White Paper

Achieving Representation in Clinical Research

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Clinical Trial Diversity: Achieving Representation

By Power, Quita Beeler Highsmith, M.B.A., Rodrigo Garcia, M.D., M.S.H.S., Lloryn Hubbard, and Kenneth Mahafey, M.D.

Racial and ethnic minority groups comprise 36% of the total US population but only 15-20% of clinical trial participants collectively.[1] This widespread failure to recruit representative populations leads to disparate health outcomes[2,3] and places a **multi-billion dollar down-stream cost** on both industry sponsors[4,5] and the US economy annually.[6]

Today, industry players are inundated with information on what's going wrong in research, but there is minimal thought leadership on what to do about it. This white paper gathers stories and evidence from across industry and academia to compile the best set of recommendations to improve racial and ethnic diversity in research.

In compiling this white paper, the researchers performed:

- Original quantitative research on the publicly available methodologies from **14,000+ trials** in the clinicaltrials.gov database as well as on demographic distribution from over **9,000 trials** from the clinicaltrials.gov database, totaling over **1 million participants.**
- **Over 100 hours of interviews** with stakeholders across sponsoring organizations, CROs, large academic medical institutions (AMCs), and industry clinical trial sites.
- A comprehensive literature review of **over 100 peer-reviewed journal articles, legal documents, reports, and news sources.**

The result is the most comprehensive set of tactical solutions to improve racial and ethnic diversity in research. The recommendations encompass 14 structural barriers, their associated solutions and real-world examples of their implementation.

Power

Lens	Structural Barriers	Solutions	Implementation
1 **Recruitment Strategies and Participant Outreach**	• Sites and trials do not engage communities proactively. • There is no explicit funding for diverse recruitment activities.[7–10] • Traditional recruitment channels are not representative.	**People:** Consider evergreen community engagement activities. **Process:** Budget for diverse recruitment activities. **Tools:** Prioritize channels based on representativeness.	**People:** Hire a dedicated Community Engagement Coordinator. **Process:** Earmark 5% of recruitment spend for diverse recruitment-specific activities. **Tools:** Develop partnerships with platforms that have representative populations
2 **Site Personnel and Operations**	• Lack of diverse research teams and leadership.[11,12] • Lack of metrics or systems to report site-level demographics. • Minority patients are asked to participate less.[7,13,14]	**People:** Build diverse research teams. **Process:** Normalize site-level demographic reporting. **Tools:** Roll out implicit bias training across research teams.[15]	**People:** Attend events for racialized candidates. **Process:** Define and request explicit representative enrollment KPIs of sites. **Tools:** Use free web-based implicit bias resources like the NetCE implicit bias training.
3 **Site Selection**	• Traditional research sites do not have representative patients. • Patients find it difficult to transfer into active sites. • Working with new sites is expensive and time-consuming.	**People:** Assess the diversity of patients at prospective sites. **Process:** Facilitate no-cost provider transfer . **Tools:** Create a diverse site network to accelerate start-up.	**People:** Use local demographic information if site stats are unavailable. **Process:** Prioritize sites that enable no-cost provider transfer. **Tools:** Use the RECRUIT method for site selection.
4 **Trial Protocol Design**	• Reimbursement logistics are overly confusing.[16] • Trial criteria are unintentionally exclusionary. • Data collection methods are unintentionally exclusionary.[17]	**People:** Streamline reimbursement support. **Process:** Challenge exclusionary criteria.[18,19] **Tools:** Accelerate the adoption of hybrid trial designs.[20]	**People:** Provide childcare compensation via on-site services. **Process:** Create a cohort of 'real world' participants for each phase. **Tools:** Perform data collection at patients' local clinics vs central research sites.
5 **Regulation and Economic Incentives**	• There is a lack of industry-wide benchmarks to guide progress. • There is a lack of industry-wide economic incentives.[21,22]	**Process:** Standardize benchmarks across industry. **Tools:** Explore quantifiable economic incentives.	**Process:** Challenge exclusionary inclusion/exclusion criteria in protocols.[18,19] **Tools:** Approve positive claims, i.e. "certified tested in representative population".

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1.0 Introduction

Clinical trial participants are typically not representative of the population of people who carry the disease burden.[23] This lack of representation has caused disparate health outcomes, poor implementation of novel therapies, and high downstream costs to stakeholders. Systemic barriers to research participation for underrepresented groups are well-documented, but most publications that discuss methods to break down these barriers do so at a conceptual, rather than tactical, level.[24,10,25,26,21]

First, this white paper explores the impact of historically poor diversity in clinical research. Then, it delineates structural barriers and proposes tactical solutions across 5 lenses: recruitment strategy and participant outreach; site personnel and operations; site distribution; trial design; and regulatory and economic incentives.

Many stakeholders are actively working to tackle this issue and have made meaningful progress. A steadfast, concerted effort is necessary to continue moving the needle. This framework will hopefully serve as a roadmap for stakeholders to facilitate change in their areas of responsibility, and to petition for change in areas where they have influence. It is crucial to note that there is no catch-all solution; instead meaningful change will require small and continuous shifts, and all members of the trial ecosystem will have a role to play.

1.1 Methods

In compiling this white paper, our team performed:

- Original quantitative research on methodologies from over 14,000 trials on the clinicaltrials.gov database.
- Original quantitative research on demographic distribution from over 9,000 trials from the clinicaltrials.gov database, totaling over 1 million participants.
- Over 100 hours of interviews with stakeholders across sponsoring organizations, CROs, large academic medical institutions (AMCs), and industry clinical trial sites.
- A comprehensive literature review of over 100 peer-reviewed journal articles, legal documents, reports, and news sources.

The researchers used the insights from this data to group structural barriers and solutions via granularity, from small-scope to industry-wide topics. The overarching tags of 'People, Process, and Tools' were used to further analyze and group proposed solutions. This research has informed a thorough understanding of the current state of diverse recruiting in clinical trials, opportunities for improvement, and strategies for success.

1.2 Racial and ethnic minorities are underrepresented in clinical research

In 2020, racial and ethnic minority groups comprised 36% of the total US population but only 15-20% of clinical trial participants.[1]

- Covid-19 vaccines: Black patients accounted for 21% of deaths attributed to Covid but only 3% of enrollees in vaccine trials.[27]
- Cancer: the leading cause of death in the Hispanic/LatinX community in the US is cancer, yet in both adult and pediatric populations they only comprise 2.3-3.9% of therapeutic trial participants.[28]
- Lupus: People who identify as Black make up 43% of systemic lupus erythematosus cases but only represent 14% of trial enrollees.[29]

These disparities may get worse before they get better. Industry trials, which have historically less diverse enrollment and slower improvement margins on enrollment, are becoming more prevalent (Figure 1a). NIH-funded trials, which enroll more representative participants and are more responsive to enrollment guidelines, are becoming less prevalent (Figure 1b).

