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PEER REVIEWED

Overcoming the Barriers to Recruitment of Underrepresented Minorities

Stephanie Lynn Williams, MS, CCRC

Racial and ethnic disparities among research subjects in clinical trials continue to persist despite the changing demographics in the United States.{1} The percentage of racial and ethnic minorities in the general population is steadily growing, but that growth is not reflected in clinical trials. There is vast literature confirming this underrepresentation, and much of it focuses on the existing barriers to subject participation.{2,3} The gold standard for clinical research continues to be randomized clinical trials, yet diversity in these trials remains extremely low and lack of representative sampling continues to be an issue.

In an attempt to correct this underrepresentation, the National Institutes of Health (NIH) mandated the inclusion of women and racial minorities with the passage of the Revitalization Act of 1993.{4} Recognizing the importance of including these groups, the Act was intended to increase the number of women and individuals from disadvantaged backgrounds, including racial and ethnic minorities, in the fields of biomedical and behavioral research and diversify research populations. The Act's intended purpose has not been fully realized, and barriers continue to impact the enrollment of many racial and ethnic minority groups. Some insight as to why the Act has been less effective than anticipated will be discussed in the sections ahead, along with some of the known barriers to recruitment and ways to address these barriers.

Importance of Minority Participation

Racial and ethnic minorities currently make up 38.7% of the U.S. population, but estimates place the rate of inclusion in research studies between 2% and 16%.{5,6} The term racial and ethnic minorities in this context refers to anyone who is not considered "white alone" for purposes of census classification. According to the U.S. Census Bureau, the country's diversity remains on

the rise, with all racial and ethnic minorities growing faster than whites from 2015 to 2016.{7} Minority residents of the U.S. are expected to comprise more than 40% of the nation's population by 2035, 47% by 2050, and 56% by 2060.{8}

The importance of minority participation in clinical trials has been garnering national attention in recent years. Countless articles and opinion pieces have been written on this topic, including a blog post from the U.S. Food and Drug Administration (FDA). As of the post, the FDA was planning a variety of activities to push for greater inclusion, including more minority participation. The author acknowledged FDA's awareness that certain groups of patients may respond differently to different therapies, and that "a wide range of people should have the opportunity to participate in trials, both for access to new therapies and to have the chance to contribute to better treatment of everyone."{9}

In his 2015 State of the Union address, President Obama announced the launch of the Precision Medicine Initiative (PMI), designed to revolutionize the approach to health improvement and disease treatment.{10} The PMI includes NIH's "All of Us" program, an effort to recruit a large research cohort to advance individualized prevention, treatment, and care for people of all backgrounds. One of the core values of the program is that participants reflect the rich diversity of the U.S.{11} National enrollment officially opened for the program on May 6, 2018. The press release announcing the enrollment date stated that "the overall aim is to enroll 1 million or more volunteers and oversample communities that have been underrepresented in research to make the program the largest, most diverse resource of its kind."{12}

There are also economic and social justice reasons for reducing these disparities. Eliminating racial and ethnic health disparities would have decreased U.S. medical costs by more than $1.2 trillion for the years 2003 to 2006. This estimate includes direct and indirect medical costs, such as loss of productivity, as well as the cost of premature death.{13} As of 2015, racial disparities continued to be associated with substantial annual economic losses nationally. Diversity in biomedical research often does not reflect the U.S. population, and in order to remain consistent with the values of our society, health-related disparities caused by this underrepresentation should be addressed.

The NIH Revitalization Act

The Revitalization Act is often referenced when discussing racial disparities and inadequate representation in clinical research. It was seen by many as a culmination of efforts to overcome the lack of representative sampling in clinical trials, and was anticipated to increase the enrollment of underrepresented groups. However, this was not the first act of legislation aimed at increasing enrollment in clinical trials, nor the first act addressing disparities in the health status of racial minorities in the U.S.

The National Research Act of 1974, enacted a mere two years after the public disclosure of the Tuskegee Syphilis Study, established ethical principles to govern clinical research and put protections in place for human subjects involved in research.{14} The Tuskegee Study is commonly perceived as the worst example of medical research exploitation in U.S. history, and was ongoing for 40 years (1932 to 1972). The U.S. government conducted the study on unknowing "subjects"—hundreds of African American men living in the Deep South who were excluded from life-saving treatment while being subjected to clinical testing so doctors could determine the natural progression of syphilis.{15} Unsurprisingly, death and disability for many men and their families resulted. Knowledge of this unethical exploitation contributes to the mistrust that some minority communities still feel today when it comes to research.

Other legislative acts followed, mostly in response to Congressional findings demonstrating a growing health disparity gap among racial minorities.{16} These disparities helped prompt the enactment of the Revitalization Act, which mandated the inclusion of racial minorities in clinical trials as a condition to receive federal funding and required that research participant characteristics be disclosed in research documentation as a way to measure inclusion.{2}

Twenty years after the implementation of the Revitalization Act, researchers assessed minority rates to see if the intended diversification had occurred in cancer clinical trials. The results showed that little progress had been made; the number of cancer trials with a primary emphasis on any racial or ethnic group was found to be less than 2%.{17} To put that in perspective, cancer is the second leading cause of death in the U.S., regardless of race or ethnicity.{18} Less

than 5% of NIH-funded respiratory research reported inclusion of racial and ethnic minorities, and similar rates are found in cardiovascular and diabetes clinical trials.{19}

One major limitation of the Revitalization Act is that NIH guidelines only apply to federally funded trials. From 2006 through 2014, newly registered NIH-funded trials steadily decreased, with a few exceptions, whereas industry-funded trials increased substantially. In 2014, pharmaceutical companies funded 6,550 trials while NIH funded 1,048 trials.{20} A majority of clinical trials leading to drug approvals are funded by pharmaceutical companies which are not held to NIH guidelines and do not require increased enrollment of racial minorities.

