

A Comprehensive Literature Review Addressing the Range of Factors that Prevent Inclusion in Clinical Trials and Research

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Introduction

In 1993, the NIH Revitalization Act (Public Law No. 103-43) was signed into law. This bill instructed the NIH to create guidelines that would ensure federally-funded research would be done “in a manner sufficient to elicit information about individuals of both sexes/genders and diverse racial and ethnic groups and . . . to examine differential effects on such groups” (1). Given the lack of women and underrepresented populations in clinical research up until that point, authors of the bill aimed to improve the pattern of research representation.

Despite this and an increased focus on the lack of women and underrepresented minorities in US-based clinical trials and research, participants in medical research remain mostly White and male (2-4). Review of clinical research published in major medical journals in the years immediately following passage of the 1993 bill did not show any improvement in either the enrollment of women or the reporting of gender-specific results (5, 6). Analysis of all cancer trials between 2003 and 2016 actually noted a decrease in Black and Latinx Americans’ enrollment over that time (7). Although more contemporary reviews have shown modest increases in participation of women, underrepresented populations, and older patients, persistent and significant underrepresentation remains the standard. This has been shown across research in a number of medical disciplines and diseases, including cardiology, Alzheimer’s Disease, and HIV/AIDS (8-11).

The reasons for continued disparities in the representation of women and ethnic minorities in clinical trials remains an active topic of discussion and investigation. Common themes have historically centered around cultural differences and/or personal resistance, yet a robust evidence-base demonstrates a much more complex system of structural barriers to engagement. In this

manuscript we review research addressing long-standing theories on how trust reduces participation, as well as other individual-level factors including socioeconomic and cultural realities that may impact research engagement. Our discussion of these factors is in no way intended as a criticism of those underrepresented populations, but rather is meant to describe the current reality of the situation. We then shift to the influence of systemic and structural obstacles, including attitudes and biases of research teams, recruitment methods, inclusion and exclusion criteria, and health care access. There is significant overlap in many of these areas, and every effort has been made to bring the many threads together in a clear and actionable way. Ultimately, we argue that attempts to increase inclusion of underrepresented groups in clinical trials and research should include a major focus on the systemic and structural obstacles described, rather than solely on issues of trust or other individual-level factors. The evidence base suggests that structural domains are the high-yield areas and, because they are internal to the research community, they are the domains over which researchers have considerable influence (Table, shaded box). We believe that through changing these internal discriminatory structures, researchers can positively affect researcher-community relations and begin to change the historical narratives related to trust.

Table. Factors internal and external to current research infrastructure that influence diverse inclusion in clinical research

Internal	External
A. Attitudes/biases	A. Trust
B. Recruitment methods	B. Willingness to participate
C. Inclusion/exclusion criteria	C. Socioeconomic
D. Cultural literacy	D. Cultural
	E. Health care access

Definitions

Throughout this paper we use a number of terms that would benefit from definition. When we refer to clinical or medical research, we are including 1) research conducted with human subjects or on material of human origin for which direct human subject interaction is needed, including clinical trials, 2) epidemiologic and behavioral studies, and 3) outcomes and health

services research. To describe and discuss underrepresented racial and ethnic groups, we have adopted new recommendations from the *Journal of the American Medical Association* (12) that recommend the use of the terms Asian American, Black American, Latinx American, Native American/Native Alaskan, Native Hawaiian/Pacific Islander, and White American, acknowledging that race and ethnicity are social – rather than biological – constructs, and that these terms do not capture the complexity and intersectionality between and within these groups. When referring to these groups collectively, we use the term “underrepresented.” When possible, we use more specific terms such as Mexican American and Hmong individuals. Literature on other underrepresented groups, including women, the elderly, LGBTQI individuals, and residents of rural areas, is not nearly as complete or detailed as that for ethnic and/or racial groups. The literature that does exist is most often at the intersection of these groups with the ethnic or racial populations of which they are generally considered a part (i.e. older Hmong populations, Black women). We therefore discuss these groups only when relevant and/or specific data is available.

Barriers External to Research Infrastructure

A Matter of Trust

Any conversation regarding the low participation rates of underrepresented individuals in medical research must include the issue of distrust and/or mistrust of the health care system. Whether caused by distrust (an individual’s sense that her/his trust has been violated by a specific act, person, or institution) or mistrust (a less specific but no less legitimate feeling that a person or institution may not be acting in an individual’s best interest) (13), it is practically doctrine that the legacy of both historical and contemporary abuses is a primary factor driving the engagement of underrepresented populations with both health care and research. Certainly, much data exists to support this perspective in many underrepresented groups, including Asian American, Black American, Latinx American, and Mexican American (14-35).

In qualitative studies with Black Americans, those who decline to participate or express lower willingness to participate frequently mention the offenses committed at Tuskegee as well as more recent personal stories of distrust as reasons for their declinations (24, 25, 27, 28, 36). The authors of a survey study regarding differences in willingness to participate in a cardiovascular drug trial suggest that this type of distrust/mistrust can explain much of the participation gap between Black and White Americans (29). In a clinical trial exploring barriers in motivators to participation in clinical trials among 67 Black Americans, focus group themes included the perception that research would benefit White participants or the research institution more so than any underrepresented individuals enrolling in the study (37). A study of 17 Black women at high-risk for HIV found that, despite expressing favorable attitudes toward medical research in general, distrust was a commonly cited reason for not participating (38). Similar studies exist regarding Black individuals' participation in blood/tissue donation for genetic studies (30), psychiatry research (31), and cancer research (32). These studies propose historical abuses as a major source of distrust among Black Americans and further assert that this distrust is a large factor in their unwillingness to enroll in medical research.

This issue of trust is of course not limited to Black Americans, and reasons for the distrust vary depending on the group or individual. In interviews with an older population of Hmong individuals, specific concerns arose about possible researcher misuse of information that might lead to loss of financial support from governmental agencies (33). In a study of 50 Filipino and Hawaiian/Pacific Islander people, major focus group themes included negative feelings about the purpose and intent of the research (39). Research into Latinx Americans and Mexican Americans as well as Asian Americans of Filipino descent suggests that at least some of their distrust is rooted in fear surrounding their own or a family member's immigration status (20, 34, 35, 40). Perceptions about health insurance coverage have also been reported. A study of 88 Black Americans toward genetic research identified fear of the loss of health insurance coverage as a result of targeted

discrimination as a barrier to participation (41). Populations who participate in illegal or culturally-stigmatized behaviors, including intravenous drug users, people with substance abuse disorders, LGBTQI individuals, and people who are HIV-positive, also may not trust that their personal information will be kept private by research teams (19, 38).

The presence of distrust/mistrust and its association with underrepresented populations' participation in health care and medical research is a fact. Furthermore, the historical abuses and ongoing structural inequities that underpin these issues of trust cannot be denied. However, a thorough review of the literature reveals that issues of trust may not be responsible for as much of the lack of diversity as current view suggests. There are many studies showing that – despite well-founded issues of trust – underrepresented individuals are just as willing (and sometimes more willing) to participate in clinical research as White individuals (42-50).

Extensive research done by the Tuskegee Legacy Project (TLP) provides an excellent case study of this phenomenon. The TLP was created in 1994 with the specific goal of examining the validity of the long-held belief that the Tuskegee Syphilis Study was responsible for Black Americans' distrust of the health care system and their reported unwillingness to participate in medical research. Between 1999 and 2003, TLP researchers surveyed a total of 2,295 Black, Mexican, Puerto Rican, and White Americans over the course of two separate studies in seven US cities: Tuskegee, Alabama; Birmingham, Alabama; Hartford, Connecticut; San Antonio, Texas; San Juan, Puerto Rico; New York City; and Baltimore, Maryland (42-45). Their major findings related to two domains: fear of participating in research and willingness to participate in research. The domain related to fear was termed the "Guinea Pig Fear Factor" (GPFF), while the domain related to willingness was termed the "Likelihood of Participation" (LOP). In the first study, researchers found that Black respondents had higher GPFF than White respondents; in the second study, both Black and Puerto Rican Americans reported higher GPFF. Yet in both studies, no difference was found between any of the groups in overall LOP (42, 44). When comparing knowledge of the Tuskegee

Syphilis Study between respondents in Tuskegee, Birmingham, and Hartford, there was a clear difference in the awareness rates in each city but no relationship between awareness and LOP (43). Perhaps the most interesting finding was that, among survey participants in Birmingham, Tuskegee, Hartford, and San Antonio, awareness of the offenses at Tuskegee actually had a larger negative impression on White respondents' LOP compared to Black respondents (45).

