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ORIGINAL RESEARCH

Recruitment of Black Adults into Cardiovascular Disease Trials

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BACKGROUND: Although disproportionately affected by cardiovascular disease, Black adults remain underrepresented in clinical trials. The National Institutes of Health recommends that studies define goals for recruitment of underrepresented populations. However, the extent to which cardiovascular trials incorporate evidence-based recruitment strategies in their protocols is understudied.

METHODS AND RESULTS: We systematically reviewed National Institutes of Health-funded cardiovascular clinical trials registered in ClinicalTrials.gov between 2000 and 2019. Based on publicly available or requested protocols, we focused on enrollment of Black adults as well as the following recruitment strategies: community-based, electronic medical record-based, and provider-based recruitment. A total of 100 clinical trials focused on cardiovascular disease were included in our analysis, of which 62% had published protocols, and 46% of trials had enrolled populations that were <25% Black. In our analysis of available trial protocols, 21% of trials defined a recruitment target for underrepresented groups; however, only one study reported achieving its enrollment goal. While 13% of trial protocols referenced community-based recruitment strategies, 5% explicitly mentioned involving community members in the trial design process. Defining recruitment targets was associated with higher enrollment of Black participants.

CONCLUSIONS: Black adults are underrepresented in National Institutes of Health-funded cardiovascular trials, and the majority of these trials did not specify a Black enrollment target, did not meet targets, and largely did not report specific plans to enroll Black adults in their studies. Future interventions should target trial design and planning phases before study initiation to address these enrollment disparities.

Key Words: cardiovascular disease ■ recruitment ■ race and ethnicity ■ disparities ■ meta-analysis

See Editorial by Lakdawala

Cardiovascular disease disproportionately affects Black communities within the United States.[1] However, Black adults have been underrepresented in clinical trials.[2] This ultimately results in the care of Black adults being informed by data from predominantly non-Black participants. There is an even greater dearth of trials specifically focused on Black adults. In 2018, 6.2% of hypertension trials enrolled on ClinicalTrials.gov specifically focused on Black participants.[3] There is a critical need to increase the enrollment of Black participants in clinical trials to ensure that the scientific literature guiding clinical practice better reflects the diversity of individuals in the United States.

Prior efforts to understand lower participation by Black adults have focused on individual or community characteristics: mistrust, transportation, or socioeconomic factors.[4–7] However, investigators also play a critical role during the study design phase by defining recruitment goals and formulating recruitment strategy to meet those goals. In 1994, the National Institutes of Health (NIH) Policy and Guidelines on

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CLINICAL PERSPECTIVE

What Is New?

- The underrepresentation of Black adults in cardiovascular disease trials is well-documented.
- Our systematic review is the first to examine the role of trial protocols to accrue diverse research participant populations.
- Among National Institutes of Health-funded cardiovascular disease trials registered on ClinicalTrials.gov, few studies explicitly defined goals for recruitment of Black participants or described recruitment strategies aimed at underrepresented groups in their protocols; furthermore, defining recruitment targets was associated with better representation of Black participants.

What Are the Clinical Implications?

- Recruitment is a critical part of a trial's success that is ideally developed in the design and protocol development phase to create a diverse and representative participant population.
- Both at the institutional and national level, more work needs to be done to standardize protocols to include recruitment strategies and recruitment goals for underrepresented groups.
- This would ensure that representation remains a priority throughout trial implementation.

Nonstandard Abbreviations and Acronyms

EMR	electronic medical records
NIH	National Institutes of Health

the Inclusion of Women and Minorities as Subjects in Clinical Research emphasized setting targets for recruitment of underrepresented populations to ensure adequate power for subgroup analysis.[8] Furthermore, evidence-based research strategies are essential to raise awareness and improve access for participation in clinical trials. These include defining minority recruitment goals and active strategies such as community-based participatory research and recruitment by healthcare providers.[9–13] Community-based participatory research strategies allow for the inclusion of local stakeholders in the trial design process and potential opportunities for co-authorship. Newer recruitment strategies such as electronic medical record (EMR)-based recruitment have also been developed in recent years; however, there are few studies evaluating their efficacy for recruiting Black participants.[12] In fact, there has not been a review to date that characterized the use of these methods among cardiovascular clinical trials.

As such, the objectives of this systematic review were to (1) characterize the representation of Black adults in NIH-funded cardiovascular trials in the United States over the past 20 years (since 2000), (2) identify recruitment strategies associated with greater representation of Black participants among the trials with published protocols, and (3) examine trends in recruitment of Black participants over time. We hypothesized that the following key features developed during the design phase are critical to success: (1) setting a recruitment target for Black participants and (2) involving communities in the trial design process to ensure Black participants are reached during the trial recruitment campaign.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. The protocol for this systematic review was registered on International Prospective Register of Systematic Reviews database on November 4, 2020 (Data S1). This systematic review was determined by the institutional review board at Beth Israel Deaconess Medical Center to be non-human subjects research.