Known Barriers to Recruitment

Barriers to recruitment can be identified through a variety of sources. Much research has gone into determining whether minorities are reluctant to participate in clinical research and discovering other barriers. Some of this research focuses on issues of mistrust stemming from past abuses like Tuskegee and the story of Henrietta Lacks, which has seen renewed interest in recent years following the film adaptation of a book about her life and beyond.{21} A poor African American woman, Lacks went to Johns Hopkins for treatment and without her knowledge or consent, her cancer cells were used and have now become one of the most important cell lines in medical research.{22} These types of research abuses involving minorities occurred prior to the establishment of many of the ethical requirements that now govern clinical research.

The identification of barriers to recruitment can come through prescreening interviews, research participant interactions, and literature review. Prescreening interviews are valuable interactions; potential research participants call a research site to see if they qualify for a trial, and while someone may meet the initial qualifications, that person may decide not to participate for various reasons. Those reasons are barriers to participation. Similarly, through participant interactions with enrolled subjects, barriers can be identified. A participant may enroll in a study and then miss visits or discontinue the study prematurely. The reasons why a participant fails to complete a trial can sometimes be barriers to consider. The literature also explores barriers that have been identified.

From the sources mentioned above, some identified barriers include lack of awareness, logistics, mistrust, lack of diversity among the research and clinical professionals, research not being conducted in the community, disconnect between researchers and the community, limited access to specialty centers that refer patients to clinical trials, minorities not being as willing to participate in research, and fear of exploitation in clinical research. Lack of awareness can include a lack of awareness in available trials or of clinical trials as therapeutic options. Logistics can include issues surrounding costs associated with participation, transportation, and convenience. Mistrust can include not wanting to be a "guinea pig" and mistrust of the medical or research fields in general. All or some of these barriers may apply at different times and to different groups, and it is common for some of the solutions addressing these barriers to overlap.

Overcoming Known Barriers

Identifying known barriers is the first step toward addressing them. Awareness of the minority populations in the recruitment area is essential so the appropriate recruitment methods can be employed. Depending on location in the country, minority populations will differ and recruitment considerations may change depending on the population sought.

To address the lack of awareness barrier, there are a number of proposed solutions. Lack of awareness can simply mean that people are not aware of the clinical trials available to them or are unaware that clinical trials are available for numerous medical conditions. Solutions to this barrier include advertising and education. Targeted advertising, for example on public transportation or in advertising forums specific to the targeted population, can be effective. This includes going to community healthcare providers to advertise or to educate providers on available trials, rather than relying on referrals from specialty centers or other medical institutions that may not be where the target population is receiving care. Education can also occur at community health events or town hall meetings.

To address the logistics barrier, concerns such as costs associated with participation, transportation, and inconvenience must be dealt with. Possible solutions to issues concerning cost include ensuring that studies are appropriately budgeted to account for time and commitment expectations.

Another way to address this issue is by providing travel or meal vouchers that may ease the financial burden. Travel vouchers also apply to the transportation barrier along with mindfulness of where the research site is located. Knowing whether a site is along a bus route, if there is ample parking, and if a site is easy to find are all aspects of participation that can be challenging to potential participants if unclear. Some research sites are located on huge academic campuses and can be daunting to someone visiting the institution for the first time, so providing clear directions to the actual location where the trial will be conducted within the institution is also important.

When it comes to inconvenience, extending office hours outside the typical "9 to 5" can allow working participants more flexibility and potentially increase the recruitment population. The option to conduct visits over the phone or at satellite locations can make visits more convenient.

Addressing mistrust really comes down to being transparent about what is being done for a particular trial, like what is expected of the participant, what research questions are being answered, and what benefits and risks are anticipated. Education about the research process and addressing specific concerns are key. Having enough information and knowledge about commonly known research exploitations and acknowledging past abuses if they come up add credibility to the team members conducting the research, and can go a long ways toward gaining the trust of potential participants. Transparency and education are some of the best tools to combat fear of exploitation.

Further, a lack of diversity in the research team has repeatedly been reported as problematic.{23} In the fields of science, technology, engineering, and math (STEM), there is a significant underrepresentation of minority students, resulting in fewer minority scientists and physicians.{24} Efforts to increase the numbers of minorities involved in STEM fields should be made to address this problem. Minority scientists and physicians are more likely to conduct research in minority populations, may more easily be able to gain the trust of those communities, and participants may be more likely to sign up for a clinical trial if the recruiter looks like them.{23}

Ways to address the barrier of a lack of diversity in the research team include recruiting research team members from diverse backgrounds, including community advocates and student workers. Other suggestions include ensuring that language options are available for the target demographic and considering a community-research liaison.

Barriers dealing with research outside the community or disconnect between researchers and the community can be addressed by taking the research project into the community. Attending community health events where researchers can talk to members of the community about available opportunities and allow the chance for questions can be beneficial for recruitment. Setting up mobile offices or establishing satellite locations within the community can also help to overcome this barrier. Researchers who go where the participants are rather than waiting for the participants to come to them may have more success reaching populations that have historically been underserved.

Minorities being less willing to participate in clinical trials may no longer be the barrier it once was perceived to be. Recent research suggests that racial and ethnic minorities are as willing as whites to participate in clinical research.{25} Accordingly, some of the other barriers discussed should be the future focus of increasing enrollment in underrepresented groups.

Conclusion

Increased clinical trial participation by racial and ethnic groups continues to be an imperative endeavor because diseases present differently in different groups of people, certain medications have been proven to be more or less effective depending on racial or ethnic background, and increasing diversity in clinical research will help ensure that medial products are safe and effective for everyone.{26} The NIH Revitalization Act attempted to address some of the racial disparities in clinical trial populations, but limitations have rendered the Act less effective than originally anticipated. Known barriers to recruiting underrepresented groups have been identified and suggested solutions have been proffered. Discovering ways to increase the enrollment of racial and ethnic minorities continues to be an issue worthy of further exploration.