Researchers in a number of other disciplines have asked broader questions of trust and have found the same result as the TLP: distrust/mistrust exists but is not associated with willingness to participate in medical research (46-49, 51). A study of 5,139 Black individuals and 2,670 White individuals in Florida found that while Black people had mildly lower levels of trust in both researchers and research studies than White people, level of trust did not predict intent to participate for either group (48). A survey of over 600 Black, Mexican, and White Americans in Chicago asked about level of agreement with certain questions regarding general trust in research as well as conspiracy beliefs about HIV/AIDS, such as "medical research treats people like 'guinea pigs'" and "the government is not telling us the whole story about how AIDS is spread" (49). All three groups had similar levels of trust in research, while agreement with HIV/AIDS conspiracy statements was generally higher among Black and Mexican Americans; yet Black and Mexican Americans reported being over 2.5 and 1.5 times more willing, respectively, to participate in research than their White counterparts. Finally, a systematic review of 40 years of research on barriers to enrollment in cancer studies found that, although mistrust was the most commonly cited individual-level reason for not participating in research, the most common barriers overall were related to the opportunity to participate.

Fundamentally, we may never know exactly how much historical and current discrimination and abuses impact underrepresented individuals' participation in clinical research. The data is variable and the question itself is exceptionally complex. The research done in this area may be limited by participants' unwillingness to openly discuss trust issues with research teams

that represent the very entities that the participants distrust. Additionally, people with the highest levels of mistrust are unlikely to participate and thus be represented in any research. Persistent and systemic effort to delegitimize, underemphasize, or ignore the link between historical and contemporary occurrences of scientific misconduct/abuse and the mistrust of underrepresented populations toward research will certainly only continue to worsen current disparities in participation. Moreover, an inability or unwillingness of the research community to acknowledge and make efforts to address the roots of distrust/mistrust in underrepresented communities would stymie any movement towards increasing the trustworthiness of researchers in the eyes of underrepresented populations. Yet the acknowledgment of issues of mistrust/distrust by research teams, although necessary, is not in and of itself a sufficient step toward understanding barriers to participation, recruitment, and retention. We suggest that actions – in the form of changing internal research structures and processes as described in the second part of this paper – will do more to improve trust between underrepresented populations and the research community than efforts directed solely at so-called trust building.

Willingness to Participate

Like issues of trust, overall willingness to participate is frequently given as cause of poor representation of underrepresented populations in research. Unlike the conflicting data on the question of trust, the data on this issue is clear: Asian, Black, Latinx Americans, and Native Americans/Alaskan Natives are no less likely, and in some cases are more likely, to participate in research if asked (20, 21, 23, 26, 31, 47, 52-71).

A 2014 national review of over 4,500 Asian, Black, and Latinx Americans who were eligible for cancer trials found the same willingness to participate among equal groups and, not unexpectedly, equal enrollment rates (59). Perhaps surprisingly, similar data exists for HIV, despite early narratives of stigma and discrimination related to the illness. Among Asian American, Black

American, and White American college students in Atlanta, a 2006 study found no difference in willingness to participate in an HIV vaccine trial (60). Results with older patients are equally convincing: among a population of 417 HIV-positive Black and Latinx people (60% male) in Chicago with an average age of 43, 95% would either agree or consider participating in a study (21). In this analysis, the strongest predictor of participation was simply being asked.

Rural populations are increasingly recognized as an underserved population, with underrepresented individuals from rural areas particularly at-risk for poor health outcomes. Enrollment of rural populations into clinical research is especially challenging given structural barriers including access to health care and transportation issues. Yet again, it does not appear that people living in rural areas are any less willing to participate, based on a large study of 5,256 people in Arkansas and a smaller study of 533 people in Alabama, Florida, Georgia, Louisiana, Mississippi, and Puerto Rico (56, 61). Among the respondents in the Arkansas study, over 45% said they would participate in research if asked, with another 22% being undecided; only 32% said they would not participate (56). The smaller multi-state study further analyzed the data by ethnicity and rurality and found that among Black and Latinx residents of both rural and urban areas, 75% were willing to participate in research but over 90% had never been asked (61).

Population-specific studies confirm what the more general studies above suggest: underrepresented populations are not underrepresented because they are unwilling to participate. Attitudes of 204 Black men with regard to a variety of types of clinical research, including surveys, focus groups, clinical trials, and genetic studies, found that 74% endorsed a willingness to participate (26). Regarding specific willingness to be randomized in a surgical versus non-operative study of spinal disorders, Black Americans expressed equal willingness to be randomized as White Americans (62). The same results have been found in studies on Black individuals' participation in HIV treatment trials, studies on aging, and recruitment for clinical trials on kidney disease (47, 63,

64). In the HIV treatment study, like the more general 2014 study mentioned above, the major barrier to participation of HIV-positive Black people was having never been asked (47).

Data suggests that Latinx populations may in fact be more likely to participate than non-Latinx populations. A 2014 study of women in Texas reported that Latinx women were 44% more likely than non-Latinx women to participate in a gynecologic malignancy clinical trial (65). In New York City, Latinx patients were more than twice as likely to say they would join a cancer clinical trial compared to non-Latinx patients (47.7% to 20.8%) (66). A qualitative study of 59 Latinx men and women at the Texas-Mexico border demonstrated significant enthusiasm on the part of this group to get involved in research (67). “If I had the opportunity to participate in something like this, I’d love to,” said one respondent.

Although not as extensive, studies on Native Americans echo those on Black and Latinx Americans. A study of Native American college students found that, depending on the specifics of the trial, anywhere between 63% and 84% would be probably or definitely agree to participate in a cancer clinical trial (68). Only in cases where a significant amount of travel or risk of a confidentiality breach existed did willingness drop below 50%. In a separate study comparing Native Americans with Asian, Black, Latinx, and White Americans, there was no difference between the groups in refusal to participate in a cancer clinical trial (69)

Just as willingness is the same among all groups, actual consent and participation rates are also at least equal. A literature review, published in 2006, combined data from 20 studies that examined the consent rates of people of different races and ethnicities; 18 of these studies took place either entirely or mostly in the US, while the remaining two studies took place in Europe, Australia, and/or New Zealand (70). Combining data from these studies to create a cohort of over 70,000 individuals, this analysis found that Black and Latinx people had equal consent rates as White people. For clinical intervention studies, Latinx individuals actually had statistically significantly higher consent rates, 55.9% compared to 41.8%, respectively. A more recent study of

1,126 post-partum women in Philadelphia found that consenting women were actually more likely to come from underrepresented compared to those who did not consent (71).

The inability to harness the willingness of underrepresented individuals to participate in research has implications beyond exclusion from specific trials. In almost all papers on predictors of willingness to participate in research, prior exposure to or participation in research is associated with increased likelihood for participation and a more positive attitude towards research (24, 48, 57, 68). In a study of over 7,800 people in Florida, the positive influence of prior exposure on future participation was higher for Black respondents than for White respondents (48). Unfortunately, misunderstanding or lack of knowledge regarding the willingness of underrepresented populations to enroll in clinical research has created a pattern by which failure of researchers and/or clinicians to ask these groups to participate contributes to their lack of enrollment, which further decreases their chances of future involvement, and thus the cycle continues.

There is overwhelming data that underrepresented individuals are just as willing to participate in clinical research if given the opportunity. As Wendler et al suggested in their 2006 literature review on this issue, “efforts to increase minority participation in health research should focus on ensuring access to health research for all groups, rather than changing minority attitudes” (70). Thankfully, changing the structure of clinical research, although no easy task, is within the control of researchers and, if done appropriately, would contribute to increasing the trustworthiness of research institutions. Before discussing these structural barriers, however, we will address socioeconomic and personal characteristics that also have important impact on research participation.

Socioeconomic Factors

In addition to the issues discussed above, there are other individual characteristics that may inhibit interest, ability, and willingness to participate in clinical research. Broadly, these characteristics can be sorted into economic – including issues of health care access – and cultural

domains. Although an individual's socioeconomic status is the result of a multitude of factors both within (individual level) and outside (structural level) her/his control, we discuss socioeconomic issues here at the individual level in an attempt to describe how these issues drive individual decision-making.

A variety of possible socioeconomic factors have been described in the literature. The importance of educational background or highest level of grade completion has been studied in terms of its effect on research participation. Several studies support the notion that educational status is more relevant than income level when it comes to the participation of Black Americans in research (26, 46). In a study of perceptions influencing research enrollment among low-income Black, Latinx, and White residents of New York City, respondents who had less a than high school education were more likely to have increased feelings of exploitation associated with research participation (22). However, other studies have found no specific association with participant highest level of education and willingness to participate in research (55). Challenges related to the frequent need for relocation and lack of landline telephone access are often cited as a primary reason for low enrollment and low retention (19, 72). Reliable telephone access is a significant barrier for those living at or near the poverty line and has been associated with limited insurance coverage, health care access, and health behaviors (19). Perceptions around neighborhood safety have also been reported as reasons for reduced research participation of underrepresented individuals (67, 73).