Search Strategy

On 11/07/2020, we searched ClinicalTrials.gov for NIH-sponsored interventional cardiovascular disease trials that were completed between January 1, 2000 and December 31, 2019 with ≥1 clinical site in the United States, and ≥1 intervention assignment. Our decision to require that the trials be NIH-funded was based upon the NIH's focus on the inclusion of women and underrepresented groups in its funded research since 1994.[8] The Food and Drug Administration also issued similar guidelines in 2016; however, given its narrow time frame of applicability, we excluded trials that were only subject to the Food and Drug Administration guidelines, such as industry-funded trials.[14] The specific search query is available in Data S2. Two authors (A.P., A.P., O.O., or Y.W.) independently reviewed each trial to determine eligibility for our review, with a primary and secondary reviewer assigned to each trial. We excluded trials enrolling participants aged <18 years, those that did not assess a cardiovascular disease end point, cluster-randomized design trials, ancillary trials, trials that did not require informed consent because of an emergency treatment setting, trials that did not report race categories per NIH guidelines,[15] trials that studied a condition affecting a small subgroup of the population, or trials that enrolled <100 participants. Additionally, we excluded trials that began before 2000, which was when ClinicalTrials.gov was initiated.

Recruitment Strategies

Characterization of recruitment strategies was restricted to the subset of trials with protocols. If protocols were not available on ClinicalTrials.gov or as a publication or supplemental material in a peer reviewed journal, trial investigators or corresponding study authors were contacted via email. If no response was received, 1 follow-up attempt was made per investigator or author. Recruitment strategies of interest included active recruitment, passive recruitment, use of community-based recruitment, EMR-based recruitment, and healthcare provider referrals. Active recruitment was defined as any strategy involving direct outreach to potential participants initiated by the research team as opposed to passive recruitment, where participants had to initially express interest from information obtained from flyers/radio advertisements, etc. Community-based recruitment was defined by use of community spaces and/or community members outside of the medical institutions conducting research to recruit participants.

Data Extraction

Two reviewers (A.P., A.P., O.O., or Y.W.) independently extracted data of qualifying trials from results reported on ClinicalTrials.gov, available protocols, and their primary publications, if applicable. Discrepancies were adjudicated by consensus. Trial characteristics extracted included study period, location, inclusion of non-English speakers, goals for minority representation, and actual reported demographic data of participants. Additionally, recruitment strategies and inclusion of subgroup analyses by sex, race, and/or ethnicity were noted where available. Ethnicity and race data were categorized following NIH guidelines.[15]

Statistical Analysis

We summarized trial characteristics and recruitment information derived from published papers or protocols if available. We tabulated characteristics of the trials by timeframe of enrollment, type of intervention, distribution of female participants, and distribution of White and Black participants. Percentage categories for female and Black participants were derived from percentages of these populations as described in the 2010 US Census and chronic disease burden reported in non-Hispanic Black adults. We used a benchmark of 25%, which is approximately equivalent to the burden of mortality in cardiovascular disease among Black adults.[16,17]

We assessed whether specifying a minority recruitment target or using specific recruitment strategies (ie, community-based, EMR-based, or provider-based recruitment) were associated with a greater proportion of Black enrollees by tabulating recruitment characteristics of trials by the ultimate proportion of Black participants who were enrolled. We performed subgroup analyses based on whether there were publicly available protocols and stratified by percentage of Black participants enrolled. To assess if proportion of Black participants or use of recruitment modality varied over time, we tabulated these characteristics by timeframe.

We quantified the proportion of Black participants enrolled, the number of trials with or without minority recruitment targets, and the number who did and did not meet those recruitment targets, using mosaic charts by timeframe. Analyses used Stata SE 16.1 (StataCorp, College Station, TX). We considered a 2-sided $P<0.05$ to indicate statistical significance without adjustment for multiple comparisons.

Results

Among the 156 trials identified on ClinicalTrials.gov, 54 were excluded for 1 of the prespecified eligibility criteria and 2 for starting trial enrollment before 2000 (Figure 1). The total number of trials analyzed was 100, and among those, 62% (62 of 100) of trials had protocols available. Forty-six percent of trials reported enrolling <25% Black participants. There are also notable gaps in reporting participant demographics, as 24% (24 of 100) of trials did not specify what percentage of their trial population identified as Black. Additional characteristics of included trials are detailed in Table 1.