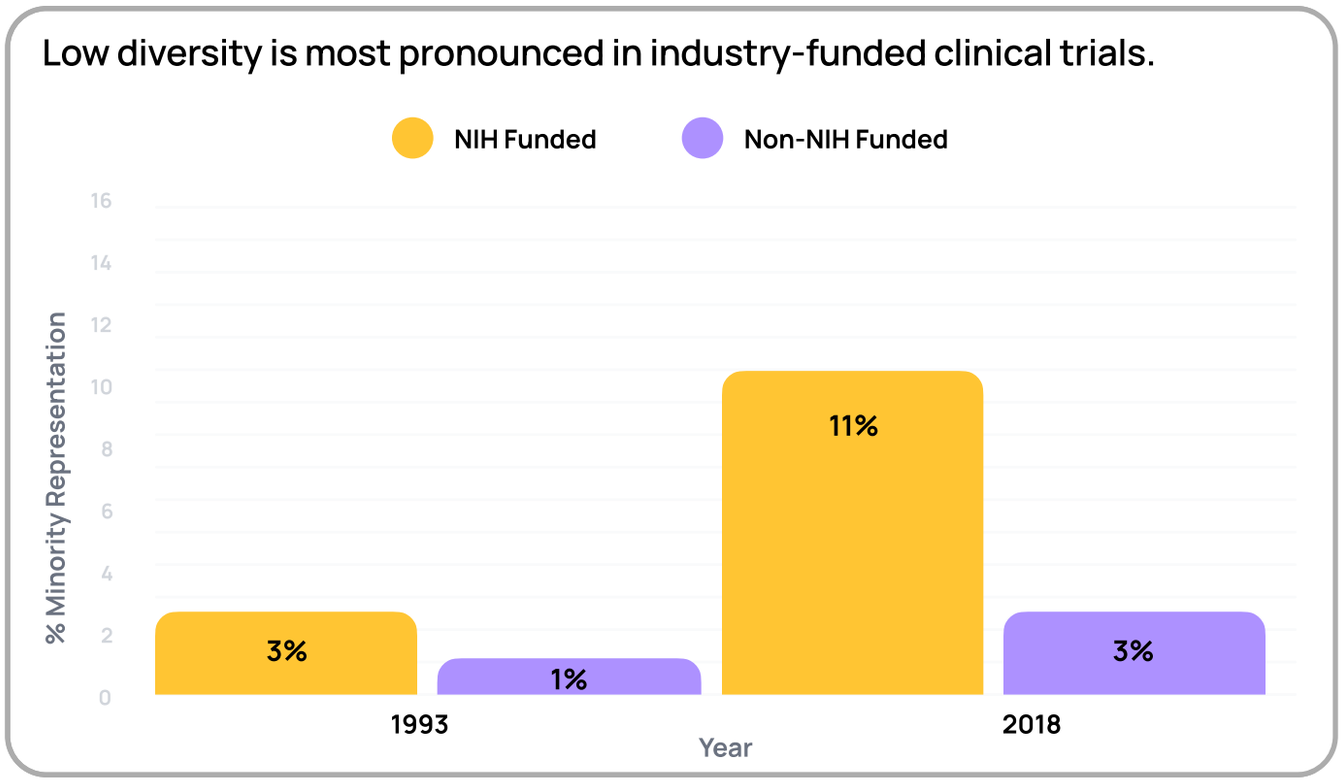

Figure 1a. Proportion of reported levels of minority representation in 36 randomized controlled trial manuscripts in PubMed in 1993 and 2018.[30,31]

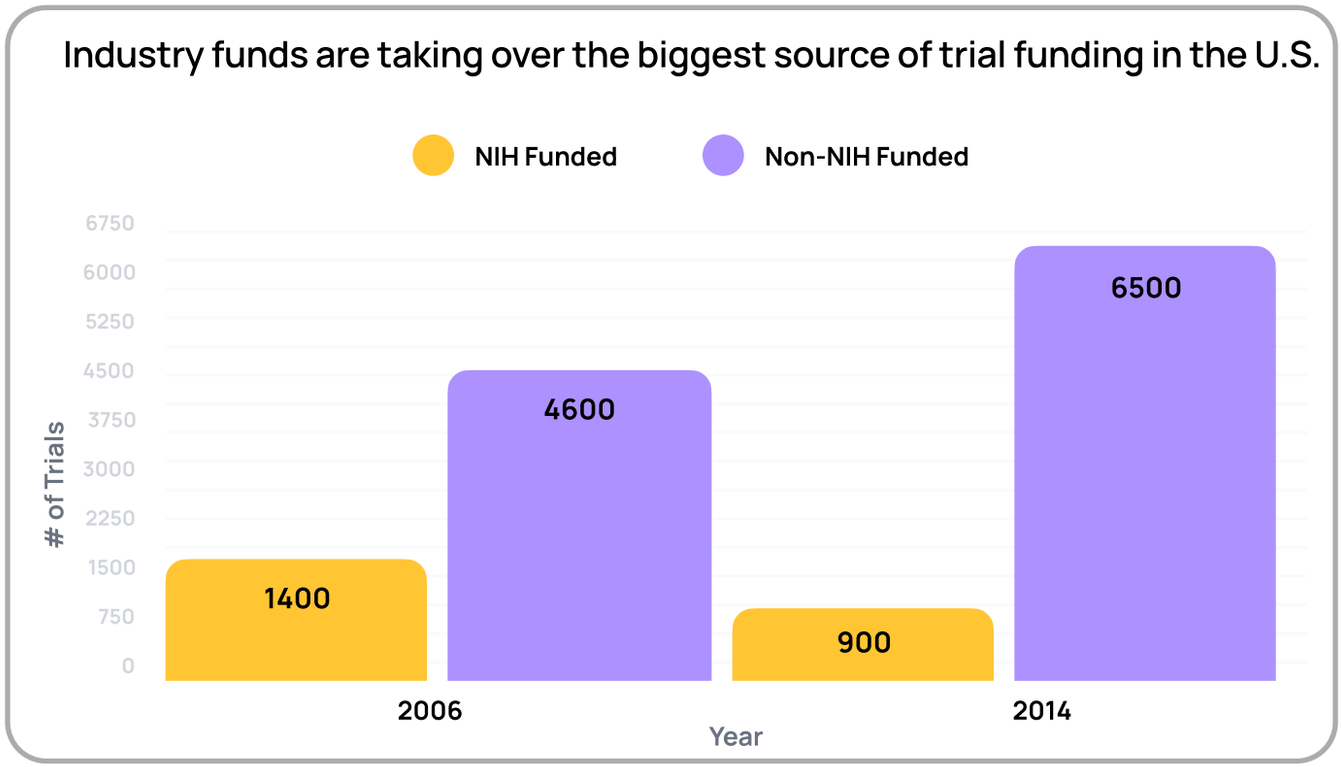

Figure 1b. Number of industry-funded versus NIH-funded trials in 2006 and 2014 .[32]

1.3 Why does it matter that racialized communities are not represented?

1.3.1 Drug performance varies in different populations.

Research that does not reflect target populations may be less effective post-market. Unrepresentative research also makes it more difficult to understand biological and socioeconomic factors that affect drug safety and effectiveness.[27] An individual's likelihood of developing an adverse drug response (ADR) is dependent on genetics, epigenetics, and environmental factors, all of which vary across racial and ethnic populations.[33,34] Some specific examples include:

- 5-Fluorouracil: Hematological toxicities are a major side effect of this cancer chemotherapy drug.[35,33] While they are more prevalent in racial/ethnic minorities than white/European Americans, the latter population was more represented in clinical investigations.[2]

- Warfarin: There are important differences in the appropriate dosage of the most commonly prescribed drug for thrombosis and embolism based on race and ethnicity. This discrepancy is not mentioned in usage guidelines.[3]

1.3.2 Low diversity costs everyone money.

Adverse drug responses cost the US economy $30.1 billion annually.[6] Sponsor-level costs incurred from FDA or insurance rejections increase the overall cost to stakeholders:

- The Eli Lily phase 3 trial for sintilimab was rejected by the FDA in 2022 for lacking a representative pool of participants because the original research was performed in China with participant racial demographics that were not reflective of the US. In light of this rejection, the FDA panel recommended Eli Lily conduct another, more representative trial, with an estimated price tag of hundreds of millions of dollars above the original research costs.[4]

- Due in part to the lack of diverse participants in phase I-III trials for Adulhelm, Centers for Medicare & Medicaid Services recently determined that they will not cover the Biogen Alzheimers' drug unless patients are enrolled in a trial. A lower demonstrated efficacy in phase III also helped guide the decision. This move cut potential consumers from a projected 50,000 to less than 5,000.[5]

In a public statement about the Aduhelm decision, the CMS director of the coverage and analysis group stated that:

> "Diversity is extremely important in any CMS approved trial, and it is a criterion in any protocol or any study that is submitted to CMS for approval."[36]

1.4 Current definitions of diversity are not comprehensive enough.

This table outlines the current categories for race and ethnicity data widely used in the US:[37]

Race categories	Ethnicity categories
• White • Black or African American • American Indian or Alaska Native • Asian • Native Hawaiian or Other Pacific Islander	• Hispanic or Latino • Not Hispanic or Latino

These categories were created in 1997 and are lacking in granularity. For more updated classifications of race and ethnicity, see Appendix I. While diversity encompasses many metrics including sex, gender, socioeconomic status, geography, ability and many more, this white paper focuses on racial and ethnic diversity because:

1. These metrics drive major differences in health outcomes.
2. These metrics are most commonly measured by researchers.

As per the most recent FDA guidelines (Appendix II), stakeholders should aim for even greater representation of smaller populations like American Indians/Alaska Natives to achieve statistically meaningful sub-group comparison. In cases where statistical significance is not possible, ensuring that every population is represented in the clinical trial remains essential. Even small data samples can reveal early differences in clinical outcomes and highlight the need for further investigations.