Perhaps most important are issues of opportunity costs, which include the loss of any potential gains that a participant might be able to make if she/he chooses to participate in research rather than the other potential activities. Whether it be a one-time 10-minute survey or a years-long clinical trial, study participation requires time away from work, family, and other commitments. Given this, it is perhaps not surprising that economics plays an outsized role in who gets included in clinical research. Worldwide, nearly 50% of the people who participate in clinical

trials are considered “high income,” despite representing only 16% of the total population; conversely, the “lower middle class” makes up 38% of the population and 13.5% of the people who participate in clinical trials (74). A prospective study of cancer trials within the US confirms that this global pattern holds true in the US, even after accounting for factors such as age, race, and education (75).

American women and underrepresented individuals are more likely to make less money and live below the federal poverty line compared to White men (76, 77). Reduced economic resources can make elective participation in research a challenge as individuals may not have time or resources to balance their commitments with research activities. Jobs with fewer options in terms of earned time, sick days, vacation days, and remote work may make participation in research impossible. Individuals with lower incomes are also frequently responsible for caring for children, elderly family members, and sometimes both at the same time, while also working outside the home (78). Under these circumstances, even those individuals who do have the time to participate may not see the value in altering their regular routines as this may pose much higher opportunity costs, including the loss of potential wages, than for those with more resources (79-81). (Issues of remuneration are also at play here, and are discussed in later sections.) One study on HIV/AIDS research in Black men with a history of drug use found that, despite their willingness, eligible participants were often not able to participate due to competing interests related to work and family (82). In focus groups and in-depth interviews with Asian American women assessing perceived barriers to participation in cervical cancer prevention research, reasons for non-participation included lack of time and inconvenience (83). Time conflicts and child care responsibilities also emerged as barriers to participation in research for a study examining the perspectives of Black- and Latinx immigrant participants (84). A systematic review of barriers to study retention found that the most commonly reported barrier was competing priorities related to participants’ socially disadvantaged status (19).

Health Care Access

Closely related to socioeconomic status is access to health care. Lack of or limited health care access is a root cause of inequitable health care throughout the US. Besides obvious health care consequences, this inequity also has implications for research. Patients who are not actively engaged with the health care system will have limited opportunity for enrollment in studies.

Strong, trusting relationships with primary care providers (PCP) have been noted to have significant impacts on research engagement (21, 25, 64, 85, 86). In one study performed in a five geographically diverse health care centers (New York City; Baltimore, Maryland; Birmingham, Alabama; Iowa City, Iowa, and Boston, Massachusetts) found that the positive endorsement of a PCP led to increased likelihood of participation, while a negative attitude almost always led to a refusal to enroll (24). In another study, simply having a primary care provider was the strongest predictor of clinical trial follow-up among a population of predominantly ethnically underrepresented individuals; socioeconomic status, interestingly, was not significantly associated with follow-up (85). A North Carolina study on the involvement of Black male cancer survivors in research found that these patients and their families expressed significant trust in their physicians and would be open to enrollment in a research study if their physician suggested it (86). Conversely, patients who are reluctant to visit their PCPs are more likely to be non-participants in medical research (64). This pattern also holds for other members of the health care team, such as nurses, with patients reporting that they would not participate in a trial if their nurse does not recommend it (21).

A number of studies have determined that the distance to health care and clinical research from patient home or home communities is also a barrier. Most clinical research takes place at or near large academic centers that are less frequently used by underrepresented populations in comparison to community health settings. The greater the distance between home communities and where patients are required to present for initial involvement, study visits, or exit interviews, the less likely they are to participate (2, 68, 75). Given the issue of distance, challenges with

transportation have also been identified amongst the most common reasons for not participating in research studies (81). Conversely, a qualitative study assessing the effectiveness of offering transportation via a research van that would pick up participants in their home communities and then drive them to the research study site found that participants were highly satisfied with the convenience that transportation offered (87). This relationship has been specifically established with regard to Native Hawaiian and Pacific Islander populations where individuals may be more likely to be living in more remote areas and in under-resourced settings away from where research usually takes place (88). Research activities that do not offer transportation thus do so at the risk of excluding those without access.

Finally, limited knowledge of physicians and other health care providers who work outside of academic centers regarding available research opportunities is a barrier to recruitment. This may be particularly true in rural communities, such as those in eastern North Carolina where even an intervention to increase cancer study enrollment was only minimally successful (89). The same is often true for physicians near academic medical centers; in a survey of over 100 physicians in New Jersey, lack of awareness of cancer research opportunities was reported by 95% of PCPs, 84% of non-oncology specialists, and even 50% of oncologists (90).

Cultural Characteristics

It would be impossible in the scope of this or any manuscript to describe the multitude of cultural factors that might shape an individual or group's willingness to engage in research. However, there are some broader themes for underrepresented populations and women that are important to highlight. Cultural beliefs affecting willingness to participate in research related to posthumous brain donation have been deeply explored. For example, the need for the brain to be removed from the body and the need for autopsies for educational or research purposes has been shown to be well-accepted among a diverse group of individuals including Asian, Black, Latinx, and

White Americans. One study found that there were few differences between English and non-English fluent individuals for brain donation in cancer trials (91). One relevant difference was that there was more emphasis on family and interpersonal decision-making for Spanish speakers compared to more individual decision-making for English speakers. Alternatively, some Chinese participants wondered how aspects of the actual brain removal process might be in line with or in conflict with their values (91).

Faith-based barriers to research enrollment have also been explored and there is little evidence to suggest that this is a common or significant driver against participation; on the contrary, the data suggests that faith can have a positive impact on underrepresented individuals' willingness to participate in research. A study done on a nationwide sample of Black and White Americans found that an association with religious activity was a positive predictor for Black Americans and a negative predictor for White Americans (92). In another study, Black respondents were more likely to look to their churches as reliable sources of information and guidance on research opportunities (93).

Stigmas regarding specific areas of research may also serve as barriers among specific populations. An exploration of perceptions among Black American participants for a psychiatry study demonstrated concerns related to the types of study procedures involved, a lack of confidentiality surrounding mental health illness, and potential medical record exposure (23).

Finally, a lack of concordance between researcher and participant race and ethnicity has also been suggested as a potential barrier to enrollment of underrepresented individuals. While the absence of diversity in both the medical and research communities has been well-documented (72), there is little in the way of evidence to suggest that increased concordance would increase participation. In one study of HIV-positive adults only 12% of respondents felt that having a research staff of the same race was important (21). Another study promoting group management of heart failure among Black individuals found that most participants did not request a Black group

leader (94). However, a number of Black participants did ask that the people helping to manage their diets provided culturally-relevant suggestions. Respondents to a survey of Hmong-speaking people said that speaking the same language was less important for participation than having a trusting relationship with researchers who were known and had created relationships within their communities (33). Finally, an analysis of Black Americans who either elected or declined to participate in a study on kidney disease found that neither the gender nor the ethnicity of the recruiter had any influence on likelihood of enrollment (64). Perhaps similar to the issues of trust and willingness to participate, racial, ethnic, and gender concordance may be a commonly presumed barrier to research engagement that simply does not have a major real-world impact.

Barriers Internal to Research Infrastructure

The structure and organization of medical research that has developed over the past decades has led to amazing leaps in medical knowledge and therapies. Unfortunately, the existing system also reduces or even excludes participation by a diverse participant population. The authors of a systematic review of 40 years of cancer treatment or prevention trials summed up the issue well writing that “[b]ecause opportunity barriers largely reflect protocol design as well as the process of study implementation, investigators play a major role in determining the extent to which trials are accessible to underrepresented groups” (51). A number of barriers in this area have been described including attitudes and biases of research staff, recruitment methods, inclusion and exclusion criteria development, and issues surrounding cultural awareness and literacy.

Research Team Attitudes and Biases

Despite their demonstrated willingness, underrepresented populations are often not asked to participate in clinical research. Evidence suggests that at least part of the reason for this lies in the attitudes and biases of the research staff and health care providers who are responsible for

recruitment. Whether intentional or unconscious, the power of this bias is real and often starts at the top with principal investigators (PIs).

In a 2020 survey of 440 PIs doing work funded by the National Heart, Lung, and Blood Institute, only 2.7% set recruitment goals for underrepresented racial and ethnic groups (95). Among those who did set recruitment goals for one or more groups, they failed to meet those goals frequently and more often for Asian, Black, and Latinx participants than for White participants. The lack of enrollment goals negates any postulated theory that the size of available minority participant pools dictate inclusion in clinical research. Rather, there seems to be a lack of attention paid to even identifying which participant pools should be targeted and with what intensity. There is also evidence that, while acknowledging the importance of diversity in an abstract way, PIs may not see diversity as an important factor in their own work. A recent study of 313 researchers at a large research university found that while 87% of respondents believed that diversity was very or extremely important, only 38% reported that it was a priority in their own research programs (96).