Overall, 21% (13 of 62) of trial protocols explicitly mentioned target goals for recruitment of historically underrepresented populations, with 1.6% (1 of 62) of trials reporting that it met the goal for recruitment of Black participants (Table 2); 71% (35 of 49) of trials that did not define recruitment goals and 90% (1 of 10) of trials that did not meet defined recruitment goals had study populations that were <25% Black (Table 2). All of the trials (100%) that did not report race or ethnicity data of participants also did not specify recruitment goals for underrepresented groups. In terms of recruitment strategies, 90% (56 of 62) reported active recruitment strategies including EMR-based recruitment (29 of 62 trials, 47%), community-based recruitment (8 of 62 trials, 13%), and provider-based recruitment (36 of 62 trials, 58%) (Table 2). Five percent (3 of 62) of trial protocols explicitly mention involving community members in the trial design process and 3% (2 of 62) of trials had community members outside of academic medical institutions as co-authors.

We did not observe a significant change in the recruitment of Black adults between 2002 and 2017

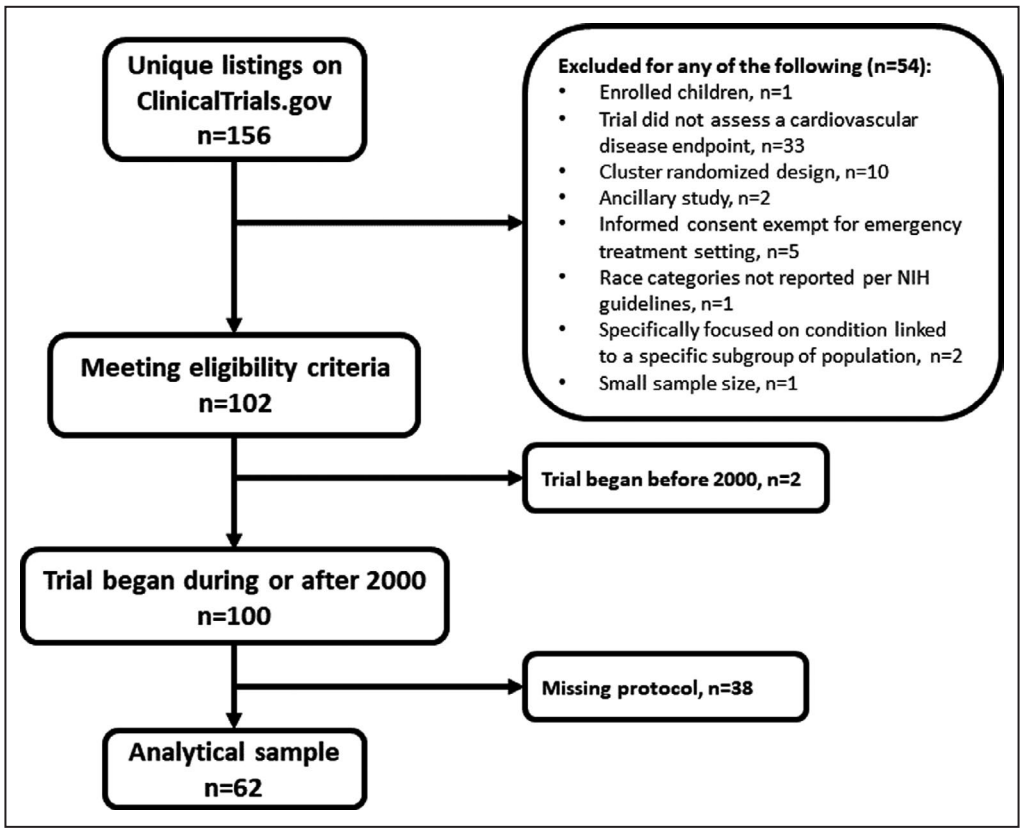

Figure 1. Preferred reporting items for systematic reviews and meta-analyses diagram showing the flow of study selection.*
NIH indicates National Institutes of Health. *Small samples were trials enrolling <100 participants.

(Table 3, Figure 2A). Additionally, there were no significant changes in the number of trials defining enrollment targets and use of community-based or EMR-based recruitment strategies (Table 4, Figure 2B). Notably only 1 trial explicitly documented achieving recruitment goals for Black participants during this period (Figure 2C).

Discussion

This systematic review identified critical gaps in the representation and recruitment of Black adults in NIH-funded cardiovascular disease trials. Beyond inconsistent reporting of participant race, there is still significant underrepresentation of Black participants, which has not improved over time. Trials that did not define recruitment targets often had inadequate representation of Black participants. There were a wide variety of recruitment techniques used across the trials reviewed; however, despite these recruitment techniques, there was overall low representation of Black adults in NIH-sponsored clinical trials. Furthermore, there is limited publicly available data to evaluate the use of recruitment strategies such as community-based and EMR-based recruitment over time.