Clearly, the gap in racial representation is pervasive and material to both marginalized communities and the broader health system. Continue reading to learn about 14 barriers that reinforce the status quo, and their specific solutions to improve participant diversity in future trials

2.0 Fourteen Structural Barriers to Diversity and their Solutions.

This framework outlines fourteen structural barriers and tangible solutions across the clinical trial industry. These barriers are framed through five lenses, representing 5 areas of responsibility across the clinical trial ecosystem. These lenses are ordered by granularity; lens 1 looks at how industry engages patients themselves while lens 5 calls for wider systemic change.

2.1 Recruitment Strategy and Participant Outreach.

2.1.1 Barrier: Sites and trials do not engage communities proactively.

> "There's not a lot of trust in the research process from groups who have been abused or underrepresented in research."
>
> -Recruitment Manager at a large AMC

A distrusting, disengaged community is not the place to successfully recruit participants. Comprehensive engagement is crucial to dissolve barriers between communities and research. Sites are spending more time in the community than before, but there is still minimal understanding and validated frameworks on how to use these practices effectively.

Barriers to better community engagement include:

1. Few dedicated engagement coordinator roles, which means the time required to engage thoughtfully falls to other coordinators, researchers, and recruiters.
2. Significant financial investment to hire dedicated engagement coordinators, which is unattractive without external incentives.
3. Existing patient populations that are easily accessible without investment in community engagement. Without external pressure to make research populations representative, there is minimal motivation to find alternative channels for recruitment.
4. Community engagement funded with short timelines doesn't foster long-term trust or relationships with the community for future research.

2.1.1 Solution 1: Consider evergreen community engagement activities.

PEOPLE

> "If you don't drive long-term trust in the community now, future researchers won't be able to recruit patients and won't get funding or approvals."
>
> -Co-Chair of Health Equity at a large AMC

Lots has been said about the utility of community engagement to recruit diverse populations, but there is little validated evidence that these methods work, perhaps due to the short-term nature of many such projects. Anecdotally, longer-term investment has proven effective at engaging the community in research and driving more diverse recruitment.

One Principal Investigator shared how they budget for a dedicated community engagement coordinator. The goal of this role is to maintain a consistent presence between recruitment sessions instead of exclusively arriving when the site needs to recruit participants. Their day-to-day job involved outreach at churches, community centers, grocery stores, schools, and assisted living facilities. The PI specified that if it is not possible to invest in an engagement coordinator, PIs and coordinators could perform these tasks themselves.

Interviewers also heard about "lunch and learn" programs from a clinical research coordinator at an industry sponsored trial site. They have recruited several trial participants from the community as a result of this initiative.

2.1.2 Barrier: No explicit funding allocated to diverse enrollment activities.

> "I do believe that things have evolved dramatically during the pandemic, but I have not had the time to catch up. Things have changed so much, but we have not been given any time or resources to adapt."
>
> -Program Manager at a large AMC

Industry should expect a cost to accompany every activity in pursuit of representativeness. Most researchers and sponsors care about recruiting a representative research population (Figure 2). But without explicitly designated funds, sites are stuck trying to do more with the same budget. Multiple researchers shared that they often lacked adequate funds to support:

1. A centralized database with patient race/ethnicity information.[8]
2. Dedicated staffing for diverse recruitment.[9]

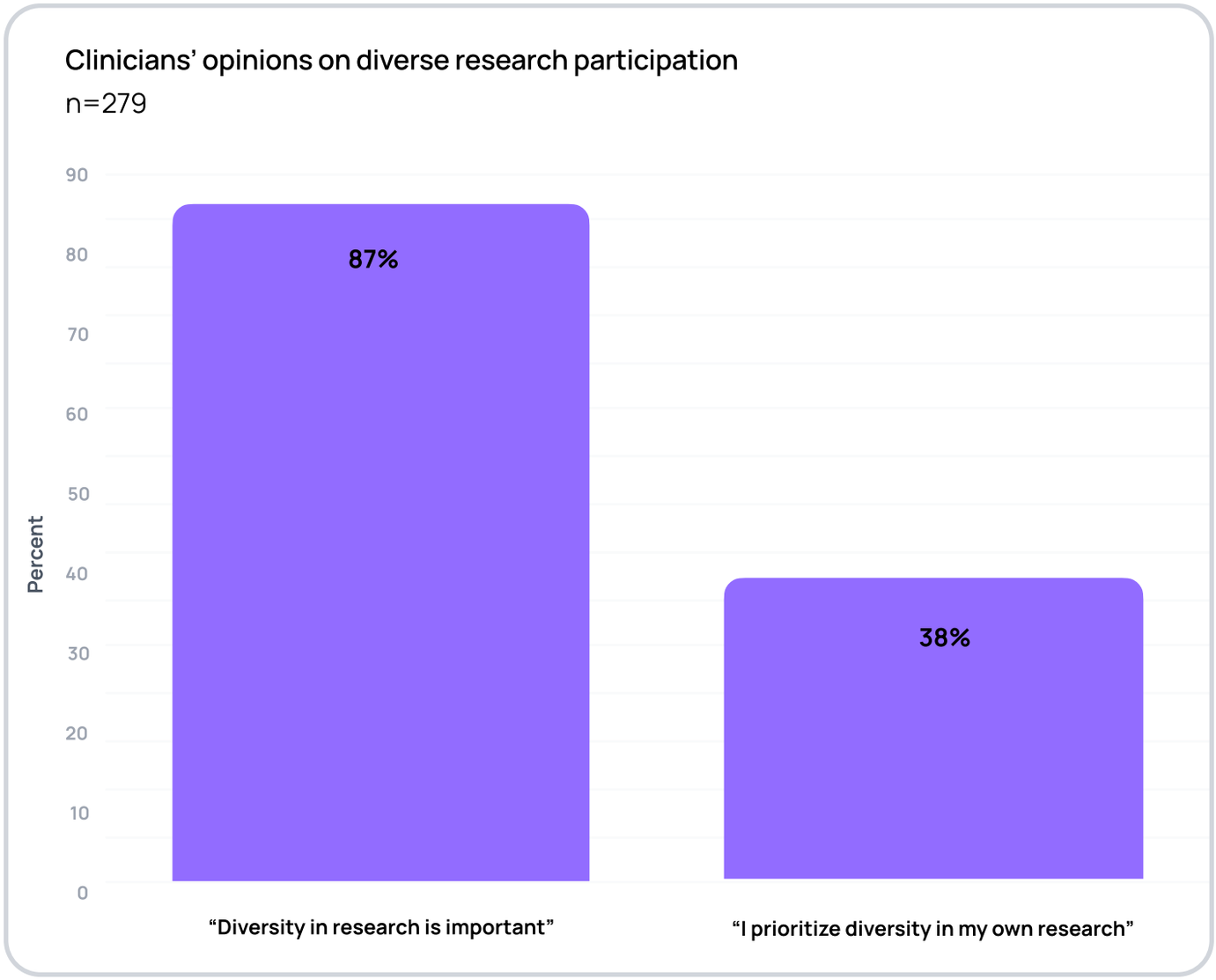

Figure 2. Amalgamated "agree" and "strongly agree" responses to 2 prompts concerning diversity in research.[7]

Barriers to budget reallocation include:

1. It is difficult to quantify the ROI of investments in diverse enrollment activities without a body of data on their impacts.
2. Without external financial motivation to enroll diverse participants, it is easier to maintain current budgets that recruit less diverse patient populations.

The fact that diverse recruitment is a nascent discipline means that early investments necessarily have an uncertain ROI. The industry has not yet invested enough in these initiatives for practitioners to have a strong sense of how any given initiative will or won't translate into patient diversity.

2.1.2 Solution 2: Earmark at least 5% of patient recruitment spend for diverse recruitment-specific activities.

PROCESS

New types of activities are required for diverse enrollment, so sites and sponsors must reassess budgets to enable these new activities. To make progress in this relatively new discipline executives should adopt a 'test-measure-learn' approach to identify what activities bear fruit in which communities.

Stakeholders could start by reallocating funds for recruitment channels that drive less diverse enrollment to new channels with a high potential for representative patient populations. The co-chair of the Health Equity Steering Committee at a large AMC explained that his site has a defined budget set aside for diverse enrollment activities. These activities have been anecdotally invaluable to the success of diverse enrollment at the AMC for the last 20 years.