In addition to PIs, so-called “gatekeepers” have been described as the individuals who actually control the flow of participants into research studies. These gatekeepers, whether medically or non-medically trained, may carry paternalistic biases that prevent them from even attempting to enroll certain groups (19, 73). Gatekeeper ideas about a potential participant’s reliability, health literacy, language skills, and social support, among other factors, all play into whether the potential participant will be offered information on enrollment (97). In one study, 92% of HIV/AIDS researchers felt that IV drug users would need more support during trial participation than so-called ‘traditional’ participants; 50-60% of these researchers believed that Black and Latinx individuals, as well as women, also need additional support (98). In the same study, these researchers also had biases regarding the willingness of different groups to enroll in studies: 77% felt that White men were generally highly interested compared to 33% for White women, 20% for Black men, 16% for Black women, 13% for Latinx men, and 11% for Latinx women. These numbers

are in direct opposition to the actual results of willingness to participate studies as previously discussed. Although it may be true that some individuals or groups do, in fact, need extra support to participate successfully in a research project, the apparent (and inaccurate) inverse relationship these researchers seem to see between amount of support needed and willingness to participate suggests a bias against trying to enroll these underrepresented populations.

Although efforts to decrease implicit bias and increase cultural awareness are on the rise, this remains a significant gap in our current system (99). As a result, research team members do not spend as much time or effort trying to recruit participants from so-called 'hard-to-reach' populations. In one study, oncologists used far fewer words and spent significantly less time with Black than White patients, both in terms of the overall visit and with regard to clinical trial enrollment (100). Additionally, discussion of clinical trials was less robust for Black patients, with more emphasis on voluntary participation and less focus on the purposes and risks of participation. A different survey of Black cancer patients found that only one-third of eligible patients reported being given written information on possible clinical trials (101). Among a population of HIV/AIDS patients throughout the US, Latinx respondents were less likely to know about research opportunities compared to both White and Black respondents, and Latinx and Black patients were less likely to be notified about possible enrollment by any member any clinical or research team (102).

The consequence of the combined above factors is a research system where underrepresented minority groups are not given the information or the opportunity to participate and thus remain underrepresented in clinical research. While often underemphasized, the attitudes and biases of research team members represent important domains in the lack of inclusion of underrepresented racial and ethnic populations and women in clinical research.

Recruitment Methods

A number of characteristics of the research recruitment structure contribute to the limited inclusion of women and underrepresented populations in research. Statistical methods, such as random sampling, may decrease the chances of diverse enrollment. Often, random sampling methods simply do not result in large enough study populations to capture the needed diversity (19). Random sampling can miss people who may want to remain hidden for a myriad of reasons, such as LGBTQI individuals or people who use IV drugs (19). In addition, our current research infrastructure increasingly values statistically robust research methodologies (e.g., randomized controlled trials) as the most compelling way to demonstrate effect size. However, it should be emphasized that it is community-based participatory research (CBPR), and not randomized controlled trials, that excels in engaging participants from communities that have been historically excluded from research participation. While CBPR is considered to be outside the realm of clinical trials with a focus on cultural appropriateness and alignment with community needs, understanding the context of these communities is essential to engaging them and thus increasing participation.

Different recruitment methods have been shown to work for different populations. Mass media, including television, radio, and newspaper ads, may work well for one group, while word-of-mouth is much more suitable for another (103-105). Unfortunately, though perhaps not surprisingly given the heterogeneity of communities within racial and ethnic groups, the data in this area is not consistent, though there is a trend towards referral and word-of-mouth methods as being more effective for underrepresented populations as compared to more traditional methods (103, 104). Specific challenges exist when trying to recruit Native Americans related to both their physical locations and the structure of the Indian Health Service (IHS). Over 50% of Native Americans live in urban areas, while only 2% of IHS funds are allocated to clinics in these areas; opportunities to interact with possible researchers is thus significantly limited. Additionally, most

studies require IHS and/or tribal approval, in addition to standard IRB approval, posing another hurdle to successful recruitment of this population for research teams who may be limited in terms of time and resources they can spending orchestrating recruitment (88).

Remuneration methods may impact enrollment, especially for women. In a study examining recruitment and enrollment of people with HIV, men were found to be better retained by interventions associated with financial resources, while HIV-positive women had increased enrollment and retention when incentives involved social and emotional resources as a part of the remuneration (106). The development and delivery of these social and emotional resources is almost certainly more difficult than obtaining financial resources. There is also evidence that Black individuals, both men and women, feel that the financial compensation offered for participation is inadequate (72). Separate data confirms this is a factor especially for working women (58). In the same study, some respondents stated that additional incentives were needed outweigh the challenges associated with making time to participate. Women with lower incomes have been shown to be especially concerned about their ability to manage unexpected requests or unforeseen consequences of participation due to their limited resources (38).

This data conflicts with current research dogma that discourages high levels of remuneration, particularly for people with lower socioeconomic status (107-110). This is a product of fears of coercive remuneration on the part of research entities and concerns about reducing an individual's agency to decline enrollment by offering remuneration that they would otherwise be unable to obtain. These dictums, however, are mostly theoretical products of game theory that reflect the historical approach to research recruitment rather than any evidence.

Concerns around insurance have also been posited as a possible reason for increased hesitation to enroll. The data on this question, however, do not show much difference between racial or ethnic groups (57, 111). In a study related to cancer-focused clinical trials, worries about insurance coverage of trial activities were the most commonly cited barriers for all groups

surveyed (White, Latinx and Black) (57). A study among Black cancer patients found that, not surprisingly, those who felt overwhelmed by their diagnoses were also more likely to have fears about insurance coverage issues (46). Researchers who do not address these concerns will have difficulty enrolling patients from all backgrounds, and more data is needed in this area to further delineate the effect of insurance coverage on various groups.

Finally, the length and complexity of the research process, especially the consent process and consent forms, has also been reported as a barrier to enrollment for underrepresented populations (21, 59, 112). In one study of HIV-positive Black and Latinx individuals, 19% cited the consent form being too hard to understand as a reason why they did not participate (21). The long timeframe of most research projects may also reduce willingness to participate or remain enrolled in a clinical trial. A model created using data from potential cancer research participants found that the longer the time between a potential participant's consent to first contact by a study team member predicted probability of attrition; this effect was higher among racially underrepresented people compared to White individuals (112). Current consent process and consent forms are linguistically and culturally inappropriate for many underrepresented groups.

All of the above mentioned challenges—study design, outreach methods, choice of incentives, and research processes—are exacerbated by time and financial restrictions placed on researchers. Prioritizing speed, combined with a historically uninformed approach to minority recruitment, has led to a system in which research trials do not include adequate underrepresented population participation. More time, money, and effort need to be put into recruitment methods if researchers are to successfully attract a diverse participant population.

Cultural Literacy

Conversations around literacy in the field of medicine and medical research often focus on the so-called “health literacy” and language barriers of patients and potential participants. In

reality, the problem is one of cultural literacy on the part of researchers and within the research structure. Although there is certainly a varied level of understanding of medical and scientific topics among individuals, it is possible to engage across a spectrum of participants if appropriate efforts are made. A study of Asian, Black, Latinx, and White men with prostate cancer in California found no difference between people with low health literacy – measured using three validated questions – and those with medium or high health literacy with regard to their willingness to participate in clinical trials (55). The same study used a questionnaire to assess general knowledge of clinical trials and, again, found no difference in willingness to participate based on the respondent's understanding of research.

Researchers are often not trained or skilled in terms of explaining research methodologies or the potential positive impacts of research outcomes in ways that actively engage ethnically underrepresented populations (19, 113). Studies examining recruitment with regard to publicity and advertising of research studies have identified that there is a general failure to message the positive implications of research outcomes. Yet there is evidence that this problem can be solved or mitigated. In a qualitative study exploring reasons for consent or refusal to participate in a comparative effectiveness study, researchers found that further explaining how a comparative effectiveness study works – for example, emphasizing that it does not test new medications – increased respondent's positive views of the study (24). A group of researchers in Baltimore were able to successfully recruit a diverse cohort of over 3,700 participants into a 20-year longitudinal study on aging in part by focusing on the direct benefits to the enrollees of their participation (73). Similar studies have shown increased interest in research when people believe the research might provide personal, familial, or societal benefits (64, 91). Expanding the research infrastructure to include more patient education would likely have a significant impact on increased enrollment among underrepresented individuals.