A common critique of clinical trials is the inclusion of study populations that are not representative of diverse populations. Trials have historically underenrolled non-White adults including Black, Hispanic, American Indian/Alaskan Native, Asian, and Native Hawaiian/Pacific Islander populations.[2] This limits the generalizability of their findings. In response to inadequate representation in biomedical research, in 1994 the NIH recommended that historically underrepresented populations be adequately represented in trials to enable analyses of differential effects of an intervention between subgroups. The NIH also recommended that study proposals discuss recruitment plans for underrepresented groups.[8] However, for 35 novel cardiometabolic drug trials between 2008 and 2017, Black participants represented only 4% of the total trial participant pool, despite representing 13.4% of the US population[16,18] and despite the disproportionate burden of cardiovascular disease among Black adults.[17] The most recent update in 2017 to these guidelines specifies that phase III trials are required to report subgroup analyses to ClinicalTrials.gov.[19] The current state of representation in clinical trials described in our systematic review suggests a continued need for such policies and increased measures of accountability.

Table 1. General Characteristics of Systematic Review

	Protocol Not Obtained	Protocol Obtained
	n=38	n=62
Enrollment size, n	159 (127–352)	305 (159–523)
Drug and/or biological intervention?		
Drug and/or biological intervention without other intervention	22/38 (58%)	28/62 (45%)
Drug and/or biological intervention with other intervention that isn't a drug or biological agent	2/38 (5%)	9/62 (15%)
Not drug and/or biological intervention	14/38 (37%)	25/62 (40%)
Behavioral intervention?		
Behavioral without other intervention	6/38 (16%)	8/62 (13%)
Behavioral with other intervention that isn't behavioral	4/38 (11%)	3/62 (5%)
Not behavioral intervention	28/38 (74%)	51/62 (82%)
Device without other intervention	1/38 (3%)	4/62 (6%)
Device with other intervention that isn't a device	1/38 (3%)	4/62 (6%)
Not device intervention	36/38 (95%)	54/62 (87%)
Procedure intervention?		
Procedure without other intervention	0/38 (0%)	5/62 (8%)
Procedure with other intervention that isn't a procedure	2/38 (5%)	4/62 (6%)
Not procedure intervention	36/38 (95%)	53/62 (85%)
Publication available on PubMed	34/38 (89%)	57/62 (92%)
Exclusion of any non-English speakers	4/34 (12%)	6/33 (18%)
Distribution of female participants		
<25%	10/38 (26%)	12/62 (19%)
25% to <50%	14/38 (37%)	37/62 (60%)
50% to <75%	10/38 (26%)	11/62 (18%)
75% to 100%	3/38 (8%)	2/62 (3%)
Missing	1/38 (3%)	0/62 (0%)
Distribution of White participants		
<65%	12/38 (32%)	17/62 (27%)
65% to <80%	9/38 (24%)	17/62 (27%)
80% to <95%	12/38 (32%)	23/62 (37%)
Missing	5/38 (13%)	5/62 (8%)
Distribution of Black participants		
<5%	1/38 (3%)	7/62 (11%)
5% to <15%	3/38 (8%)	19/62 (31%)
15% to <25%	8/38 (21%)	9/62 (15%)
≥25%	11/38 (29%)	18/62 (29%)
Missing	15/38 (39%)	9/62 (15%)

Percentages for breakdown of Black participant representation were based off cardiovascular mortality burden as documented by the Centers for Disease Control and Prevention.[17]

However, even with the NIH recommendations to define recruitment goals for underrepresented groups, only 1 trial in our analysis explicitly defined and documented achieving its target. Additional barriers to recruitment include skepticism in the trial process, limited study referral opportunities attributable to gaps in healthcare and technology access, and lack of recruitment programs focused on the inclusion of underrepresented groups at research institutions.[20–22] Mistrust of research among the Black community is considered a significant barrier to recruitment, fostered in part by a long history of unethical studies conducted on Black patients.[23] Therefore, these barriers highlight the importance of comprehensive recruitment plans during protocol development.

Our protocol-oriented process of evaluating trial recruitment strategies revealed that a large proportion of cardiovascular disease trials do not have publicly available protocols online. ClinicalTrials.gov

Table 2. Recruitment Characteristics of Trials With Protocols by Achieved Enrollment of Black Participants, n=62