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PEER REVIEWED

African American Screening and Enrollment in the CLEAR III Trial

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By 2050, members of racial and ethnic minorities will represent the majority of the population in the United States.{1} While clinical trials are designed to inform the scientific workforce about the safety, efficacy, and effectiveness of medical strategies, treatments, or devices for evidence-based healthcare decision-making, the under-enrollment of minority patients reduces the generalizability of research findings.{2} Enrolling an adequate proportion of minorities into clinical trials has proven difficult in the past; however, concerted efforts must be made to overcome barriers to enrollment.{3–12} Proportional recruitment practices can provide data about health disparities and better serve the needs of minority populations.

Such is the case with hemorrhagic stroke, a devastating disease with a global mortality of 45%. Recent estimates indicate that 70,000 new hemorrhages occur in the United States each year.{13} Minority patients are disproportionally affected in incidence and severity; African Americans, particularly, have a greater risk, incidence, prevalence, and mortality compared to white Americans.{14–26} Not only does this evidence contribute to the overwhelming economic burden of sustained health disparities, it also suggests a barrier to health equity and social justice.

In 2009, the total direct and indirect cost of stroke in the United States was estimated at $68.9 billion.{17} Minority populations contribute to a significant portion of stroke costs due to higher admission rates, greater severity and mortality, increased disability-adjusted life-years, and loss of productivity from stroke incidence at younger ages.{13,16,27} Enrolling more minorities into stroke trials is an important part of any solution to alleviate the economic burden incurred

through health disparities, improve the generalizability of trial results, and raise the standard of patient-centered stroke care.

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage III (CLEAR III) (ClinicalTrials.gov; NCT00784134), a 500-participant randomized controlled trial evaluation of alteplase in hemorrhagic stroke, presented an opportunity to assess African American (AA) trial enrollment in a hemorrhagic stroke population. As detailed in the following sections, the authors of this paper evaluated the CLEAR III screening and enrollment data to better understand if recruitment efforts provided diversity and, more importantly, to improve recruitment efforts in the future.

Methods

Trial

This Phase III randomized, double-blinded, placebo-controlled, multicenter trial was conducted at 73 sites in Brazil, Canada, Germany, Hungary, Israel, Spain, the United Kingdom, and the United States from 2009 to 2014.{28} The investigators were either neurointensive care or neurosurgical service teams. This was a first-of-a-kind trial; it combined a catheter device with up to four days of intensive care unit (ICU)–based drug treatment.

For the analysis of AA to non-AA participation, we limited the evaluation to U.S. sites. Over a five-year period, investigators across 61 U.S. hospitals screened 8,587 patients (see Figure 1) admitted to ICUs in 42 U.S. cities with stable, small non-traumatic intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH) with a clinical diagnosis of obstructive hydrocephalus, and an extraventricular drain (EVD) placed pre-trial. Participants were randomly assigned to receive alteplase (Genentech, Inc.) or normal saline (placebo) via the EVD.

Subjects

Participants were aged 18 to 80 years with known symptom onset within 24 hours of the initial CT scan. CT scans were obtained every 24 hours throughout dosing. Initial eligibility criteria required supratentorial ICH volume 30 mL or less; additional criteria included a historical

modified Rankin Scale (mRS) score of 1 or less (no disability prior to ICH), no limitations to hospital care, and no ongoing coagulopathy, suspicion of aneurysm, arteriovenous malformation, or other vascular anomaly.{28}

Consent

CLEAR III was a complex trial, with a long screening window of 72 hours. After the local principal investigator determined eligibility, the patient's family was approached and informed of relevant risks, benefits, and alternative treatments. During the study, the investigators were provided guidelines, a checklist for consent, a smartphone application with procedural bedside guidance, and training consent videos modeling best and worst consent practices, both in the general case and specific to the CLEAR III intervention.{29}

The consent training program included an annual, mandatory refresher webinar on best practices, as well as training on how to engage colleagues to refer patients into the trial. After the families were given time to consider and comprehend the elements of participation, the families of fully eligible patients were again approached, and informed consents were obtained or refused. We then compared AA and non-AA timelines for presentation, signed consent, and randomization.

Data

All data were captured electronically, and pertinent source documents were uploaded by local site personnel using a web-based electronic data capture (EDC) system (VISION, Prelude Dynamics, LLC). All participants and trial personnel, except for the local and central pharmacists and the unblinded statistician, were masked to treatment assignments. Site personnel randomly assigned patients (1:1) within 72 hours of ictus. The EDC system transmitted a treatment allocation by e-mail directly to the local, trained pharmacist.

Screening

The same EDC system was used to enter all participants screened. Study coordinators were trained to enter all admissions with a primary or secondary diagnosis of IVH in the electronic screening log. Protocol inclusion/exclusion (I/E) criteria were collected in the EDC via

prespecified selections and then categorized as either medical reasons (e.g., biologically ineligible or predetermined I/E ineligible) or nonmedical reasons (e.g., access, personal choices, mistrust).

EDC compliance was monitored, and sites were encouraged to make screening entries in real time. To limit coordinator burden, only a single exclusion factor was required for screen failures; sites were compensated for screening activities. Enrolling teams were trained to screen admissions, in person, every morning and afternoon or round with the ICU care teams. Remote screening, using electronic admission and medical records, was discouraged. Teams were trained to consider some I/E conditions as temporary and to conduct multiple screening attempts on such subjects during the 72-hour window.

Race/Ethnicity

Race was collected as part of screening data and entered locally into VISION. Investigators or study coordinators selected one or more of the following to report race: American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Black or African American, Asian, or White. From these categories, we grouped patients into two categories when race was listed—as either AA if Black or African American was selected (including those who chose other races in addition to AA) or non-AA if Black or African American was not selected (see Figure 1).

Analysis

We analyzed AA participation using randomization (Stage 1) and screening (Stage 2) data. Our first inspection compared trial enrollment to an National Institutes of Health aggregate report{30} and to U.S. population data from 1990, 2000, and 2010, obtained via census.gov. To inform end-of-trial comparisons, forecast projections were calculated to determine the likely AA percentage for a 2014 U.S. population.