Part of this expanded infrastructure should include putting increased resources towards developing language-appropriate recruitment materials. The lack of suitable study materials in their respective languages has been shown to reduce participation of Asian, Creole, Hmong, Latinx, and Native Americans, as well as Native Hawaiian/Pacific Islanders (33, 35, 57, 83, 84, 88, 114-117). And even when language-specific materials are available, the quality and integrity of those materials may not be high. An additional factor is that for many languages, it is important not to translate verbatim; these simple translations are unlikely to capture the true meaning of the materials without incorporating commonly used idioms and culturally appropriate phrasing. This may especially be true for Spanish-speaking groups, as there are significant differences among the languages spoken in different Spanish-speaking countries (35). Translations that do not reflect the appropriate dialect or accepted verbal usage patterns can further push targeted populations away from enrollment rather than toward. Fundamentally, it is incumbent on the research team leadership, including PIs and institutions themselves, to not only allow for time and money to be put towards these efforts, but to require it.

Inclusion and Exclusion Criteria

Another element of the existing research structure that serves as a barrier to diverse research populations is the development of inclusion and exclusion criteria. These eligibility criteria must be intentionally restrictive based on the science of the question being evaluated, yet these restrictions often lead to the unintentional exclusion of certain groups (59, 79).

An example of this is when inclusion criteria require baseline clinical values that fall within a certain range—a range that has been developed based on data that itself has been collected from a population that may not include diverse cohorts. Asthma researchers trying to assess differences in bronchodilator response found that potential underrepresented individuals had inadequate responses to the methacholine challenge, one of the inclusion criteria (34). The methacholine

challenge cut-off number may have lacked sensitivity for underrepresented populations given previously reported differences in methacholine responsiveness among different racial/ethnic groups (118). Similarly, a lack of pre-existing or baseline data may unintentionally exclude possible participants. Initial chart review to determine eligibility for a study on COPD, for example, unintentionally missed patients without baseline spirometry data, despite the designers' intentions to minimize exclusion criteria and maximize enrollment of underrepresented populations (119).

An analysis of the exclusion criteria for a study on smoking cessation found that the exclusion criteria did indeed more frequently exclude Black and Latinx patients as compared to White patients (120). In this analysis, White patients were usually excluded for a single reason, such as difficulty with attendance or medical conditions, whereas Black patients were more than twice as likely to be excluded for three or more reasons. Another report, also on eligibility for a smoking cessation study, found that despite being nearly twice as likely as White contacts to complete initial telephone screening, Black contacts were less likely to be eligible for enrollment (103). This difference persisted even when controlling for demographic factors such as education, gender, and income level. These analyses illustrate how the structure of our current inclusion and exclusion criteria are – intentionally or not – reducing the opportunities for underrepresented individuals to participate in research.

Finally, a basic lack of access to adequate health care, as previously discussed, is more common among traditionally underrepresented populations and can lead to delayed diagnoses (121, 122). Having a more advanced form of a disease can often make individuals ineligible for study enrollment. Review of cancer trial recruitment among a medically underserved population that included Native Americans found that restrictive inclusion criteria was one of the top two major reasons for lack of enrollment—the other being a lack of protocols available for participant review (69). Among the 88 potential Native American, advanced stage/poor performance was the number one reason for non-enrollment (27%).

Conclusions

The past 20 years have seen an expansion in interest in both diversifying clinical research and investigating the root causes of the current lack of inclusion. There are certainly a number of individual level characteristics that can affect likelihood of enrollment into a research trial. Among these are issues of distrust/mistrust, socioeconomic challenges, cultural characteristics, and general access to health care. Although they should not be minimized given their very legitimate foundation, we believe that issues of distrust/mistrust are more likely to be impacted by addressing the systematic and structural barriers to participation that exist within the research infrastructure, rather than by dedicated trust-building efforts. Likewise, researchers have limited ability to change the overall economic challenges or health care access issues of potential participants. Certainly efforts to change cultural conventions of participants should not occur. Rather, there are a number of structural factors that exist within the current research infrastructure that are well-within the control of the research community and should therefore be the primary focus of future attempts at increasing diversity in clinical trial recruitment. In implementing practical and resource-based counter-measures to solve for these structural barriers, movement toward more inclusive, accessible, equitable, and trustworthy research operations can occur.

Broadening recruitment methods as well as the inclusion and exclusion criteria for research studies in an equitable and non-biased way would increase the pool of participants eligible to be enrolled. Increasing the time and money spent on improving cultural literacy among research teams is essential for studies to be carried out in truly culturally- and language-appropriate ways. Finally, changing the attitudes and reducing the biases of researchers would be an effective way to create an environment in which the inclusion of diverse participants becomes the norm, rather than the exception. We believe that by focusing on these areas of intervention (Figure), the research community can significantly change the structure of clinical research and trials in a way that

improves the recruitment of underrepresented individuals and women, ultimately contributing to improved research programs and more useful research findings.

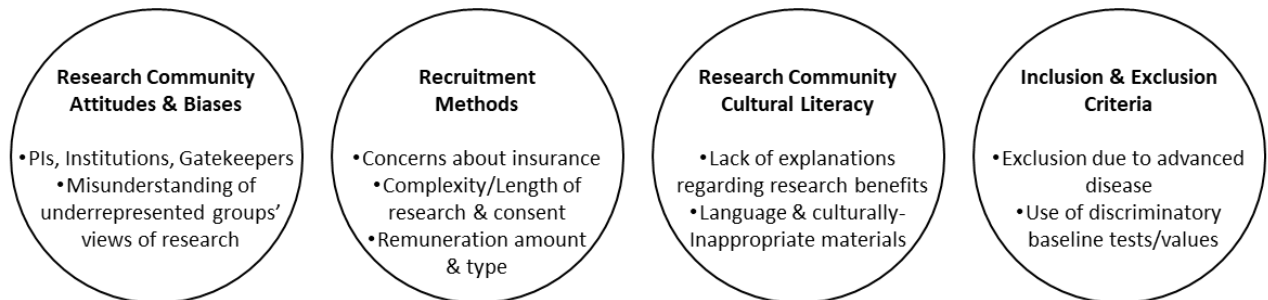


Figure. Internal Research Domains with Associated Barriers to Inclusion of Underrepresented Populations

References

1. NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research. Bethesda, Maryland: National Institutes of Health; 2017.
2. Coakley M, Fadiran EO, Parrish LJ, Griffith RA, Weiss E, Carter C. Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities in Clinical Trials. *Journal of Women's Health*. 2012;21(7):713-6.
3. Diversifying clinical trials. *Nat Med*. 2018;24(12):1779.
4. Wissing MD, Kluetz PG, Ning YM, Bull J, Merenda C, Murgo AJ, et al. Under-representation of racial minorities in prostate cancer studies submitted to the US Food and Drug Administration to support potential marketing approval, 1993-2013. *Cancer*. 2014;120(19):3025-32.
5. Ramasubbu K, Gurm H, Litaker D. Gender bias in clinical trials: Do double standards still apply? *J Women's Health Gender Med*. 2001;10(8):757-64.
6. Vidaver RM, Lafleur B, Tong C, Bradshaw R, Marts SA. Women subjects in NIH-funded clinical research literature: Lack of progress in both representation and analysis by sex. *J Women Health Gen-B*. 2000;9(5):495-504.
7. Duma N, Aguilera JV, Paludo J, Haddox CL, Velez MG, Wang YC, et al. Representation of Minorities and Women in Oncology Clinical Trials: Review of the Past 14 Years. *J Oncol Pract*. 2018;14(1):e1-e7.
8. Tahhan AS, Vaduganathan M, Greene SJ, Alrohaibani A, Raad M, Gafeer M, et al. Enrollment of Older Patients, Women, and Racial/Ethnic Minority Groups in Contemporary Acute Coronary Syndrome Clinical Trials: A Systematic Review. *JAMA Cardiology*. 2020;5(6):714-22.
9. Tahhan AS, Vaduganathan M, Greene SJ, Fonarow GC, Fiuzat M, Jessup M, et al. Enrollment of Older Patients, Women, and Racial and Ethnic Minorities in Contemporary Heart Failure Clinical Trials: A Systematic Review. *JAMA cardiology*. 2018;3(10):1011-9.
10. Ashford MT, Eichenbaum J, Williams T, Camacho MR, Fockler J, Ulbricht A, et al. Effects of sex, race, ethnicity, and education on online aging research participation. *Alzheimers Dement Transl Res Clin Interv*. 2020;6(1):e12028.
11. Huamani KF, Metch B, Broder G, Andrasik M. A Demographic Analysis of Racial/Ethnic Minority Enrollment Into HVTN Preventive Early Phase HIV Vaccine Clinical Trials Conducted in the United States, 2002-2016. *Public Health Rep*. 2019;134(1):72-80.
12. Flanagan A, Frey T, Christiansen SL, Committee AMAMoS. Updated Guidance on the Reporting of Race and Ethnicity in Medical and Science Journals. *JAMA*. 2021;326(7):621-7.
13. Griffith DM, Bergner EM, Fair AS, Wilkins CH. Using Mistrust, Distrust, and Low Trust Precisely in Medical Care and Medical Research Advances Health Equity. *American Journal of Preventive Medicine*. 2021;60(3):442-5.
14. Hoyo C, Reid ML, Godley PA, Parrish T, Smith L, Gammon M. Barriers and strategies for sustained participation of African-American men in cohort studies. *Ethni Dis*. 2003;13(4):470-6.