	% Black Participants Not Reported	<25% Black Participants	≥25% Black Participants	*P* Value (Fisher exact test)
	n=9	n=35	n=18	
Was a specific minority recruitment target defined?				1.00
No or not reported	9/9 (100%)	26/35 (74%)	14/18 (78%)	
Yes	0/9 (0%)	9/35 (26%)	4/18 (22%)	
Was the defined racial/ethnic minority recruitment met for Black participants?				0.18
No	0/9 (0%)	9/35 (26%)	1/18 (6%)	
Yes	0/9 (0%)	0/35 (0%)	1/18 (6%)	
Missing	9/9 (100%)	26/35 (74%)	16/18 (89%)	
Was recruitment active and/or passive?				0.80
Active	8/9 (89%)	26/35 (74%)	14/18 (78%)	
Passive	0/9 (0%)	1/35 (3%)	0/18 (0%)	
Active and passive	1/9 (11%)	4/35 (11%)	3/18 (17%)	
Missing	0/9 (0%)	4/35 (11%)	1/18 (6%)	
Was there EMR-based recruitment?				0.15
No or not reported	4/9 (44%)	22/35 (63%)	7/18 (39%)	
Yes	5/9 (56%)	13/35 (37%)	11/18 (61%)	
Was there community-based recruitment?				0.42
No or not reported	9/9 (100%)	31/35 (89%)	14/18 (78%)	
Yes	0/9 (0%)	4/35 (11%)	4/18 (22%)	
Was there recruitment by a referring healthcare provider?				0.15
No or not reported	4/9 (44%)	17/35 (49%)	5/18 (28%)	
Yes	5/9 (56%)	18/35 (51%)	13/18 (72%)	
Did the investigators use community input when designing the study?				1.00
No or not reported	9/9 (100%)	32/35 (91%)	17/18 (94%)	
Yes	0/9 (0%)	3/35 (9%)	1/18 (6%)	
Were participants financially compensated, other than for travel?				0.46
No or not reported	7/9 (78%)	27/35 (77%)	16/18 (89%)	
Yes	2/9 (22%)	8/35 (23%)	2/18 (11%)	
Were community members included as co-authors?				0.54
No or not reported	9/9 (100%)	33/35 (94%)	18/18 (100%)	
Yes	0/9 (0%)	2/35 (6%)	0/18 (0%)	

EMR indicates electronic medical records.

The *P* value does not include the "% Black Participants Not Reported" trials. "Missing" indicates not reported in available sources (eg, ClinicalTrials.gov or published results).

requires trials with a primary completion date on or after January 18, 2017 to submit a protocol to their registry. All studies meeting this criterion had protocols, suggesting that this policy has been effective in creating more transparency about clinical research for the general public. Recruitment strategies are a recommended section in the NIH protocol template for clinical trials and represent an opportunity for investigators to formulate goals and strategies for achieving their targeted study population.[24] Nevertheless, among the trials with protocols available, this section was frequently missing, contributing to our observation of absent details related to specific recruitment strategies planned to be used during trials' recruitment campaigns. This was particularly true with regards to strategies intended to increase the enrollment of Black participants.

Table 3. Odds Ratio for Enrollment of ≥25% Black Participants by Timeframe

Timeframe	OR (95% CI)	*P* Value (Pearson Chi-Squared test)
2002 to 2005	Ref	
2006 to 2009	2.25 (0.33–15.33)	0.41
2010 to 2013	2.18 (0.35–13.76)	0.41
2014 to 2017	0.60 (0.07–5.45)	0.65

OR indicates odds ratio.