2.1.3 Barrier: Traditional recruitment channels are not representative.

There is almost no data on the utility of specific channels to recruit diverse participants. Without transparency into representativeness on a per-channel basis, sites, sponsors, and CROs are left guessing what will work.

Based on current recruitment statistics, it is evident that the status quo is not effective at recruiting diverse participants. Today, it is too hard to find trial recruitment information because:

1. Websites like clinicaltrials.gov are not accessible for most patients to navigate.
2. When patients do find trials, the information is often overly complex.
3. Almost all trial information is exclusively presented in English.

Stakeholders must prioritize channels that are best at driving diverse recruitment. But it is currently difficult to rank channels based on representativeness because:

1. There is no established practice for data collection or reporting on the ability of various channels to recruit diverse participants (i.e., how many people from a certain group are enrolled from physician referrals vs. social media outreach vs. public access websites).
2. There is minimal empirical data on the utility of alternate formats to recruit diverse populations.

2.1.3 Solution 3: Prioritize channels based on the representativeness of their patient population.

TOOLS

Sites, CROs and sponsors should evaluate and prioritize patient population representativeness during recruitment vendor selection. These stakeholders should also build redundancy into their representative recruitment strategy, so as not be overly reliant on one channel to ensure participant diversity. A simple starting point for recruitment teams includes:

1. Ensuring that resources are default multilingual, contain representative imagery, and adhere to the Web Content Accessibility Guidelines.
2. Leveraging partners who have demonstrated that their patient population is nearly representative of the census, such as patient education platforms like Power, disease-specific advocacy groups, and diverse patient support groups.

In any case, trials must go to where their patients are. The Chief Diversity Officer of a top 10 pharma company is exploring

> "...relationships with pharmacies, because they're in the community already. If patients are getting heart disease medication at Walgreens, put a QR code for local heart disease trials somewhere there."

The recruitment manager at a large AMC also told us that he found great success walking around an arts festival with a Bluetooth speaker wearing a sandwich board saying "ask me about clinical trials".

2.2 Site Personnel and Operations.

2.2.1 Barrier: Lack of diverse research teams and leadership.

> "[Having a] diverse staff is a huge part of the trust. A lot of physicians of color typically aren't PIs. There are rarely new PIs, some have been around for decades, so this issue is going to take a long time to change."
>
> -VP of a major CRO

Most research teams are not representative of the patient population they're treating. Only ⅓ of the research staff at large medical institutions self-identify as belonging to a minority population.11 Diverse research staff are crucial because:

1. Sites with high levels of racial and ethnic diversity amongst the staff attracted a more diverse pool of participants.[12]
2. Participants are more likely to feel comfortable asking the necessary questions, and more likely to entrust their safety as research participants, to researchers who look like them.[11]
3. Sites with diverse staff are more likely to value diversity as a central part of their research, mission statements, and operating procedures.[11]

2.2.1 Solution 4: Build more diverse research teams.

PEOPLE

> "You can talk generally about diversity all you want, but if you want to recruit diverse patients, you need a diverse research team. People will just ask the right questions and respond better to people who look like them."
>
> -Clinical Research Coordinator at an industry trial site

One study from the University of Hawaii Cancer Center reported similar or higher rates of enrollment of Asian and Native Hawaiian minority cancer patients as White patients. They attribute this success, in part, to the strong association between hiring and involving diverse healthcare and research staff and increasing minority accrual.[1] Given the impact of diverse research teams on patient diversity, it would be logical for sponsors and CROs to consider this data point in their site selection process.

Consequently, sites should aim to hire research staff, scoping from MD and non-MD trial leaders, trial coordinators, site investigators, receptionists, and beyond, from a variety of racial/ethnic and socioeconomic backgrounds. There is already a strong body of literature about the utility of diverse research teams and their association to recruiting more diverse trial participants.[38] They should also prioritize hiring staff who speak languages that are relevant to the local community. They can begin this hiring process by:

1. Recruiting at Historically Black Colleges and Universities.
2. Sponsoring or attending events hosted by professional groups for racialized candidates.
3. Auditing their hiring funnel and finding steps where there is a disproportionate drop-off for racialized candidates.

One Spanish-speaking PI at a large AMC explained that he attends Spanish town halls to chat about his research. Anecdotally, he has found this channel successful at recruiting participants for studies at his site.

2.2.2 Barrier: Lack of metrics and systems for reporting site-level demographics.

> "Most sites do not report on recruitment demographics as a key performance indicator, nor do sites and sponsors expect this granularity of detail."
>
> -VP at a major CRO

The deficit in site-level demographic reporting creates a self-reinforcing cycle:

1. The lack of standardized metrics for reporting patient demographics means that sponsors are unable to make make effective comparisons between sites.
2. The lack of ability to make comparisons means that individual sites don't have an incentive to publish their demographic data.
3. The lack of available data means there's no impetus to develop standardized metrics for reporting said data.
4. (and again) the lack of standardized metrics for reporting patient demographics means that sponsors are unable to make make effective comparisons between sites.

2.2.2 Solution 5: Normalize site-level demographic reporting.

PROCESS

> "Data transparency on a site level is the goal. Today, sites are frequently hesitant to share information that may negatively impact their chance of getting a study. In reality, we want to provide resources and support to the sites most struggling, and more granular reporting helps us provide more support."
>
> -Associate Director, Patient Diversity at a major CRO

Sponsors and CROs should define and request explicit representative enrollment KPIs of their sites and lead with the expectation that sites use these metrics to evaluate their own progress. Sponsors should also explicitly prioritize sites that share these metrics.

Simultaneously, sites should measure & share KPIs when trying to win trials. As this practice becomes more common at the site level, it will naturally incentivize other sites with similar profiles to share KPIs, and make it more feasible for sponsors to require these metrics when building site networks.

2.2.3 Barrier: Diverse patients are approached less frequently to participate.

> "Industry thinks of diversity as a risk because of people not showing up to appointments or being late. No one has the training to understand and address these misconceptions."
>
> -Board member of a midsize pharma company

White coordinators and physicians feel uncomfortable discussing race and report feelings of anxiety when choosing the appropriate language to discuss inclusion in research.[7] Partly due to this discomfort, people from underrepresented groups are invited to participate in clinical trials at a lower rate.

This lower rate of within-clinic enrollment is not for lack of interest. One study found that Black, Hispanic, and Asian patients enrolled in cancer clinical trials at comparable rates to white patients when given the same information.[13] Furthermore, almost all Black breast cancer patients are interested in participating in research, but few hear about trial options from their care team (Figure 3).

