition to practicing cultural competency, participants identified several strategies that investigators and trial coordinators can employ to improve patient interest and retention in clinical trials: a cultivated rapport with participants; attentiveness and sensitivity to patients' concerns or needs; flexible scheduling to accommodate participants after hours and on weekends; postvisit follow-up telephone calls to assess participants' well-being and address any concerns; and regular touch-base contacts with participants. Based on our findings, keys to successful communication between trial coordinators and patients include being knowledgeable and confident about the trial; showing enthusiasm about the trial and patients' participation; being available, accessible, and willing to discuss concerns and answer questions; showing warmth and compassion; making patients feel welcome and appreciated; and connecting with the patient.

TABLE 4. Inclusive clinical trials implementation checklist*.

Building trust	
Do the investigator and trial coordinator have ongoing communications and true partnerships with "trusted" individuals and community groups (eg, providers, community leaders, and faith-based community) in a manner that is effective, transparent, and culturally appropriate for their service area?	✓
Common understanding of the goal	
Do all stakeholders involved in the clinical trial process or recruitment, accrual, and retention understand the goal of attracting and retaining a representative study population?	✓
How does the sponsor demonstrate this commitment throughout the clinical trial process?	✓
Is this information communicated during investigator meetings?	✓
When is this communicated, and how and by whom is it reinforced?	✓
Clinical trial awareness	
Do all key stakeholders involved in the clinical trial process, particularly the patients' referring physician and trusted community leaders, understand and have comfort with the clinical research process and awareness of resources (available from sponsors, national patient organizations, and local sources) to assess eligibility and participation and consent?	✓
Are all stakeholders able to effectively communicate and reinforce the process of a clinical trial as a treatment option to potential and ongoing participants?	✓
Do all stakeholders have this information in a format that is health literate and accessible?	✓
Optimizing the role of the study coordinator	
Does your program have clarity of the role of designated study coordinator(s) with all stakeholders (importantly, the primary provider care partners and community partners) to ensure understanding of patient situation and new questions so that they can proactively and quickly address situations in a manner that is effective and coordinated?	✓
Does the study coordinator ensure that the appropriate leaders are engaged to thank the patients for their participation throughout the study (before, during and completion)?	✓
Addressing resource and time constraints	
Has the investigator unit had a discussion with sponsor(s) or patient organizations and other local resource sources for anticipated and ongoing support measures for patients (such as travel, housing, parking, and child or elder care)?	✓
Do patients and care partners know to ask the study coordinator about resources available to them in the recruitment stage so that this does not become a barrier to ongoing participation or retention?	✓

* Suggested for use by multiple stakeholders: clinical trial investigators, primary provider, sponsors, health care professionals, trial coordinators, community leaders, patients, and care partners.

Sponsors. Sponsors also can play a crucial role in overcoming barriers to participant diversity in clinical trials, beginning with their own recognition and appreciation of the moral and scientific value of diversity, and communicating the importance to investigators and clinical trial site teams. Sponsors can increase diversity in clinical trials by implementing solutions identified in our study through collaborations and partnerships with key stakeholders, community and civic organizations/leaders, and the faith-based community. During investigator meetings, sponsors can increase awareness of the importance of diversity and the corresponding scientific and educational rationales, as well as provide appropriate culturally sensitive and health-literate educational materials to be used during recruitment, enrollment, and retention activities. Sponsors should also establish partnerships and collaborations with appropriate community organizations to increase awareness, participant and community trust, and trustworthiness of their organization and industry.