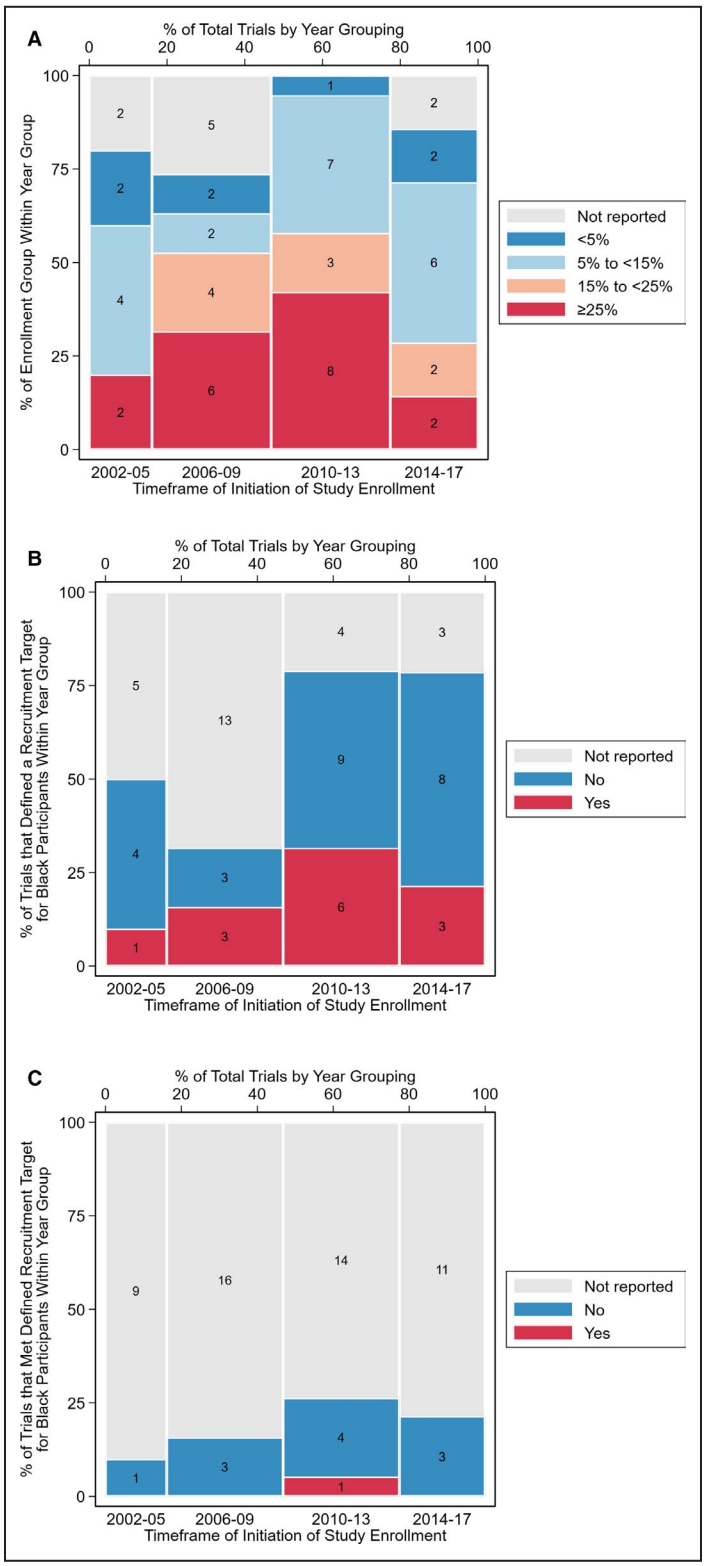

Figure 2. Trends in recruitment of black adults in trials from 2002 to 2017.*

A, Number of clinical trials population composed of Black participants, by timeframe. **B**, Number of studies that defined a recruitment target for Black participants, by timeframe. **C**, Number of studies that met recruitment target for Black participants, by timeframe. *"Missing" indicates not reported in available sources (eg, ClinicalTrials.gov or published results).

Table 4. Recruitment Characteristics of Trials with Protocols by Year Groups

	2002 to 2005	2006 to 2009	2010 to 2013	2014 to 2017	*P* Value (Pearson Chi-Squared test)
	n=10	n=19	n=19	n=14	
Distribution of Black participants					0.40
<25% Black Participants	6/10 (60%)	8/19 (42%)	11/19 (58%)	10/14 (71%)	
≥25% Black Participants	2/10 (20%)	6/19 (32%)	8/19 (42%)	2/14 (14%)	
Missing	2/10 (20%)	5/19 (26%)	0/19 (0%)	2/14 (14%)	
Was a specific minority recruitment target defined?					0.51
No or not reported	9/10 (90%)	16/19 (84%)	13/19 (68%)	11/14 (79%)	
Yes	1/10 (10%)	3/19 (16%)	6/19 (32%)	3/14 (21%)	
Was the defined racial/ethnic minority recruitment met for Black participants?					0.59
No	1/10 (10%)	3/19 (16%)	3/19 (16%)	3/14 (21%)	
Yes	1/10 (10%)	0/19 (0%)	0/19 (0%)	0/14 (0%)	
Missing	8/10 (80%)	16/19 (84%)	16/19 (84%)	11/14 (79%)	
Was recruitment active and/or passive?					0.47
Active	8/10 (80%)	17/19 (89%)	12/19 (63%)	11/14 (79%)	
Passive	0/10 (0%)	0/19 (0%)	1/19 (5%)	0/14 (0%)	
Active and passive	2/10 (20%)	1/19 (5%)	4/19 (21%)	1/14 (7%)	
Missing	0/10 (0%)	1/19 (5%)	2/19 (11%)	2/14 (14%)	
Was there EMR-based recruitment?					0.80
No or not reported	5/10 (50%)	10/19 (53%)	9/19 (47%)	9/14 (64%)	
Yes	5/10 (50%)	9/19 (47%)	10/19 (53%)	5/14 (36%)	
Was there community-based recruitment?					0.25
No or not reported	7/10 (70%)	18/19 (95%)	16/19 (84%)	13/14 (93%)	
Yes	3/10 (30%)	1/19 (5%)	3/19 (16%)	1/14 (7%)	
Was there recruitment by a referring healthcare provider?					0.93
No or not reported	4/10 (40%)	8/19 (42%)	9/19 (47%)	5/14 (36%)	
Yes	6/10 (60%)	11/19 (58%)	10/19 (53%)	9/14 (64%)	
Did the investigators use community input when designing the study?					0.63
No or not reported	9/10 (90%)	18/19 (95%)	19/19 (100%)	13/14 (93%)	
Yes	1/10 (10%)	1/19 (5%)	0/19 (0%)	1/14 (7%)	
Were participants financially compensated, other than for travel?					0.43
No or not reported	9/10 (90%)	16/19 (84%)	13/19 (68%)	12/14 (86%)	
Yes	1/10 (10%)	3/19 (16%)	6/19 (32%)	2/14 (14%)	
Were community members included as co-authors?					0.59
No or not reported	10/10 (100%)	19/19 (100%)	18/19 (95%)	13/14 (93%)	
Yes	0/10 (0%)	0/19 (0%)	1/19 (5%)	1/14 (7%)	

EMR indicates electronic medical records.
N/A is reported when a "No" option is not available. "Missing" indicates not reported in available sources (eg, ClinicalTrials.gov or published results).