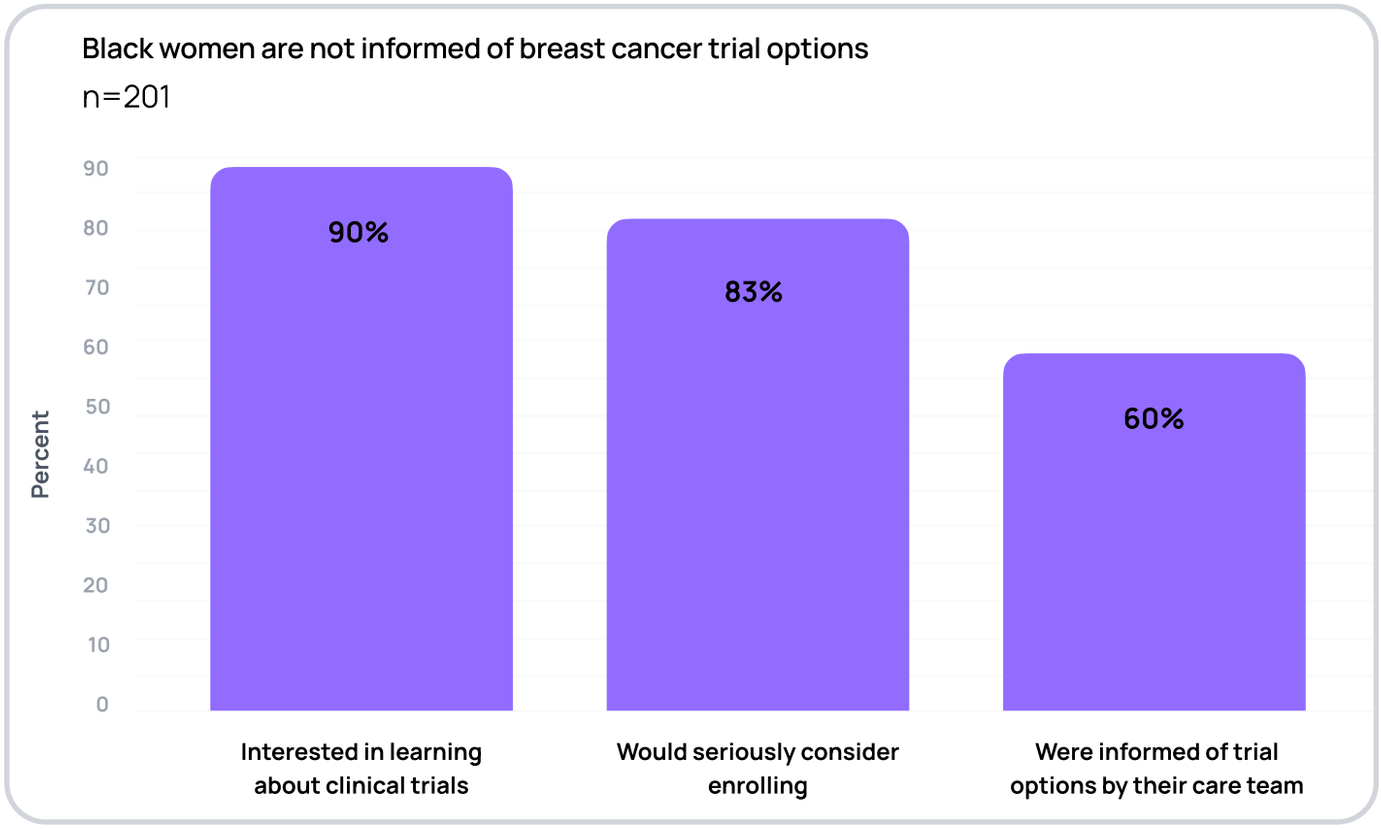

Figure 3. Black breast cancer patients' experience learning about clinical trial options.[14]

Current barriers to large-scale implementation of implicit bias training include:

1. Misconceptions about the cost and time commitment of implicit bias training.
2. Lack of awareness of the positive impacts of implicit bias training.

2.2.3 Solution 6: Roll out implicit bias training across research teams.

TOOLS

> "Diversity in research teams is important, but social and emotional intelligence for any research coordinator is as or more important."
>
> -Recruitment Manager at a large AMC

Implicit bias training is one potential way to overcome the invitation hurdle. A 2022 pilot study conducted by the ACCC and ASCO supports the feasibility and usefulness of implicit bias training programs.[15]

Sponsors & CROs can push for implicit bias training across their network by prioritizing sites that have provided previous implicit bias training to their staff. Simultaneously, sites can preemptively provide implicit bias training to demonstrate proficiency to potential sponsors. There are abundant free, web-based options including:

1. 5 unbiasing guides from Google
2. Implicit bias training from the AAFP
3. NetCE implicit bias training
4. Think Cultural Health training from the Department of Health and Human Services

Researchers can also consider the 'ask all patients' approach, according to a VP at a major CRO. This approach requires that physicians inform all patients about trials regardless of perceived logistical barriers and use trial budgets, if necessary, to address the reasons that might have otherwise caused them to not inform the patient of trial options.

2.3 Site Selection.

2.3.1 Barrier: Traditional research sites do not have representative patient populations.

> "Trials often start with academic research hospitals that have large patient pools, so they never go to lower socioeconomic status areas if they don't need to. Unfortunately, these hospitals tend to serve more affluent, white, patients."
>
> -Chief Diversity Officer of a top 10 pharma company

A major barrier to representative recruitment is the underlying diversity of the patient population at historically preferred sites. If the established patient population is not diverse then the site is unlikely to recruit diverse patients. Underlying reasons for this trend include:

1. Sites with the best track record for research (i.e., large AMCs) are generally in less racialized, higher socioeconomic status (SES) areas.
2. These sites tend to be "destination" medical centers where affluent patients can afford the time and travel to visit.
3. Internal physician referrals often drive patient recruitment, and these referrals pull from the established patient population.
4. People become patients at clinics in their neighborhoods, so internal referrals will likely be less racialized and higher SES.

2.3.1 Solution 7: Assess the diversity of existing patients at prospective sites.

PEOPLE

> "We need to balance the focus on quick enrollment because quick sites enroll more white patients. This method hasn't been really effective for diverse recruitment."
> -Associate Director, Patient Diversity at a large CRO

As sponsors choose their default trial sites, they should consider the demographics of the sites' existing patient populations. Regardless of external recruitment methods, a meaningful proportion of patients will likely come from internal physician referrals.

A common theme among all interviews was that, up to now, sites have not been collecting rigorous data on their patient demographics. If sponsors lead with the expectation that sites should begin collecting this information, a larger body of demographic data will become quickly available.

Some sites are already collecting this information, and these sites can serve as proxies for demographic proportions of other local sites if they do not have available data. For example, one coordinator at Lyndon B. Johnson Hospital has been collating a database of patient information for future department-wide trials, with special attention to demographic reporting.

2.3.2 Barrier: Patients find it hard to transfer into active sites.

If the established patients at traditional sites are not representative, then those sites need to make it easier for external patients to transfer in. Unfortunately, even if diverse patients are willing and able to transfer into active sites, they can still be blocked. Barriers to transferring between sites include:

1. Physicians outside of major physician referral networks (i.e., at a community health clinic) are less likely to know about and refer patients to trials.
2. Large AMCs require participants to register as patients at the site before screening. This process is often a large time and financial commitment, which is unattractive if patients have no guarantee that they will be able to enroll.
3. If trials do not fund screening activities, insurance logistics can also be a barrier. If patients are not guaranteed access to the trial, there is less motivation to go through the insurance claims process.

Consequently, the network of internally-referred patients skews toward patient populations in overserved regions.

2.3.2 Solution 8: Make it easier to transfer providers for a clinical trial.

PROCESS

Ultimately, the ease of accepting outside patients needs to be a consideration on the trial design level. According to the Associate Director for Patient Diversity at a global CRO,

> "Sponsors and CROs can encourage this behavior by making ease of patient transfer an important site evaluation criteria."

Here are some criteria to consider:

1. Can the site conduct a full screening visit before establishing the patient?
2. Can screening be made easier by running lab work out of patients' local clinics where they have established insurance information?

Lastly, sponsors and CROs can work with platforms like Power to help physicians identify and refer their patients to promising local trial sites that are easy for their patients to access.

2.3.3 Barrier: Working with new sites is expensive and time-consuming.

Expanding to new sites with more diverse patient populations requires an investment that many sponsors and CROs are hesitant to make, especially if current sites produce reasonable results. New sites take 20-30% longer to start up for several reasons, according to the Chief Medical Officer of a global midsize biopharma company:

1. New sites have more uncertainty about data quality and protocol adherence.
2. New sites need more oversight and training to effectively follow trial protocols.
3. Trial monitors must frequently check up on sites, and these individuals prefer to work close to home - which is often in denser, higher-educated, higher SES areas.
4. It can be complicated to navigate review boards (IRBs) for new sites.

As a result, sponsors reuse the same sites if they have a good track record, without incorporating diverse enrollment statistics into that track record. Therefore, the same sites continue to receive trials and deliver the same results.

2.3.3 Solution 9: Proactively create a diverse site network to accelerate start-up.

TOOLS

> "Sponsors and CROs can take a portfolio management approach to site selection when it comes to ability to recruit diverse patients."
>
> -VP at a major CRO

These groups can evaluate a mix of sites on the basis of strong recruitment and diverse patient engagement using the RECRUIT method for site selection:

RECRUIT	Definition
Research staff	Research staff is representative of populations the site would like to enroll.
Enrollment history	Site has a history of diverse enrollment, and willingly provides and updates enrollment demographic data.
Cultural competency	Site provides cultural competency or implicit bias awareness training to its staff.
Readiness to adapt	Site is ready and willing to adapt their practices to enroll representative populations.
Underserved areas	Site is located in an underserved area, is easily accessible to individuals living in underserved areas, or has logistics set up to facilitate participant travel from underserved areas.
Implement effective recruitment strategies	Site uses recruitment strategies that drive diverse enrollment and collects information on which strategies are most effective at enrolling different populations.
Transfer into site	Site makes it easy for patients to transfer in for the purpose of participating in a trial.