Multistakeholder Approach. Another important finding of the current study was the identification and recognition of the enhanced value of a multistakeholder approach to increasing diversity in clinical trials because barriers and corresponding solutions often exist across the key stakeholders. A coordinated, multistakeholder approach will likely result in more effective, sustainable solutions than strategies focused on a single barrier or a single stakeholder. Our approach and resultant roadmap may also serve as a tool for enhancing the success of existing partnerships and collaborations addressing clinical trial diversity such as (1) the national education program launched in 2013 by National Minority Quality Forum, Microsoft, and Pharmaceutical Research and Manufacturers of America, designed to engage underrepresented populations and increase awareness about clinical trials[34] and (2) the partnership between the pharma company Eli Lilly and the National Center for Bioethics in Research and Health Care at Tuskegee University to determine how to reestablish trust of the African American community and the medical research establishment through research, education, and community engagement.[35]

Implications

While the FDA, National Heart Lung and Blood Institute, industry sponsors, and others have taken important steps to address the challenges of clinical trial diversity, progress has been limited. A unique feature of our research and its potential to contribute to greater success is that recommended solutions resulted from direct feedback and input from minority patients and other key stakeholders who participate in and conduct the research. Key stakeholders have important roles and responsibilities—which should not be abdicated—in overcoming participant barriers. A multistakeholder approach, collaborations, and partnerships may provide the greatest opportunity for effective and sustainable success. Our roadmap to success is based on solutions that resonated across stakeholders and should provide maximum opportunity for success.

Study Limitations. Though this study provided a unique opportunity to learn and develop solutions based on input from patients and other key stakeholders, an inherent limitation of qualitative research is that it is exploratory in nature and intended to be hypothesis generating. Thus, the conceptual framework and roadmap proposed here should be further tested in quantitative research. Another limitation of the present study is that the number of participants was small and limited only to African Americans, Hispanics, and Asian patients. Other minority and nonminority groups were not included. Also, the therapeutic areas of focus were limited to cardiovascular and cardiometabolic conditions. Although the key findings and the roadmap may be generalizable across therapeutic areas, they were not specifically tested outside the cardiometabolic setting.

Conclusions

Racial designation in the US is primarily a social rather than biological construct and is a poor proxy for genetics.[36] However, differences in health outcomes based on race and ethnicity are real and have been extensively documented. To ensure that medical discoveries, new treatments, and interventions are applicable to all populations for whom they are intended, appropriately representative clinical trial diversity is a moral, scientific, and medical imperative. This successful research collaboration involved a multistakeholder approach with a focus on all key clinical trial stakeholders (patients, investigators, referring physicians, and clinical trial coordinators). Through the collaborative effort, we identified potential actionable and sustainable solutions for overcoming multiple critical barriers to recruitment of racially and ethnically diverse patients. Industry and academic investigators alike should find the results of this study valuable as they develop strategies for increasing diversity in their own clinical trials.

Acknowledgments

Medical writing assistance was provided by Vidula Bhole, MD, MHSc, and Maribeth Bogush, PhD, of Cactus Communications. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. The study would not have been possible without the study participants. The authors would also like to acknowledge Michael S. Wolf (Northwestern University School of Medicine, Chicago, IL) for his review and input on all material communicated with patients to ensure consistency with principles of health literacy, Maslansky + Partners for assistance in developing the interview guides and conducting the interviews and in-person focus groups, and Judith Greener, PhD (Inside Edge; Princeton, NJ) for her contributions in developing the message map and this paper is dedicated to the memory of our coauthor, colleague and friend, Christine Pierre, based on the collaboration that she incited and inspired in the field of diversity in clinical trials through her passion, friendship and memorable leadership of the Society for Clinical Research Sites.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2018.11.002.

Appendix: Methods and Results

Barriers and Potential Mitigation Strategies Identified by Literature Review and Expert Interviews

Overall, 64 publications were included in the gap analysis. Main findings of the literature review are summarized in Table S1.

The major patient barriers included overall mistrust of process, lack of understanding the value of clinical research, fear, stigma of participating, family members' opinions, financial burden, time commitment, and transportation. Barriers related to communication style from investigator/staff, information, compensation, and logistics were also identified in expert interviews.