15. Hughes TB, Varma VR, Pettigrew C, Albert MS, Bowers BJ. African Americans and clinical research: Evidence concerning barriers and facilitators to participation and recruitment recommendations. *Gerontologist*. 2017;57(2):348-58.
16. Newman PA, Duan N, Roberts KJ, Seiden D, Rudy ET, Swendeman D, et al. HIV vaccine trial participation among ethnic minority communities: Barriers, motivators, and implications for recruitment. *J Acquired Immune Defic Syndr*. 2006;41(2):210-7.
17. James DCS, Harville C, II, Efunbumi O, Babazadeh I, Ali S. "You Have to Approach Us Right": A Qualitative Framework Analysis for Recruiting African Americans Into mHealth Research. *Health Educ Behav*. 2017;44(5):781-90.
18. Moreno-John G, Gachie A, Fleming CM, Napoles-Springer A, Mutran E, Manson SM, et al. Ethnic minority older adults participating in clinical research: developing trust. *Journal of aging and health*. 2004;16(5 Suppl):93S-123S.
19. Bonevski B, Randell M, Paul C, Chapman K, Twyman L, Bryant J, et al. Reaching the hard-to-reach: a systematic review of strategies for improving health and medical research with socially disadvantaged groups. *BMC Med Res Methodol*. 2014;14:42.
20. George S, Duran N, Norris K. A Systematic Review of Barriers and Facilitators to Minority Research Participation Among African Americans, Latinos, Asian Americans, and Pacific Islanders. *Am J Public Health*. 2014;104(2):E16-E31.
21. Adeyemi OF, Evans AT, Bahk M. HIV-infected adults from minority ethnic groups are willing to participate in research if asked. *AIDS Patient Care STDs*. 2009;23(10):859-65.
22. Smirnoff M, Wilets I, Ragin DF, Adams R, Holohan J, Rhodes R, et al. A paradigm for understanding trust and mistrust in medical research: The Community VOICES study. *AJOB Empir Bioethics*. 2018;9(1):39-47.
23. Murphy E, Thompson A. An exploration of attitudes among Black Americans towards psychiatric genetic research. *Psychiatry (USA)*. 2009;72(2):177-94.
24. Behringer-Massera S, Browne T, George G, Duran S, Cherrington A, McKee MD, et al. Facilitators and barriers to successful recruitment into a large comparative effectiveness trial: a qualitative study. *J Comp Eff Res*. 2019;8(10):815-26.
25. Buchbinder SP, Metch B, Holte SE, Scheer S, Coletti A, Vittinghoff E. Determinants of Enrollment in a Preventive HIV Vaccine Trial: Hypothetical Versus Actual Willingness and Barriers to Participation. *J Acquired Immune Defic Syndr*. 2004;36(1):604-12.
26. Byrd GS, Edwards CL, Kelkar VA, Phillips RG, Byrd JR, Pim-Pong DS, et al. Recruiting intergenerational African American males for biomedical research Studies: a major research challenge. *J Natl Med Assoc*. 2011;103(6):480-7.
27. Scharff DP, Mathews KJ, Jackson P, Hoffsuemmer J, Martin E, Edwards D. More than Tuskegee: understanding mistrust about research participation. *Journal of health care for the poor and underserved*. 2010;21(3):879-97.

28. Corbie-Smith G, Thomas SB, St George DM. Distrust, race, and research. *Arch Intern Med*. 2002;162(21):2458-63.
29. Braunstein JB, Sherber NS, Schulman SP, Ding EL, Powe NR. Race, medical researcher distrust, perceived harm, and willingness to participate in cardiovascular prevention trials. *Medicine (USA)*. 2008;87(1):1-9.
30. Bussey-Jones J, Garrett J, Henderson G, Moloney M, Blumenthal C, Corbie-Smith G. The role of race and trust in tissue/blood donation for genetic research. *Gen Med*. 2010;12(2):116-21.
31. Murphy EJ, Wickramaratne P, Weissman MM. Racial and ethnic differences in willingness to participate in psychiatric genetic research. *Psychiatr Genet*. 2009;19(4):186-94.
32. Haynes-Maslow L, Godley P, Dimartino L, White B, Odom J, Richmond A, et al. African American women's perceptions of cancer clinical trials. *Cancer Med*. 2014;3(5):1430-9.
33. Lor M, Bowers BJ. Hmong Older Adults' Perceptions of Insider and Outsider Researchers: Does It Matter for Research Participation? *Nursing research*. 2018;67(3):222-30.
34. Hardie GE, Liu R, Darden J, Gold WM. Recruitment of asthmatic ethnic minorities into a methacholine research study: Factors influencing participation. *J Natl Med Assoc*. 2011;103(2):138-49.
35. Occa A, Morgan SE, Potter JNE. Underrepresentation of Hispanics and Other Minorities in Clinical Trials: Recruiters' Perspectives. *J Racial Ethn Health Disparities*. 2018;5(2):322-32.
36. Byrd GS, Edwards CL, Kelkar VA, Phillips RG, Byrd JR, Pim-Pong DS, et al. Recruiting intergenerational African American males for biomedical research studies: A major research challenge. *J Natl Med Assoc*. 2011;103(6):480-7.
37. BeLue R, Taylor-Richardson KD, Lin J, Rivera AT, Grandison D. African Americans and participation in clinical trials: Differences in beliefs and attitudes by gender. *Contemp Clin Trials*. 2006;27(6):498-505.
38. Voytek CD, Jones KT, Metzger DS. Selectively willing and conditionally able: HIV vaccine trial participation among women at "high risk" of HIV infection. *Vaccine*. 2011;29(36):6130-5.
39. Gollin LX, Harrigan RC, Calderon JL, Perez J, Easa D. Improving Hawaiian and Filipino involvement in clinical research opportunities: qualitative findings from Hawai'i. *Ethn Dis*. 2005;15(4 Suppl 5):S5-111-9.
40. Maxwell AE, Bastani R, Vida P, Warda US. Strategies to recruit and retain older Filipino-American immigrants for a cancer screening study. *J Community Health*. 2005;30(3):167-79.
41. Sadler GR, Gonzalez J, Mumman M, Cullen L, Lahousse SF, Malcarne V, et al. Adapting a program to inform African American and Hispanic American women about cancer clinical trials. *Cancer Educ*. 2010;25(2):142-5.
42. Katz RV, Green BL, Kressin NR, Claudio C, Wang MQ, Russell SL. Willingness of minorities to participate in biomedical studies: Confirmatory findings from a follow-up study using the Tuskegee Legacy Project Questionnaire. *J Natl Med Assoc*. 2007;99(9):1052-60.

43. Katz RV, Green BL, Kressin NR, Kegeles SS, Wang MQ, James SA, et al. The legacy of the tuskegee syphilis study: Assessing its impact on willingness to participate in biomedical studies. *Journal of Health Care for the Poor and Underserved*. 2008;19(4):1168-80.
44. Katz RV, Kegeles SS, Kressin NR, Green BL, Wang MQ, James SA, et al. The Tuskegee Legacy Project: Willingness of minorities to participate in biomedical research. *Journal of Health Care for the Poor and Underserved*. 2006;17(4):698-715.
45. Katz RV, Kegeles SS, Kressin NR, Green BL, James SA, Wang MQ, et al. Awareness of the Tuskegee Syphilis Study and the US presidential apology and their influence on minority participation in biomedical research. *Am J Public Health*. 2008;98(6):1137-42.
46. Alhajji M, Bass SB, Nicholson A, Washington A, Maurer L, Geynisman DM, et al. Comparing Perceptions and Decisional Conflict Towards Participation in Cancer Clinical Trials Among African American Patients Who Have and Have Not Participated. *J Cancer Educ*. 2020.
47. Garber M, Hanusa BH, Switzer GE, Mellors J, Arnold RM. HIV-infected African Americans are willing to participate in HIV treatment trials. *J Gen Intern Med*. 2007;22(1):17-42.
48. Webb FJ, Khubchandani J, Striley CW, Cottler LB. Black-White Differences in Willingness to Participate and Perceptions About Health Research: Results from the Population-Based HealthStreet Study. *J Immigr Minor Health*. 2019;21(2):299-305.
49. Westergaard RP, Beach MC, Saha S, Jacobs EA. Racial/ethnic differences in trust in health care: HIV conspiracy beliefs and vaccine research participation. *J Gen Intern Med*. 2014;29(1):140-6.
50. Ford ME, Siminoff LA, Pickelsimer E, Mainous AG, Smith DW, Diaz VA, et al. Unequal burden of disease, unequal participation in clinical trials: Solutions from African American and Latino community members. *Health Soc Work*. 2013;38(1):29-38.
51. Ford JG, Howerton MW, Lai GY, Gary TL, Mid SB, Gibbons MC, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. *Cancer*. 2008;112(2):228-42.
52. Trant AA, Walz L, Allen W, DeJesus J, Hatzis C, Silber A. Increasing accrual of minority patients in breast cancer clinical trials. *Breast Cancer Res Treat*. 2020;184(2):499-505.
53. Bishop WP, Tiro JA, Lee SJC, Bruce CM, Skinner CS. Community events as viable sites for recruiting minority volunteers who agree to be contacted for future research. *Contemp Clin Trials*. 2011;32(3):369-71.
54. Sanderson SC, Diefenbach MA, Zinberg R, Horowitz CR, Smirnoff M, Zweig M, et al. Willingness to participate in genomics research and desire for personal results among underrepresented minority patients: A structured interview study. *J Community Genet*. 2013;4(4):469-82.
55. Kaplan CP, Nápoles AM, Narine S, Gregorich S, Livaudais-Toman J, Nguyen T, et al. Knowledge and attitudes regarding clinical trials and willingness to participate among prostate cancer patients. *Contemp Clin Trials*. 2015;45:443-8.