Strategies that have been previously identified as successful in the recruitment of Black participants include community-based recruitment involving local stakeholders, recruitment by patients' direct healthcare providers, and participant education about the clinical trial process.[9,10,25] However, our analysis demonstrated a lack of detail on recruitment strategies planned to enroll Black adults, particularly the use of community-based recruitment. This emphasizes the need for more standardization and transparency in trial protocols. At the least, documentation of recruitment strategies makes it possible to study what approaches were effective for including Black adults in clinical trials. Analyses of recruitment strategies and their effectiveness should also be encouraged by funding bodies to facilitate sharing of

effective approaches among investigators. Further, cardiovascular clinical trials would benefit from additional requirements from ClinicalTrials.gov about protocol contents as well.

There are limitations to this review. First, our search criteria were restricted to NIH-funded trials. While our findings are applicable to industry and foundation-funded trials, representation of Black participants may differ from NIH studies where representation has been encouraged since 1994. The Food and Drug Administration only issued its guidelines on representation in 2016, so the majority of industry and foundation-funded trials would not be subject to those expectations.[14] Second, of 50 trials without readily available protocols online, only 22% (11 of 50) of authors responded to our request for their protocol. In addition to non-response, there were instances that the corresponding author did not have an electronic copy of the protocol available because of the timeframe in which the trial was conducted. Further, ClinicalTrials.gov only required protocols to be uploaded for studies completed on or after January 18, 2017. These limitations may have impacted our ability to study trends in recruitment strategy over time, but they also address a key gap in documentation of minority recruitment strategies and outcomes historically. Of note, our interpretation focused on statistically significant results with *P* values <0.05; however, this approach may underplay noteworthy differences that were limited in power by our sample size. Third, there may have been recruitment strategies used that were not identified or reported in the protocol, and therefore, were not included in our analysis. For example, 1 author noted that although the available protocol did not explicitly mention recruitment of women and underrepresented groups, they were extensively discussed during the trial design phase. Fourth, our review did not analyze the underrepresentation of Black women, as several trials did not provide data on the sex distribution of their trial sample by race. Women are also known to be underrepresented in cardiovascular clinical trials.[18,26] Capturing the intersectionality of race and sex in the recruitment of underrepresented groups is an important development for subsequent research. Last, the present study does not focus on other underrepresented groups monitored by the NIH, including Hispanic, American Indian/Alaskan Native, Asian, and Native Hawaiian/Pacific Islander adults. These groups should be a focus of subsequent work.

This study also has notable strengths. This review followed a pre-specified, systematic approach to identify critical barriers in the recruitment of Black adults in cardiovascular disease-related clinical trials. Furthermore, our study focuses on NIH-funded trials, a principal funding body that provides direct guidance for the inclusion, planning, and tracking of demographic characteristics in trials. Finally, our study highlights an actionable aspect of trial implementation and design by focusing on setting recruitment targets for Black adults and delineating recruitment strategies in the design phase.

Our work has implications for clinical trial design. Cardiovascular disease is prevalent among Black adults, yet they are underrepresented. Moreover, the majority of trials had no goal, did not achieve their goal, and did not report plans to enroll Black adults in their studies. While there is a considerable need for research on effective strategies to improve enrollment of Black adults, the first step is for Black inclusion to be a priority at the trial design phase through defined recruitment targets and intentional recruitment strategies. Greater transparency, tracking of recruitment yields by demographic group, involvement of local stakeholders in trial design, and support of recruitment research may also represent long-term strategies to address this tremendous disparity in cardiovascular disease research.

CONCLUSIONS

Black adults are underrepresented in NIH-funded cardiovascular trials. The majority of these trials did not specify a Black enrollment target, did not meet targets, and largely did not report plans to enroll Black adults in their studies. These findings are immediately applicable to ongoing and planned clinical investigations.

ARTICLE INFORMATION

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Supplementary Material

Data S1–S2

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SUPPLEMENTAL MATERIAL

Data S1. Registered PROSPERO Protocol.

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Gaps in Clinical Trial Recruitment Strategies for Underrepresented Groups

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

05/11/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

05/12/2020

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Hailey Miller

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Miller

7. * Named contact email.