With CLEAR III demonstrating such substantial AA participation and robust conversion rates, we stratified AA trial randomization rate by site geographic region. We then examined city census data at our CLEAR III locations, examining whether hospital location mattered. We retrieved census percentages{31} and used simple linear regression modeling to assess the

relationship between AA census in 42 cities and the AA percent screened, as well as the AA percent randomized in each city. Site and city data for CLEAR III sites that did not enroll *any* patients (regardless of race) were excluded from the analysis.

We next stratified screening data by gender and age to test for significant demographic differences. Last, we interrogated the data for AA vs. non-AA distribution among medical, nonmedical, or combination (both medical and nonmedical) reasons for screen failure. Chi-square was used to compare the proportions between AA and non-AA for each screen failure reason.

Results

Stage 1: African American vs. Non-African American Enrollment

Overall

The U.S. respective trial *enrollment* rates were: African American, 45.1%; Asian, 3.5%; American Indian/Alaskan Native, 0.3%; Native Hawaiian or Other Pacific Islander, 0.8%; White, 48.6%; remaining mixed races, 0.3%; and Unknown, 1.4%. For our analyses, we grouped the race categories into AA and non-AA. When we compared CLEAR III recruitment to other National Institute of Neurological Disorders and Stroke (NINDS) participation data and to U.S. population data during the same period as the trial, CLEAR III recruitment outperformed population expectations and that of other NINDS trials (see Table 1). AAs comprised 45.1% of total U.S. enrollments (n=370), or more than twice the 19.8% participation rate reported by NINDS in 2011{30} and triple the projected 13.9% U.S. population in 2014.

Conversion (Randomization) Rate by Geographic Region

Conversion rates for both AA and non-AA participants were calculated as total number of enrolled divided by total number screened (see Table 2). Our planned conversion rate for trial enrollment was 5%. The randomized-to-screened ratio for AAs was 8.7% vs. 3.4% non-AA ($p<0.001$). Regional analysis showed similar differentials with AA conversion rates: Northeast

(7.7% vs. 2.9%, $p<0.001$); South (8.2% vs. 4.0%, $p<0.001$); Midwest (10.3% vs. 3.6%, $p<0.01$); and West (8.9% vs. 3.8%, $p=0.02$).

Conversion (Randomization) Rate and City Census Comparisons

Trial sites were grouped by city, and their AA enrollment percentages were compared to corresponding city census data. The proportion of AAs enrolled per city ranged from 0% to 100%, with a mean of 40.4% (see Figure 2a). The AA city census ranged from 1.3% to 82.7%, with a mean of 28.0%. The enrollment mean of 40.4% robustly exceeded the census mean (28.0%). Higher AA census was associated with higher AA *enrollment* percentage ($R^2 = 0.17$, *p* value = 0.004; $\hat{\beta}$(95% CI) = 0.7 (0.25, 1.21)). The symbol $\hat{\beta}$defines the slope of the regression line. The AA percent enrolled in a city increased, on average, 0.7% for each percent increase in AA census.

Comparing enrollment timelines, only randomization was statistically significant; AAs randomized later than non-AAs, with an average difference of five hours. Time to informed consent approached significance, averaging approximately two to three hours longer.

Stage 2: African American vs. non-African American Screening

We next looked at screening to understand conversion performance, assess who was excluded, and evaluate whether reasons for exclusion related to relevant demographic and biological variables.

Screening Rate and City Census Comparisons

The proportion of AAs screened per city ranged from 0% to 63.7%, with a mean of 23.2% (see Figure 2b). Higher AA census was associated with higher AA *screening* percentage; the AA percent screened in a city increased, on average, 0.6 for each percent increase in AA census ($R^2 = 0.46$, *p* value < 0.001; $\hat{\beta}$(95% CI) = 0.62 (0.41, 0.83)). Comparing the census and screening means, CLEAR III investigators screened slightly less than the census mean (23.2% vs. 28%).

Screening by Gender and Age

We then assessed gender and age for overall U.S. screens and screen failures, where race was listed, to detect any significant demographic differences. Out of the 8,587 U.S. screens, race was reported for 7,663 participants (see Figure 1). Of the 7,663 race-listed participants, 7,298 were screen failures and 365 were enrolled; further, gender was missing on four non-AA participants, with all of these being among the screen failures.

Of the race-listed U.S. screens, AAs consisted of 918 (47.7%) females and 1,005 (52.3%) males. Equivalently, non-AAs consisted of 2,735 (47.7%) females and 3,001 (52.3%) males. Of the screen failures, AAs consisted of 839 (47.8%) females and 917 (52.2%) males. Similarly, non-AAs consisted of 2,640 (47.6%) females and 2,898 (52.3%) males. There was no statistically significant difference in gender between race-listed U.S. screens and screen failures.

For race-listed U.S. screens, the average age of AA participants was 58 years old (standard deviation 13.7), compared to an average age of 66 years for non-AA participants (standard deviation 15.6) with a p value <0.001. For the screen failure subset, similar results hold; the average age of AA participants was 58 years old (standard deviation 14.0), compared to an average age of 66 years for non-AA participants (standard deviation 15.7) with a p value <0.001.

Medical vs. Nonmedical-Related Screen Failures

Upon review of screen failure reasons within the AA and non-AA race groups, African Americans were *less* frequently excluded due to biological/research strategy reasons (see Table 3).

For the medical screen failure category, AA had a *lower* percentage of patients excluded at the Upper Age Limit (AA: 5.6% vs. non-AA: 16.0%), Aneurysm (AA: 9.2% vs. non-AA: 13.4%), and Etiology Tumor (AA: 0.2% vs. non-AA: 0.8%). However, AAs had a *higher* percentage of exclusions for GCS/Herniation/Brain Dead/Deceased (AA: 1.4% vs. non-AA: 0.8%), Historic Rankin not 0 or 1 (AA: 2.7% vs. non-AA: 1.7%), ICH > 30 cc (AA: 14.6% vs. non-AA: 12.6%), and no obstruction of 3rd and/or 4th (AA: 14.9% vs. non-AA: 11.5%). Other remaining screen failure reasons were statistically insignificant.