56. McElfish PA, Long CR, Selig JP, Rowland B, Purvis RS, James L, et al. Health Research Participation, Opportunity, and Willingness Among Minority and Rural Communities of Arkansas. *Clin Transl Sci*. 2018;11(5):487-97.
57. Byrne MM, Tannenbaum SL, Glück S, Hurley J, Antoni M. Participation in cancer clinical trials: Why are patients not participating? *Med Decis Mak*. 2014;34(1):116-26.
58. Bieniasz ME, Underwood D, Bailey J, Ruffin 4th MT. Women's feedback on a chemopreventive trial for cervical dysplasia. *Appl Nurs Res*. 2003;16(1):22-8.
59. Langford AT, Resnicow K, Dimond EP, Denicoff AM, Germain DS, McCaskill-Stevens W, et al. Racial/ethnic differences in clinical trial enrollment, refusal rates, ineligibility, and reasons for decline among patients at sites in the National Cancer Institute's Community Cancer Centers Program. *Cancer*. 2014;120(6):877-84.
60. Priddy FH, Cheng AC, Salazar LF, Frew PM. Racial and ethnic differences in knowledge and willingness to participate in HIV vaccine trials in an urban population in the Southeastern US. *Int J STD AIDS*. 2006;17(2):99-102.
61. Thetford K, Gillespie TW, Kim YI, Hansen B, Scarinci IC. Willingness of latinx and African Americans to participate in nontherapeutic trials: It depends on who runs the research. *Ethni Dis*. 2021;31(2):263-72.
62. Arega A, Birkmeyer NJO, Lurie JDN, Tosteson T, Gibson J, Taylor BA, et al. Racial variation in treatment preferences and willingness to randomize in the Spine Patient Outcomes Research Trial (SPORT). *Spine*. 2006;31(19):2263-9.
63. Evans MK, Lepkowski JM, Powe NR, LaVeist T, Kuczmarski MF, Zonderman AB. Healthy aging in neighborhoods of diversity across the life span (HANDLS): Overcoming barriers to implementing a longitudinal, epidemiologic, urban study of health, race, and socioeconomic status. *Ethni Dis*. 2010;20(3):267-75.
64. Gadegbeku CA, Stillman PK, Huffman MD, Jackson JS, Kusek JW, Jamerson KA. Factors associated with enrollment of African Americans into a clinical trial: Results from the African American study of kidney disease and hypertension. *Contemp Clin Trials*. 2008;29(6):837-42.
65. Manders DB, Paulsen A, Richardson DL, Kehoe SM, Miller DS, Lea JS. Factors associated with clinical trial screening failures in gynecologic oncology. *Gynecol Oncol*. 2014;134(3):450-4.
66. Hillyer GC, Beauchemin M, Hershman DL, Kelsen M, Brogan FL, Sandoval R, et al. Discordant attitudes and beliefs about cancer clinical trial participation between physicians, research staff, and cancer patients. *Clin Trials*. 2020;17(2):184-94.
67. Ceballos RM, Knerr S, Scott MA, Hohl SD, Malen RC, Vilchis H, et al. Latino beliefs about biomedical research participation: A qualitative study on the U.S.-Mexico border. *J Empir Res Hum Res Ethics*. 2014;9(4):10-21.
68. Sprague D, Russo J, Lavallie DL, Buchwald D. Barriers to cancer clinical trial participation among American Indian and Alaska Native tribal college students. *J Rural Health*. 2013;29(1):55-60.

69. Guadagnolo BA, Petereit DG, Helbig P, Koop D, Kussman P, Dunn EF, et al. Involving American Indians and medically underserved rural populations in cancer clinical trials. *Clin Trials*. 2009;6(6):610-7.
70. Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, Pratt LA, et al. Are racial and ethnic minorities less willing to participate in health research? *Plos Med*. 2006;3(2):201-10.
71. Webb DA, Coyne JC, Goldenberg RL, Hogan VK, Elo IT, Bloch JR, et al. Recruitment and retention of women in a large randomized control trial to reduce repeat preterm births: The Philadelphia Collaborative Preterm Prevention Project. *BMC Med Res Methodol*. 2010;10.
72. Otado J, Kwagyan J, Edwards D, Ukaegbu A, Rockcliffe F, Osafo N. Culturally Competent Strategies for Recruitment and Retention of African American Populations into Clinical Trials. *Clin Transl Sci*. 2015;8(5):460-6.
73. Ejiogu N, Norbeck JH, Mason MA, Cromwell BC, Zonderman AB, Evans MK. Recruitment and retention strategies for minority or poor clinical research participants: Lessons from the healthy aging in neighborhoods of diversity across the life span study. *Gerontologist*. 2011;51(SUPPL. 1):S33-S45.
74. Gilmore-Bykovskiy A, Jackson JD, Wilkins CH. The Urgency of Justice in Research: Beyond COVID-19. *Trends Mol Med*. 2021;27(2):97-100.
75. Unger JM, Gralow JR, Albain KS, Ramsey SD, Hershman DL. Patient Income Level and Cancer Clinical Trial Participation. *JAMA Oncology*. 2016;2(1):137.
76. Earnings: U.S. Department of Labor; 2020 [Available from: <https://www.dol.gov/agencies/wb/data/earnings>].
77. Poverty Rate by Race/Ethnicity: Kaiser Family Foundation; 2019 [Available from: <https://www.kff.org/other/state-indicator/poverty-rate-by-raceethnicity/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D>].
78. Indorewalla KK, O'Connor MK, Budson AE, Guess DiTerlizzi C, Jackson J. Modifiable Barriers for Recruitment and Retention of Older Adults Participants from Underrepresented Minorities in Alzheimer's Disease Research. *J Alzheimers Dis*. 2021;80(3):927-40.
79. Quiñones AR, Mitchell SL, Jackson JD, Aranda MP, Dilworth-Anderson P, McCarthy EP, et al. Achieving Health Equity in Embedded Pragmatic Trials for People Living with Dementia and Their Family Caregivers. *J Am Geriatr Soc*. 2020;68 Suppl 2:S8-S13.
80. Jason T Olin et al. Increasing Ethnic Minority Participation in Alzheimer Disease Research. *Alzheimer Dis Assoc Disord*. 2002;16:A82-S5.
81. Brown DR, Fouad MN, Basen-Engquist K, Tortolero-Luna G. Recruitment and Retention of Minority Women in Cancer Screening, Prevention, and Treatment Trials. *Annals of Epidemiology*. 2000;10(8):S13-S21.