Sponsors & CROs can establish & train a representative site network ahead of time to make study startup efficient, according to the Chief Diversity Officer of a top 10 pharma company. This process should include familiarization with new IRB processes at each site ahead of time. While marginally inconvenient, an early investment here can pay dividends down the road.

PPD has recently started focussing their site recruitment efforts on community health clinics to recruit more diverse participants for their sponsors. Genentech is another leader in this space. They have created a dedicated Site Alliance for diverse recruitment, which prioritizes:

1. Sites where communities of color live and work.
2. Sites with a highly engaged investigator coordinator community that demonstrates a passion for diversity in clinical trials.
3. Sites with a proven track record for diverse recruitment.

Well-known sites in higher-income or less racially diverse areas can improve their individual reach by partnering with sites in a wider range of neighborhoods. For example, MD Anderson partners with a variety of smaller hospitals like Lyndon B. Johnson Hospital. This partnership helps a greater range of people in the Houston area access MD Anderson research via their local institution, according to a Clinical Research Coordinator at L.B.J.

2.4 Trial Protocol Design

2.4.1 Barrier: Reimbursement transparency and logistics are overly confusing.

> "Being poor is time-consuming. If you want people to travel for something that won't pay a lot, you're not going to get that participation."
> -Co-Chair for Health Equity at a large AMC

A common theme throughout the industry interviews was that higher reimbursement packages coerce people to participate in research. In reality, people from different backgrounds need different financial and logistical support to participate. This fallout manifests in the demographic makeup of trial phases: phase 1 trials, which compensate well, attract a more diverse group of participants, but when compensation drops in phases 2 and 3, diverse representation drops as well.[16]

Inequitable reimbursement practices exist for four reasons:

1. Pre-existing reimbursement methods are difficult to change without significant internal or external motivation.
2. Common fear of IRB rejection on the grounds of coercive reimbursement.
3. Lack of internal motivation to invest in diverse enrollment before drug approval. Sponsors would rather invest in representation post-approval when they are sure the investment will pay off.
4. Lack of simplified systems or platforms to manage reimbursements for the patients and sponsors.

Consequently, the network of internally-referred patients skews toward patient populations in overserved regions.

2.4.1 Solution 10: Streamline reimbursement and logistics support.

PEOPLE

Reimbursement should be conditional on means and time requirements. There are several ethical ways to support patients equitably:

- Relativize travel reimbursement with respect to the distance traveled and time spent traveling.
  - If the participant does not have a car and public transit is slow, they should be reimbursed extra.
  - Taxi service to participants who live in transit-poor regions.
- Allow additional travel reimbursement for participants with mobility impairments, or who otherwise require assisted transit.
- Support participants who require child or family care - either through onsite services, or via a child care stipend.
- Provide additional financial support for participants who do not have adequate insurance coverage.

Sponsors and sites must also make travel and logistics management as easy as possible for all participants, and these logistics should be easily available on patient-facing trial descriptions. Sponsors and sites can also take steps to make travel facilitation easier logistically by partnering with a provider of logistics services.

2.4.2 Barrier: Trial criteria are unintentionally exclusionary.

> "Let's talk about which inclusion/exclusion criteria are actually necessary, and which are cut and pasted from old trials and preventing people from participating."
> -Chief Diversity Officer of a top 10 pharma company

Inclusion/exclusion criteria are written to identify patients with few underlying health conditions who can offer the most direct results for analysis, but given the large health disparities across different racial groups, these criteria disproportionately screen out marginalized populations.39 For example, trials that exclude people with hypertension also inadvertently exclude a larger proportion of the Black population:

1. Black patients suffer from higher rates of hypertension (Figure 4a).
2. Black patients also experience higher than expected rates of HIV, COVID, and Multiple Myeloma (MM) (Figure 4b).
3. Of all the interventional trials for HIV, COVID, and Multiple Myeloma (MM), hypertension is excluded almost 4x more than it is included (Figure 4c).
4. Therefore, Black patients are unintentionally excluded from participating in research for diseases that they experience at higher rates (HIV, COVID, and MM), because they experience a comorbidity (hypertension) at higher rates.

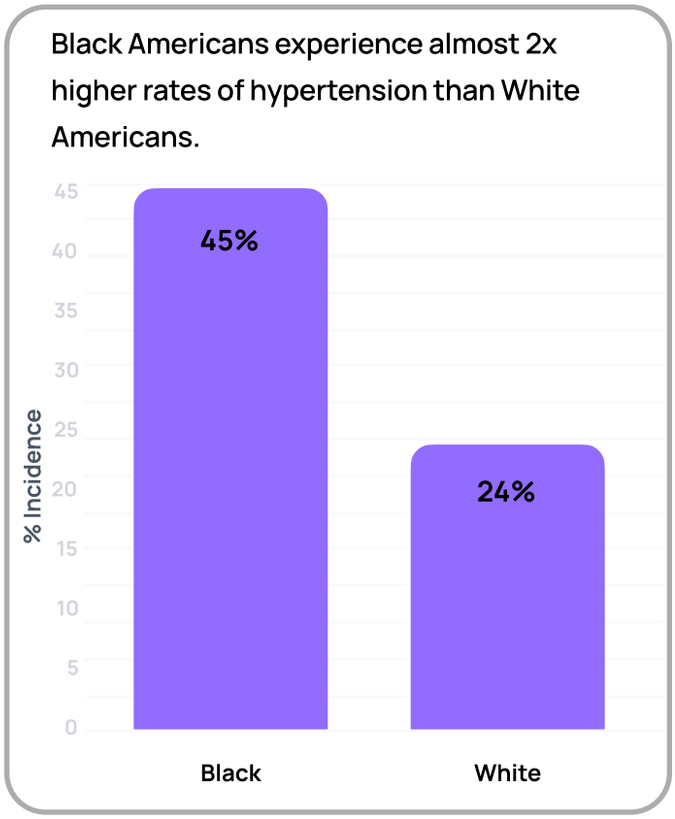

Figure 4a. Hypertension risk for Black vs White men America in 2015.[40]

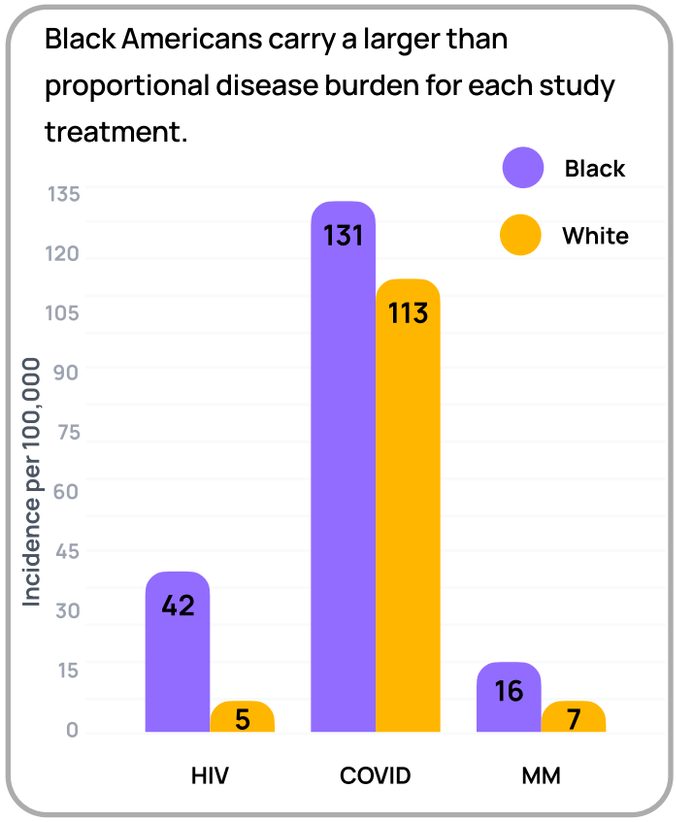

Figure 4b. Disease incidence for three study conditions in white vs. Black US populations.[41,42,43]