Investigator or coordinator barriers were addressed in very few articles, and these articles primarily focused on how patient concerns or perceptions of research (the trial is too burdensome for the patient, patient has comorbidities or other issues that may interfere with study) affect recruitment by physicians. Some concerns may be protocol driven, and therefore legitimate, while the literature cites other patient-driven concerns (patient will be nonadherent or patient will not enroll if asked) that are related to investigator bias.[37-39] Association of Black Cardiologists physicians expressed that primary care physicians are reluctant to refer patients because they are concerned that patients may not return to their practice for treatment after the study. Also, appropriate incentives for referring physicians to become involved in clinical trials are lacking. The view of the trial coordinator has rarely been explored in the literature. One study, which included the views of the coordinator, centered on time constraints related to measurement-intensive studies as being an overriding concern for staff.[40] Barriers to research in the community or involving community outreach overlapped with the patient barriers.

Solutions for Critical Barriers to Clinical Trial Participation (Steps 6-8)

Segment-Specific Stimuli Testing Results. Age-specific findings showed that patients aged ≤ 55 years were highly interested in flexible and extended hours and cell phone apps to mitigate time and resource constraints. In contrast, covering transportation costs, altruistic reasons for participating in clinical trials, and directly addressing historic events, such as the Tuskegee Syphilis Study, which may lead to concerns about participating in clinical trials resonated well with those aged >55 years.

Referring physicians, investigators, and coordinators indicated that their African American patients were more likely than those of other races to express reluctance about participating in clinical trials, possibly because of mistrust, lower education level, and socioeconomic factors. Although not mentioned as a major concern by referring physicians, investigators, or coordinators for their Hispanic or Asian patients, during patient interviews, some patients did express their own mistrust or their perception about mistrust prevalent within their community as it relates to the clinical trial process and, more generally, the medical community.

Patient and other study participants indicated that higher levels of education (beyond high school) and understanding of clinical trials correlate with greater willingness to participate in clinical trials, and higher-educated patients value altruistic reasons more than less-educated patients. Patients from lower socioeconomic backgrounds were more likely to be unfamiliar and skeptical of clinical trials and were more likely to be focused on their own health.

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Clinical trials are the main tool in evaluating the safety and efficacy of new treatments. The impact on efficacy and safety may also differ among populations depending on sex, age, race, ethnicity, lifestyle, and genetic background and therefore diversity in the patient population included is paramount. However, racial and ethnic minorities continue to be underrepresented in clinical trials. Although the barriers by which there is lack of diversity in clinical trials are well recognized, solutions for overcoming them have been difficult to pin down.

Several perspectives can be taken from this excellent collaborative research effort that involves all the stakeholders in designing and performing clinical trials in diverse populations.

First, the authors designed an eight-step process to address diversity in clinical trials. Steps 1 to 5 (literature review and evaluation, expert interviews, and development of stimuli to address barriers and find solutions). These steps formed the foundation for steps 6 to 8 which that were created to test possible solutions that were evaluated across stakeholder groups.

Second, the authors identified the importance of a multi-stakeholder approach in order to increase diversity in clinical trials. The latter is clearly related to the fact barriers and solutions often exist across the key stakeholders. Thus, a coordinated, multi-stakeholder approach will likely result in more effective, sustainable solutions than strategies focused on a single barrier or a single stakeholder.

Finally, the authors approach and resultant roadmap will also become a tool for enhancing existing partnerships and collaborations that address clinical trial diversity. Despite that there have been some progress from FDA and others in increasing diversity in clinical trials, a unique feature of these solutions reported herein is that the data results from direct feedback and input from minority patients and other key stakeholders who participate in and conduct the research. A multi-stakeholder approach, collaborations, and partnerships (patients, referring physicians, investigators, and clinical trial coordinators) may provide the greatest opportunity for success.

In conclusion, the utilization of a trans theoretical behavior model across stakeholder in clinical trials creates a communications message map to support this approach for overcoming critical participant barriers.

I like to congratulate the authors for this interesting and meaningful study in creating diversity in clinical trials that I hope in turn will achieve better results for efficacy and safety of new innovations and treatment across all populations.