For the nonmedical reasons screen failure category, AAs had a lower percentage of patients who were DNR (AA: 3.4% vs. non-AA: 4.5%) and a higher percentage of patients who were eligible but refused consent (AA: 3.1% vs. non-AA: 1.2%). Remaining screen failure reasons for this category were statistically insignificant.

One category, "MD/Surgeon chose not to enroll," had too broad a response, combining both medical and nonmedical reasons. For screen failure category, AA had a *higher* percentage of screen failures for MD/Surgeon chose not to enroll (AA: 3.2% vs. non-AA: 1.2%) and Other (AA: 10.9% vs. non-AA: 6.8%). Other reasons were statistically insignificant (see Table 3).

Discussion

AAs *enrolled* in CLEAR III at a rate greater than expected by available census data, regardless of city or geographic region. Although AAs refused consent at a greater rate, they enrolled 2.5 times more often than non-AAs.

When we compared CLEAR III performance to other brain hemorrhage randomized clinical trials during the same period, CLEAR III enrolled AAs at 45.1% compared to 9% to 30% in the other trials, though AA screening and enrollment data are not available for some trials, limiting the comparison (see Table 4). Further limiting comparison is that these trials were international and did not break out racial data by countries.

When comparing reported enrollment windows and follow-up intervals, there is one notable difference—time from onset to randomization. CLEAR III participants had a much longer enrollment window, allowing more time to communicate with families. Moreover, the communication period occurred in the ICU rather than the Emergency Department. Prospective research on the relationship between enrollment windows, follow-up intervals, social support, recruitment monitoring, and minority enrollment/retention may provider stronger correlations.

Gorelick et al. published the recruitment triangle in 1998,{32} illustrating the social support triangle that reduces barriers and lessens disparities. The design of the 72-hour enrollment time window could be essential to enrollment and retention, particularly among AA participants, allowing communication time with the social support stakeholders and within the insulated ICU

where trust reduces barriers, regardless of race or ethnicity. Initial and ongoing training of site teams emphasized that temporary I/E factors could resolve over a three-day period and the use of the entire time window.

CLEAR III utilized intensive site management oversight with strong emphasis on best screening, consenting, and enrollment practices. We evaluated recruitment monthly and retrained annually on best consent practices, and we gave a presentation on common reasons for refusals both from families and investigators and on how to solve fixable refusal reasons. Furthermore, our training included the recruitment triangle social support principles{30} of taking time and connecting with families; earning trust, not only of families but also of the ICU teams involved in the treatment and care of the patient; using best consent practices; providing family access to an interested and caring investigator; and respecting the cognitive and physical concerns of families in distress and sensory overload throughout the trial participation continuum.

Limitations

While biological/research strategy exclusions, city census, and being younger may have contributed to CLEAR III's high enrollment of AAs, any causal mechanisms behind these associations remain unclear. Several limitations impact the interpretation of our analysis.

Race categories were presented as checkboxes in the EDC and no specific definition for each category was provided, nor were directions for choosing race included in training. Thus, different interpretations of race categories may have occurred at the time of data entry. Furthermore, we recognize that there may have been inconsistencies across sites whether the race reported was determined by the patient, patient relative(s), medical record, site coordinator, or physician.

While race was more closely monitored for enrollment data, the same standards were not applied to screen failures. Of the 8,587 screens, 924 were missing race data (of which five were enrolled), introducing potential sampling error. Screen failure reasons such as "MD/Surgeon chose not to enroll," "Patient eligible but refused consent," and "Other" did not allow details, possibly obscuring causal factors related to race and recruitment. Another possible limitation is that the traditional categories "comorbidity," "likely not able to complete the protocol," and "…otherwise, in the investigator opinion, not eligible…" were grouped together and labeled as

"Investigator Decision," thus not identifying whether these screen failures were for medical or nonmedical reasons or providing further details as to who made the decision.

Screening logs were not monitored prospectively. Tracking diversity in clinical trials is essential, and monitoring screening logs monthly for content (and not just submission) can determine how teams are doing (beyond overall screening and conversion rates) as they recruit the underrepresented and underserved. Additionally, recognizing minority screen failures early allows the opportunity to redesign poorly constructed forms and retrain poorly performing teams. Further, including recruitment diversity and disparities metrics when publishing clinical trial results is imperative for comparative research where sub-populations are under active investigation.

Last, the analysis covered only city-level data; data are limited on the demographic characteristics of eligible patients at non-trial hospitals and patients coming to trial hospitals from other cities.

Conclusions

AAs were willing to enroll in a novel, acute stroke trial, such as CLEAR III. Enrollment was systematically consistent in proportion to the subjects' demographics, taken from census data, suggesting higher enrollment was a function of the overall trial characteristics and national population characteristics. The enrollment of AAs was proportional to disease prevalence and allows for a robust estimate of minority population characteristics and responses.

That CLEAR III AA enrollment exceeded census percentages is an important finding that requires further exploration. Cities densely populated by AAs should be considered when selecting recruitment sites. Census rates may be useful when setting recruitment goals, particularly for ICH trials.

Consent training in disparity recruitment methods appears to have been rewarded. Better screening instruments, screening standardization, and recruitment metrics will be important to the design of any trial. Prospective recruitment monitoring, along with surveys and interviews

following refusals, could improve understanding of screening-to-enrollment conversion rates among research participants.

Efforts are under way to understand and improve recruitment of AAs and other underrepresented minorities into clinical trials. If we are to improve proportions of minorities enrolled, then we should apply the recruitment triangle to minority recruitment, interviewing, and data-entry training at investigator meetings and as part of best consent coaching.

This trial may provide some structure to those "trial-in-progress" practices. When designing clinical trials, determining underlying reasons for participation probably helps find solutions for eliminating disparities. Interestingly for CLEAR III, such an approach during the trial might have provided information about lower participation rates of non-AAs. When the incidence of stroke or other diseases is higher in minorities, we must develop minority-specific training programs to teach investigative teams about the importance of diversity.