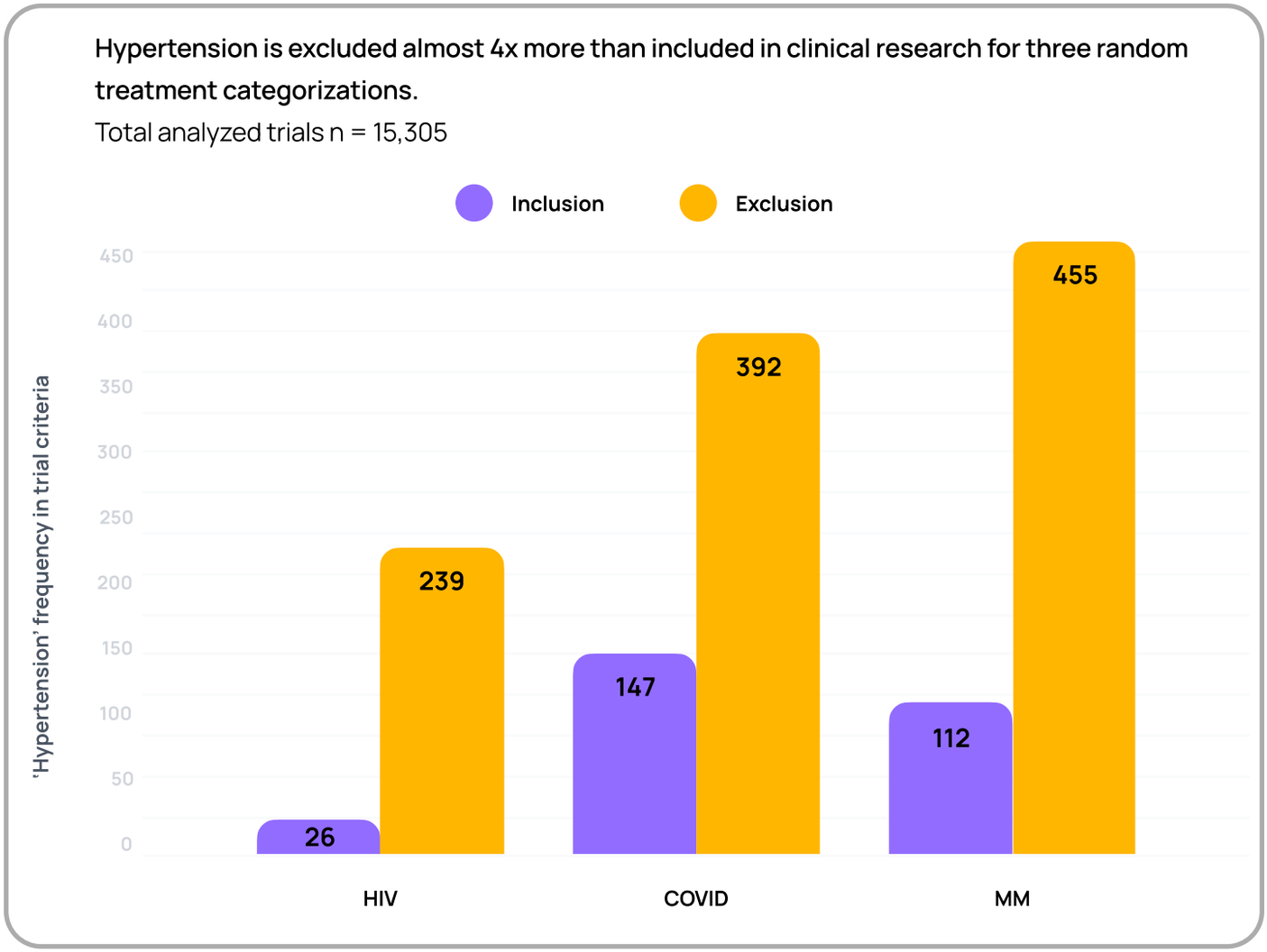

Figure 4c. Frequency of the term 'hypertension' in the inclusion versus exclusion criteria section of all interventional trials on clinicaltrials.gov for the three case study treatment conditions between 1990 and 2022 (research performed by Power team).

Trials will also frequently require contraception for people of child-bearing age, which may work to inadvertently exclude queer patients and others who do not intend to use contraception. These unintentionally exclusionary practices persist for two reasons:

1. A desire to replicate the success of previous trials that met their participant requirements.
2. A desire to adhere to protocols that have previously been accepted by IRBs.

2.4.2 Solution 11: Identify and challenge unintentionally exclusionary criteria and protocol design.

PROCESS

Medical directors should begin cross-referencing new protocols with a list of criteria that are likely to disproportionately screen out marginalized patients. IRBs should also establish practices for assessing whether protocols are unexpectedly exclusionary. As a central stakeholder in research, IRBs can act as a forcing function for thoughtful reconsideration of I/E criteria practices.

Sponsors can also consider creating two cohorts per phase: a cohort of traditionally- recruited participants, and a cohort of 'real world' participants, such as in a recent phase IV Genentech study. Vabysmo was tested on a subgroup of participants with higher HbA1c levels than are traditionally permitted in eye medication trials, giving people from underserved populations, who generally have higher HbA1c levels, a better chance of eligibility (Figure 5).

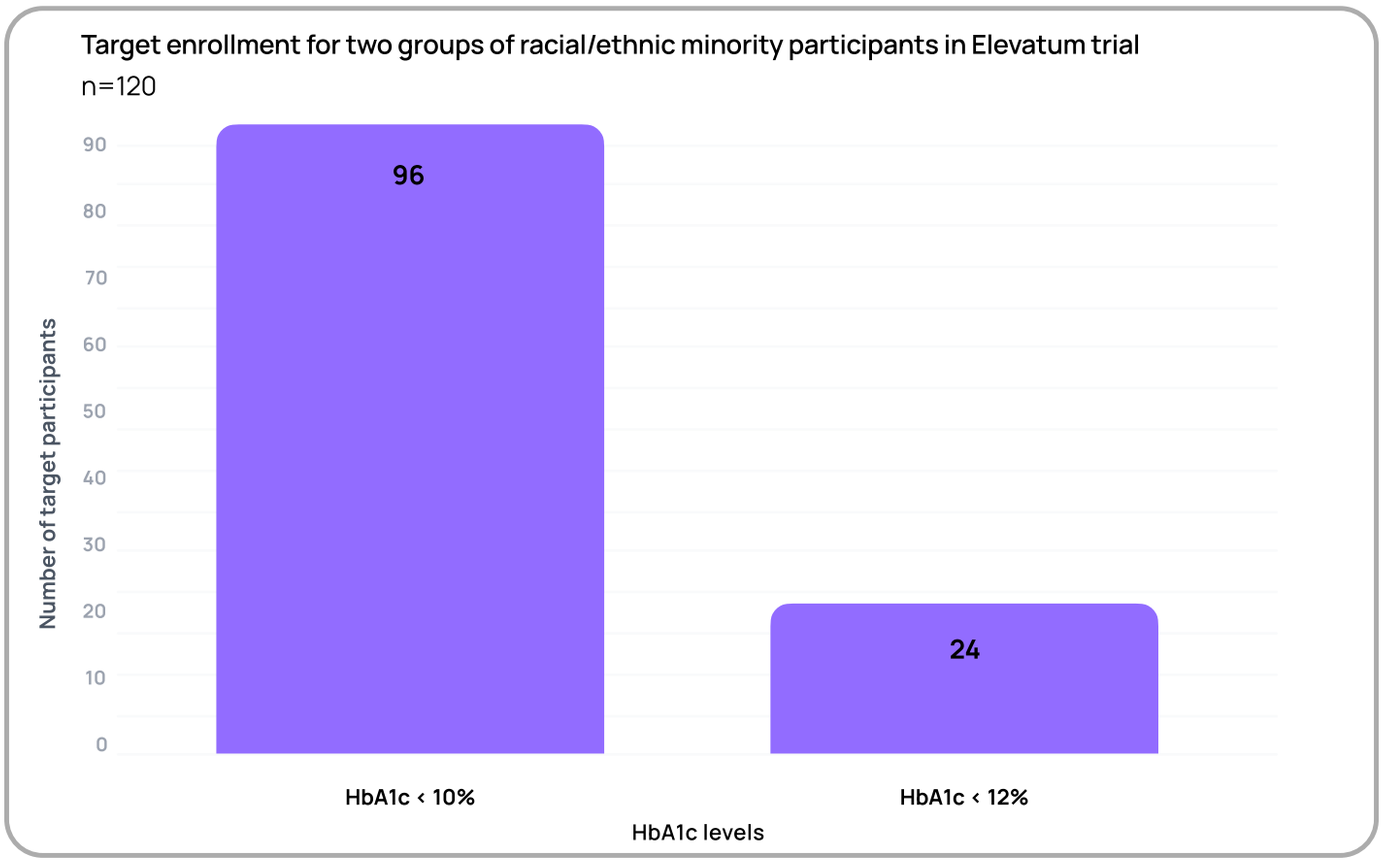

Figure 5. Elevatum trial participant categories for HbA1c levels, with target enrollment numbers.[19,18]

A recent study used AI to evaluate the utility and unintended exclusionary impacts of I/E criteria in non-small cell lung cancer trial protocols.44 Tools like this are excellent starting points for future analyses of I/E criteria.