Give the electronic email address of the named contact.

hailey.miller@duke.edu

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Duke University

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Yingfei Wu. NYU Langone Health
Dr Stephen Juraschek. Beth Israel Deaconess Medical Center
Dr Timothy Plante. University of Vermont
Miss Anagha Prasanna. Harvard Medical School
Dr Hailey Miller. Duke University

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

National Institutes of Health/National Health, Lung, and Blood Institute

Grant number(s)

State the funder, grant or award number and the date of award

National Institutes of Health/National Health, Lung, and Blood Institute grant: K23HL135273

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Are NIH-funded US clinical trials actively considering recruitment strategies for better representation of underrepresented participants? What strategies are successful at increasing enrollment of underrepresented populations?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

ClinicalTrials.gov (completed between 1/1/2000 and 12/31/2019)

- Results posted on ClinicalTrials.gov
- Study population: adults, older adults
- NIH-funded
- Interventional studies
- Study location in US

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

https://www.crd.york.ac.uk/PROSPEROFILES/218417_STRATEGY_20201101.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Cardiovascular diseases

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria:

- Adults

- Studies with enrollment size /= 100

Exclusion criteria:

- Children

- Cluster randomized trials

- International studies (with no U.S. patients)

- Studies of genetic variants specific to a single racial/ethnic group

- Trials that did not report demographics following the standardized NIH/OMB (National Institutes of Health/Office of Management and Budget) race/ethnicity categories

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Any randomized intervention that involved recruitment of patients or community dwelling adults.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Any study qualifying as a randomized trial with more than 1 intervention being compared where one of the intervention serves as a "control" intervention.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

NIH funded, cardiovascular disease, randomized control trials (any phase) involving adult populations in the U.S. with a sample of /= 100, were completed between 2000-2019, and posted results on ClinicalTrials.gov.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or

exclusion criteria.

Since their introduction in October 1948, clinical trials continue to be the gold standard for providing high quality answers to clinical research questions. One of the primary challenges and costs to conducting clinical trials is recruitment. Recruitment goals are intentional and are based on power calculations estimating the sample required to determine an effect between interventions. It has been estimated less than half of clinical trial meet recruitment goals without extending the length of the trial. This often results in trial failure, underpowered studies, and inconclusive results. Further, non-significant findings increase the risk that evaluation of potentially effective treatments would not be tested. Additionally, clinical trials should represent study populations. Trials have historically enrolled white men, while under-enrolling non-white populations and women. This limits the generalizability of their findings. Features associated with effective inclusion of non-white populations in clinical trials have not been adequately studied. However, we hypothesize that the following specifying the following key features in the study protocol at the design phase are critical to success: (1) setting a recruitment target for non-white participants, (2) having a mechanism that tracks the demographic enrollment of participants throughout recruitment, and (3) utilizing a diverse range of strategies to ensure non-white participants are reached with study recruitment materials.

The objective of this systematic review is to evaluate protocols of cardiovascular trials funded by the NIH and involving adults from the United States to identify features associated with successful recruitment of traditionally under-represented groups, namely, non-white and female populations.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

1) Enrolled population demographic characteristics, namely age, sex, race/ethnicity (following NIH/OMB categories)

2) Overall recruitment success (did the trials achieve recruitment goals)

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Proportion of non-White participants and proportion of female participants in cardiovascular studies, including compared to the U.S. population.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate

to the review

Not applicable

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Aggregated population data will be abstracted from publications or results reports on ClinicalTrials.gov.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

We will assess for publication bias with respect to protocol publication.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

We will summarize trial characteristics and recruitment information derived from published papers or protocols if available. Depending on the data distribution, we will consider performing metaregression of design features in relation to inclusion of under-represented groups with a focus on design characteristics, investigators, and recruitment strategies.

29. * Analysis of subgroups or subsets.

State any planned investigation of ‘subgroups’. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

We will perform subgroup analyses based on time of completion and whether there were publicly available protocols.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis

No

Intervention
Yes

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
Yes

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care

No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

United States of America

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint. List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Data S2. ClinicalTrials.gov Search Query

AREA[OverallStatus] EXPAND[Term] COVER[FullMatch] "Completed" AND AREA[ResultsFirstSubmitDate] NOT MISSING AND AREA[StudyType] EXPAND[Term] COVER[FullMatch] "Interventional" AND AREA[ConditionSearch] Cardiovascular Diseases AND SEARCH[Location] EXPAND[Term] COVER[FullMatch] (AREA[LocationPath] "US" AND (AREA[LocationCountry] "United States" OR CONST[0.95])) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[FunderTypeSearch] EXPAND[Term] COVER[FullMatch] "NIH" AND AREA[PrimaryCompletionDate] EXPAND[Term] RANGE[01/01/2000, 12/31/2019]