Future trials should consider such factors as incorporating minority recruitment goals in data collection design and consent training; incorporating targeted enrollment data into screening logs to manage enrollments *during* the trial to avoid falling short of minority representation; and bringing diversity awareness to the design of I/E criteria, data collection materials, and consent practices.

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The authors thank the CLEAR III patients and their families for participating in the trial and contributing to this very important research to find a treatment for a devastating and otherwise untreatable form of stroke. We especially acknowledge and thank our AA patients, who historically share the greater burden of severity, mortality, and disability, for improving the generalizability of the CLEAR III trial results and raising the standard of patient-centered stroke care. We also thank Megan Clark for her editorial assistance.

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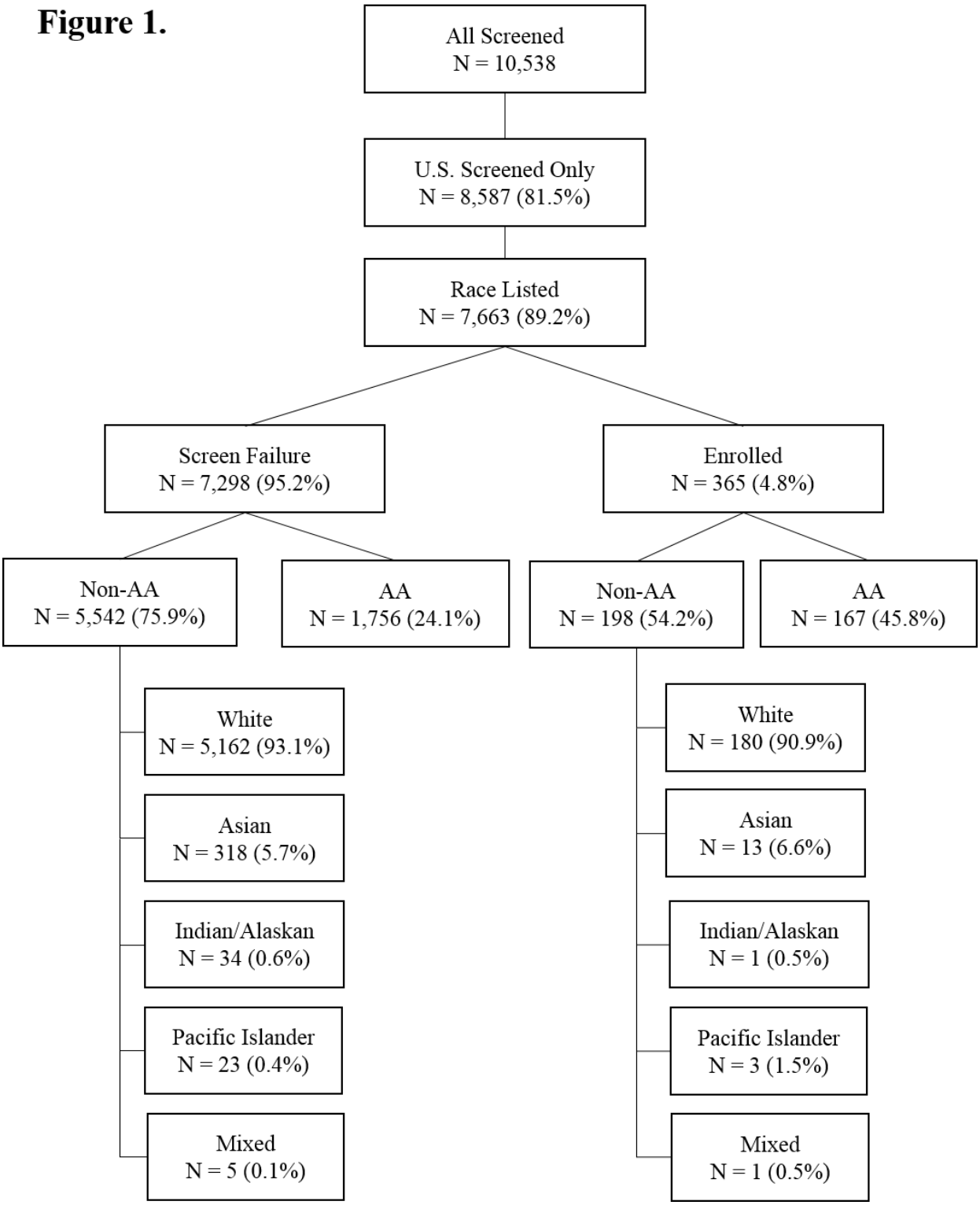
Figure 1: CLEAR III trial screens from 2009 to 2014. AAs comprised 25.1% of the U.S. screens for which race was listed.