82. Slomka J, Ratliff EA, McCurdy SA, Timpson S, Williams ML. Decisions to participate in research: views of underserved minority drug users with or at risk for HIV. *Aids Care*. 2008;20(10):1224-32.
83. Giarelli E, Bruner DW, Nguyen E, Basham S, Marathe P, Dao D, et al. Research participation among Asian American women at risk for cervical cancer: exploratory pilot of barriers and enhancers. *J Immigr Minor Health*. 2011;13(6):1055-68.
84. Calderon JL, Baker RS, Fabrega H, Conde JG, Hays RD, Fleming E, et al. An ethno-medical perspective on research participation: a qualitative pilot study. *MedGenMed*. 2006;8(2):23.
85. Friedman SH, Cunningham CO, Lin J, Haramati LB, Levsky JM. Having a primary care provider is the strongest predictor of successful follow-up of participants in a clinical trial. *J Am Board Fam Med*. 2020;33(3):431-9.
86. Trantham LC, Carpenter WR, DiMartino LD, White B, Green M, Teal R, et al. Perceptions of cancer clinical research among African american men in North Carolina. *J Natl Med Assoc*. 2015;107(1):33-41.
87. Alcaraz KI, Weaver NL, Andresen EM, Christopher K, Kreuter MW. The neighborhood voice: Evaluating a mobile research vehicle for recruiting african americans to participate in cancer control studies. *Eval Health Prof*. 2011;34(3):336-48.
88. Giuliano AR, Mokuau N, Hughes C, Tortolero-Luna G, Risendal B, Ho RCS, et al. Participation of minorities in cancer research: The influence of structural, cultural, and linguistic factors. *Annals of Epidemiology*. 2000;10(8):S22-S34.
89. Paskett ED, Cooper MR, Stark N, Ricketts TC, Tropman S, Hatzell T, et al. Clinical trial enrollment of rural patients with cancer. *Cancer Pract*. 2002;10(1):28-35.
90. Hudson SV, Memperousse D, Leventhal H. Physician Perspectives on Cancer Clinical Trials and Barriers to Minority Recruitment. *Cancer Control*. 2005:93-6.
91. Boise L, Hinton L, Rosen HJ, Ruhl M. Will My Soul Go to Heaven if They Take My Brain? Beliefs and Worries about Brain Donation among Four Ethnic Groups. *Gerontologist*. 2017;57(4):719-34.
92. Meng J, McLaughlin M, Murphy S, Pariera K. A Comparison Between Caucasians and African Americans in Willingness to Participate in Cancer Clinical Trials: The Roles of Knowledge, Distrust, Information Sources, and Religiosity. *Journal of health communication*. 2016;21(6):669-77.
93. Pariera KL, Murphy ST, Meng J, McLaughlin ML. Exploring Willingness to Participate in Clinical Trials by Ethnicity. *J Racial Ethn Health Disparities*. 2017;4(4):763-9.
94. Rucker-Whitaker C, Flynn KJ, Kravitz G, Eaton C, Calvin JE, Powell LH. Understanding African-American participation in a behavioral intervention: Results from focus groups. *Contemp Clin Trials*. 2006;27(3):274-86.
95. Durant RW, Davis RB, St George DMM, Williams IC, Blumenthal C, Corbie-Smith GM. Participation in research studies: factors associated with failing to meet minority recruitment goals. *Annals of epidemiology*. 2007;17(8):634-42.

96. Passmore SR, Farrar Edwards D, Sorkness CA, Esmond S, Brasier AR. Training needs of investigators and research team members to improve inclusivity in clinical and translational research participation. *J Clin Transl Sci*. 2020;5(1):e57.
97. Joseph G, Dohan D. Diversity of participants in clinical trials in an academic medical center: The role of the 'good study patient?'. *Cancer*. 2009;115(3):608-15.
98. King WD, Defreitas D, Smith K, Andersen J, Perry LP, Adeyemi T, et al. Attitudes and perceptions of AIDS clinical trials group site coordinators on HIV clinical trial recruitment and retention: A descriptive study. *AIDS Patient Care STDs*. 2007;21(8):551-63.
99. O'Brien RL, Kosoko-Lasaki O, Cook CT, Kissell J, Peak F, Williams EH. Self-assessment of cultural attitudes and competence of clinical investigators to enhance recruitment and participation of minority populations in research. *J Natl Med Assoc*. 2006;98(5):674-82.
100. Eggly S, Barton E, Winckles A, Penner LA, Albrecht TL. A disparity of words: Racial differences in oncologist-patient communication about clinical trials. *Health Expect*. 2015;18(5):1316-26.
101. Brown RF, Cadet DL, Houlihan RH, Thomson MD, Pratt EC, Sullivan A, et al. Perceptions of participation in a phase I, II, or III clinical trial among African American patients with cancer: What do refusers say? *J Oncol Pract*. 2013;9(6):287-93.
102. Castillo-Mancilla JR, Cohn SE, Krishnan S, Cespedes M, Floris-Moore M, Schulte G, et al. Minorities Remain Underrepresented in HIV/AIDS Research Despite Access to Clinical Trials. *Hiv Clin Trials*. 2014;15(1):14-26.
103. King AC, Cao D, Southard CC, Matthews A. Racial Differences in Eligibility and Enrollment in a Smoking Cessation Clinical Trial. *Health Psychol*. 2011;30(1):40-8.
104. Bistricky SL, MacKin RS, Chu JP, Areán PA. Recruitment of African Americans and Asian Americans with late-life depression and mild cognitive impairment. *Am J Geriatr Psychiatry*. 2010;18(8):734-42.
105. Coronado GD, Ondelacy S, Schwarz Y, Duggan C, Lampe JW, Neuhouser ML. Recruiting underrepresented groups into the carbohydrates and related biomarkers (CARB) cancer prevention feeding study. *Contemp Clin Trials*. 2012;33(4):641-6.
106. Durantini MR, Albarracín D. Material and Social Incentives to Participation in Behavioral Interventions: A Meta-Analysis of Gender Disparities in Enrollment and Retention in Experimental Human Immunodeficiency Virus Prevention Interventions. *Health Psychol*. 2009;28(5):631-40.
107. Grady C. Payment of clinical research subjects. *J Clin Invest*. 2005;115(7):1681-7.
108. Denny CC, Grady C. Clinical research with economically disadvantaged populations. *J Med Ethics*. 2007;33(7):382-5.
109. Weijer C. What's the price of a research subject? *New Engl J Med*. 1999;341(20):1551.
110. Walter JK, Burke JF, Davis MM. Research Participation by Low-Income and Racial/Ethnic Minority Groups: How Payment May Change the Balance. *Cts-Clin Transl Sci*. 2013;6(5):363-71.

111. Klamerus JF, Bruinooge SS, Ye X, Klamerus ML, Damron D, Lansey D, et al. The impact of insurance on access to cancer clinical trials at a comprehensive cancer center. *Clin Cancer Res*. 2010;16(24):5997-6003.
112. Azfar-e-Alam S, Sikorskii A, Given CW, Given B. Early participant attrition from clinical trials: Role of trial design and logistics. *Clin Trials*. 2008;5(4):328-35.
113. Hughes TB, Varma VR, Pettigrew C, Albert MS. African Americans and Clinical Research: Evidence Concerning Barriers and Facilitators to Participation and Recruitment Recommendations. *The Gerontologist*. 2017;57(2):348-58.
114. Huang H-Y, Ezenwa MO, Wilkie DJ, Judge MK. ResearchTracking: Monitoring gender and ethnic minority recruitment and retention in cancer symptom studies. *Cancer nursing*. 2013;36(3):E1-6.
115. Nguyen TT, Somkin CP, Ma Y, Fung LC, Nguyen T. Participation of Asian-American women in cancer treatment research: a pilot study. *J Natl Cancer Inst Monogr*. 2005(35):102-5.
116. Tu SP, Chen H, Chen A, Lim J, May S, Drescher C. Clinical trials: understanding and perceptions of female Chinese-American cancer patients. *Cancer*. 2005;104(12 Suppl):2999-3005.
117. Lawrence J. The Indian Health Service and the sterilization of Native American women. *Am Indian Q*. 2000;24(3):400-19.
118. Hardie G, Liu R, Darden J, Gold WM. Ethnic Differences in Methacholine Responsiveness and Word Descriptors in African Americans, Hispanic-Mexican Americans, Asian-Pacific Islanders, and Whites With Mild Asthma. *J Asthma*. 2010;47(4):388-96.
119. Huang B, De Vore D, Chirinos C, Wolf J, Low D, Willard-Grace R, et al. Strategies for recruitment and retention of underrepresented populations with chronic obstructive pulmonary disease for a clinical trial. *BMC Med Res Methodol*. 2019;19(1).
120. Hooper MW, Asfar T, Unrod M, Dorsey A, Correa JB, Brandon KO, et al. Reasons for exclusion from a smoking cessation trial: An analysis by race/ethnicity. *Ethni Dis*. 2019;29(1):23-30.
121. Ward E, Jemal A, Cokkinides V, Singh GK, Cardinez C, Ghafoor A, et al. Cancer disparities by race/ethnicity and socioeconomic status. *Ca-Cancer J Clin*. 2004;54(2):78-93.
122. Giuliano A, Papenfuss M, de Zapien JD, Tilousi S, Nuvayestewa L. Breast cancer screening among southwest American Indian women living on-reservation. *Prev Med*. 1998;27(1):135-43.