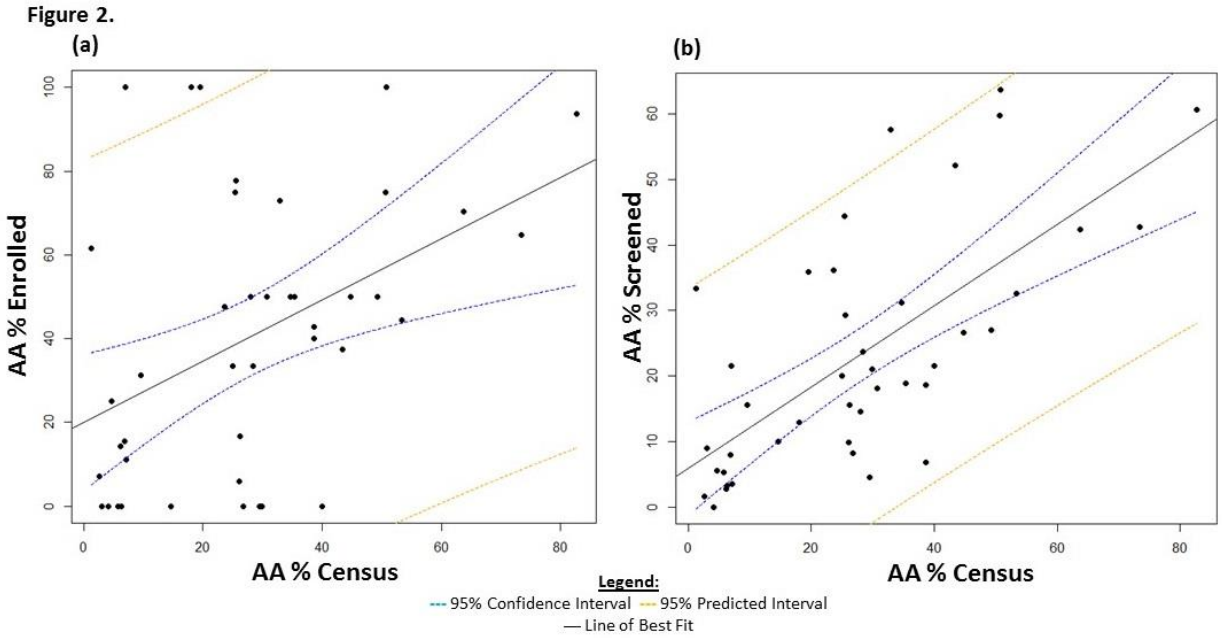


Figure 2: a. AA enrollment by city (%) compared to AA census data (%) for each city. Cities with a higher percentage of AAs enrolled more AAs into the trial (p-value: 0.004, R^2: 0.17). **b.** AA screening by city (%) compared to AA census data (%) for each city. Cities with a higher percentage of AAs screened more AAs into the trial (p-value: <0.001, R^2: 0.46). 95% confidence interval indicates the likely location of the true population parameter, and 95% predicted interval forecasts where to expect the next data point sampled.

Table 1: CLEAR III Enrollment Rates Compared to NINDS Rates and the U.S. Census Population During the Same Periods

	Period	AA Trial Representation (%)	U.S. Population (%, Year)
Pre-NIH Revitalization Act	1985-1995	11.6%	12.1% (1990)
56 NINDS trials			12.9% (2000)*
	1996-2008	19.8%	
			13.0% (2010)**
CLEAR III U.S. trial subjects (AAs)	2009-2014	45.1%	14.1% (2014)***

*** Includes persons identifying as African American and one or more additional races**

**** An additional 1% of the U.S. population identified as African American in addition to one or more other races**

***** Projected U.S. population**

Table 2: Conversion (Randomization) Rates: U.S. Overall and by Geographic Regions

Regions (n=sites)	AA (%)	Non-AA (all other) (%)	P-value
U.S. overall (n=61)	8.7	3.4	<0.001
Northeast (n=20)	7.7	2.9	<0.001
South (n=16)	8.2	4.0	<0.001
Midwest (n=16)	10.3	3.6	<0.01
West (n=9)	8.9	3.8	0.02

Table 3. Screen Failure Categories (N = 7,298)

	AA		Non-AA		P-value
	N	%	N	%	
Medical	**1,292**	**73.6%**	**4,581**	**82.7%**	**<0.001**
Abnormal PTT, PLT < 100K, INR > 1.3	34	1.9%	122	2.2%	0.503
Age < 18 or > 80 years	98	5.6%	884	16.0%	<0.001
Aneurysm, mycotic aneurysm, moyamoya, etc.	161	9.2%	743	13.4%	<0.001
Craniectomy/other surgical procedures	21	1.2%	51	0.9%	0.308
Etiology - tumor	3	0.2%	47	0.8%	0.003
GCS < 3/herniation/brain dead/deceased	25	1.4%	43	0.8%	0.014
Historic (pre-bleed) Rankin not 0 or 1	47	2.7%	96	1.7%	0.013
ICH > 30 cc on diagnostic CTC	256	14.6%	700	12.6%	0.035
Infratentorial bleed	150	8.5%	451	8.1%	0.591
No EVD placed	220	12.5%	733	13.2%	0.449
No obstruction of 3rd and/or 4th	261	14.9%	636	11.5%	<0.001
Unstable bleeding	16	0.9%	75	1.4%	0.146
Non-medical	**199**	**11.3%**	**471**	**8.5%**	**<0.001**
Improper screening	9	0.5%	21	0.4%	0.446
Participation in another trial	6	0.3%	10	0.2%	0.208
Patient eligible but refused consent	54	3.1%	66	1.2%	<0.001
Patient is DNR	59	3.4%	250	4.5%	0.037

Study staff not notified within window	11	0.6%	21	0.4%	0.171
Study staff unavailable	2	0.1%	8	0.1%	0.764
Unable to dose within time window	58	3.3%	95	1.7%	<0.001
Combination medical and non-medical reasons	**265**	**15.1%**	**490**	**8.8%**	**<0.001**
MD/Surgeon chose not to enroll	56	3.2%	65	1.2%	<0.001
Not an IVH patient	18	1.0%	49	0.9%	0.59
Other	191	10.9%	376	6.8%	<0.001
Total	**1,756**	**100.0%**	**5,542**	**100.0%**	

Table 4: Enrollment Window and Race Reporting in Major ICH Clinical Trials

Trial	Inter-national	Medical or Surgical Trial	Enrollment Window (Hours)	F/U (Days)	Total Enrolled	% White Reported	% AA or Black Reported
CHANT	N	Medical	6	90	607	*	*
ICES	N	Surgical	48	365	24	45.8	33.3
FAST	Y	Medical	4	90	841		9.0
ATACH-2	Y	Medical	4.5	90	1,000		13.1
PREDICT	Y	Medical	6	90	268	86.0	
Deferoxamine	N	Medical	18	90	20	85.0	
NovoSeven	Y	Medical	3	90	399	81.0	
MISTIE II	Y	Surgical	**48**	365	96	56.0	30.0
CLEAR III	Y	Medical	**72**	365	500	61.0	34.0
CLEAR III	U.S. only	Medical	**72**	365	370	48.6	45.1

*** Race not reported**

AUGUST 2018 CLINICAL RESEARCHER

HOME STUDY

New Perspectives on Recruitment and Retention

Overcoming the Barriers to Recruitment of Underrepresented Minorities

LEARNING OBJECTIVE

After reading this article, participants will be aware of the barriers to recruitment of minorities in research and will be able to identify the laws that were put in place to overcome these barriers.

DISCLOSURE

Stephanie Lynn Williams, MS, CCRC: *Nothing to disclose*

1. How did the National Institutes of Health (NIH) attempt to correct underrepresentation of minorities?

a) By conducting awareness program on the importance of including minority populations.
b) By ensuring that the growth of racial minorities is reflected in clinical trials.
c) By mandating the inclusion of women and racial minorities in research.
d) By increasing the average sample size asked for in study protocols.

2. The Revitalization Act was passed in 1993. What was the intended purpose of this Act?

a) To eliminate racial and ethnic health disparities.
b) To ensure correct representation of the U.S. population in clinical trials.
c) To alleviate the economic burden on the healthcare system in the U.S.
d) To increase the participation of women and racial and ethnic minorities in research.

3. What was launched during the State of the Nation address in 2015?

a) The “All of Us” program
b) The Precision Medicine Initiative
c) The NIH guidelines on racial minorities in research
d) The revitalization initiative to increase health disparities in minority populations

4. Eliminating health disparities from 2003 to 2006 would have decreased medical costs in the U.S. by how much?

a) More than $1.2 trillion
b) No more than $17 billion
c) Less than $27 million
d) Approximately $7.3 million

5. Which Act put protections in place for human subjects involved in research?

a) The Revitalization Act
b) ICH-GCP E6(R2)
c) The Precision Medicine Initiative
d) The National Research Act

6. The Tuskegee Study is perceived as:

a) An example of unacceptable medical research exploitation.
b) A breakthrough in research on minority populations.
c) The study with the highest death and disability rate.
d) The longest study ever conducted with corporate funding.

7. What is the major limitation of the Revitalization Act?

a) Minority rates were only assessed 20 years after implementation.
b) The number of minority groups in cancer trials remained unchanged.
c) NIH guidelines only apply to federally funded trials.
d) The purpose of the Act was not fully realized and barriers continue to exist.

8. How are barriers to enrollment of minorities identified?

a) Through the Tuskegee Study
b) The story of Henrietta Lacks
c) Response to advertising in local newspapers
d) Pre-screening interviews and research participant interactions

9. What are some of the best tools to combat fear of exploitation amongst minority groups?

a) Offering transparency and education about research
b) Dismissing time- and logistics-related barriers
c) Setting up mobile clinics in wealthier and more distant communities
d) Reducing the office hours and compensation at sites to force efficiencies

10. One direct method for reducing lack of diversity in the <u>research team</u> would be to:

a) Advertise to underrepresented potential patients in local newspapers
b) Conduct awareness programs about study opportunities in minority communities
c) Recruit new research staff members from diverse backgrounds
d) Encourage previous participants to tell their friends and family about clinical trials

African American Screening and Enrollment in the CLEAR III Trial

LEARNING OBJECTIVE

After reading this article, participants will understand the importance of including members of racial and ethnic minorities in clinical trials.

DISCLOSURE

Karen Lane, CCRP: *Receives grant/research support from NIH/NINDS and Genentech*

Richard E. Thompson, PhD: *Receives NIH grant funding*

Issam A. Awad, MD, MSc, FACS, FAHA: *Receives grant/research support from NIH/NINDS*

Nichol McBee, MPH, CCRP: *Receives grant/research support from NIH/NINDS and Genentech*

Wendy Ziai, MD: *Receives NIH grant funding*

Daniel F. Hanley: *Receives grant/research support from NIH/NINDS and Genentech and is a consultant to BrainScope, Neurotrope, Portola Pharmaceuticals, Op2Lysis, HeadSense, and Medtronic*

Maningbe Keita, BA; Radhika Avadhani, MS; Rachel Dlugash, MSPH; Steven May, PD, CCRA, PMP: *Nothing to disclose*

11. What impact does under-enrollment of minority populations have on clinical research?

a) Safety and efficacy results may be disproportionate.
b) Reduces the generalizability of research findings.
c) Increased economic burden incurred through health disparities.
d) Limited evidence-based healthcare decisions for a wide range of the population.

12. What is the global mortality rate of hemorrhagic stroke?

a) 45%
b) 32%
c) 22%
d) 16%

13. What was the estimated cost of stroke in the United States in 2009?

a) $13.6 billion
b) $42 billion
c) $68.9 billion
d) $103 billion

14. The study described in this article presented an opportunity to assess African American enrollment. What phase was this study?

a) Phase IV
b) Phase III
c) Phase II
d) Phase I

15. Why was the CLEAR III study a first-of-a-kind trial?

a) It reviewed the incidence, prevalence, and risk of hemorrhagic stroke in multinational settings.
b) It included the largest number of patients ever randomized to placebo for a single study.
c) It combined a catheter device with up to four days of ICU-based drug treatment.
d) It assessed disparities in study compliance between African Americans and White Americans.

16. How often were CT scans obtained during the dosing period of the CLEAR III trial?

a) Once a month
b) Every other week
c) Once a week
d) Every 24 hours

17. The consent training program included a mandatory annual webinar. What was this training on?

a) Best practices and how to engage colleagues to refer patients to the trial
b) Consent videos modelling best and worst consent practices
c) Tenets of International Council for Harmonization–Good Clinical Practice
d) Health Insurance Portability and Accountability Act expectations

18. How soon after a subject's visit were sites encouraged to enter information by electronic data capture?

a) No more than three days
b) Any time within seven days
c) No sooner than two weeks
d) Data had to be entered in real time

19. African American randomization rate was analyzed and stratified by:

a) Incidence of stroke
b) Census percentages
c) Geographic region
d) Hospital location

20. Enrollment timelines were compared, and it was noted that African Americans randomize later than non-African Americans. What was the average difference in time?

a) One hour
b) Three hours
c) Five hours
d) Eight hours