2.4.3 Barrier: Data collection methods are unintentionally exclusionary.

Data collection methods can introduce logistical requirements that are unintentionally challenging for some populations, which disincentivizes participation. For example, requiring multiple visits per week makes the trial less attractive for people who work long hours or have dependent family members.[17]

There are 2 primary barriers to implementing more accessible treatment, data collection, and reporting methods:

1. Industry is hesitant to try getting approval using accessible methodology until there is precedent for approvals of similar treatments.
2. Lack of internal motivation to permanently change the culture of accessible trial design.

Therefore, if previous similar treatments have been approved based on a certain data collection methodology, current protocols may use the same methods when equal quality data could be collected in more accessible ways.

2.4.3 Solution 12: Accelerate the adoption of hybrid trial design.

TOOLS

Sponsors should create methods templates that use new logistics and data collection models. One sample model is the decentralized trial. The COVID-19 pandemic has illustrated that these trial models are effective[45] and able to recruit more diverse participants.[46] For example, a fully decentralized phase 1 trial for fluvoxamine in treating the progression of symptoms in Covid-19 had 25% Black participants. This marks a significant increase from pre-pandemic, centralized rates, which sat around 4%.[20]

Some other strategies include:

1. Longer visits with more data collection instead of frequent, short visits.
2. Option for telehealth screening and follow-up visits wherever possible.
3. Lab work in hub and spoke model - perform data collection at local clinics vs central research sites.
4. Methods specifying the maintenance of clinic hours on weekends and evenings for people who can't take time off 9 to 5 jobs.

One PI at a large AMC is running a cancer immunotherapy trial that does not require one visit to the AMC location. Instead, they perform all screening and follow-up via telehealth and outsource all data collection to the patients' local clinics. The trial has been remarkably successful at recruiting participants across the United States, and the treatment is on its way to FDA approval.

Sponsors and sites should collaborate with the community to create strategies that work best for their research and local concerns. A community advisory board is an excellent tool to evaluate the accessibility of trial protocols, according to another PI at Johns Hopkins.

2.5 Regulation and Economic Incentives

2.5.1 Barrier: Lack of benchmarks.

> "Guidelines aren't enough because the economics are working against you. Everyone tries to do things out of the goodness of their hearts, but at the end of the day, they're not being paid spiritually. So until the FDA mandates change, the needle isn't going to move."
>
> -Board member of a global midsize pharma company

There have been several initiatives from regulatory authorities to reform the standards for diversity in research since the 1990s (Figure 6) via guidelines, but no benchmarks or incentives exist.

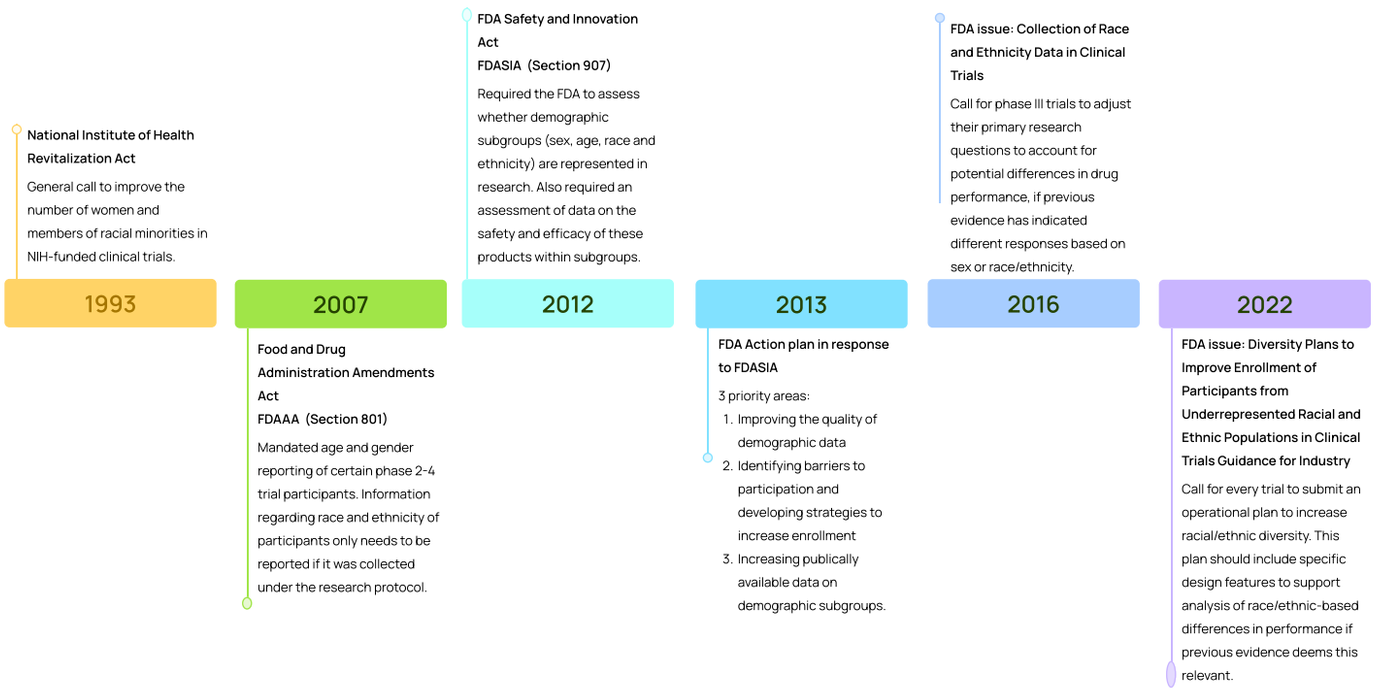

Figure 6. Timeline of guidelines and action plans.[22,47–51]

Historic reaction to guidelines versus mandates clearly demonstrates that mandates are more effective at causing change:

- Guidelines: As of 2013, 20 years after the NIH Revitalization Act, only 2% of all National Institute of Cancer trials had sufficiently enrolled participants from minority populations as per the Revitalization Act guidelines.[21,52] As of 2018, only 13.4% of trials reported results based on race/ethnicity.[21,22]
- Mandates: After section 801 of the FDAAA, reporting of any race/ethnicity enrollment data increased from 26% in 2008 to 91% in 2018. In 2008 only 11% of trials reported data for all 5 categories of race but by 2018 this number increased to 41%.22

	Guidelines	Benchmarks	Incentives
Definition	Overarching recommendations without specific goals.	Specific goals without specific repercussions.	Specific repercussions associated with specific goals.
Ease of Implementation	**Fairly easy.** There is existing precedent for updating guidelines.	**Fairly difficult.** Requires standardization across industry.	**Very difficult.** Requires significant alignment across industry.
Potential Positive Impacts	May motivate change by calling attention to the best practice.	May motivate change through comparisons across sponsors, and against a stated 'goal'.	Provides tangible, enduring motivation for industry-wide change.
Potential Negative Impacts	Rely on individual actors to motivate implementation and define success.	Poorly designed benchmarks may have companies 'optimize' the wrong measure.	Poorly designed incentives may slow research or disincentivize new entrants.

Furthermore, without a standardized source for recruitment metrics and data sharing, there is no way for sponsors or researchers to know how their recruitment measures up. This lack of transparent, accessible information limits the rate at which the industry can improve.. Specific barriers here include:

- It is not possible for sponsors to measure, report, present, and track racial representation against best-in-class performance.
- Internal change-makers within sponsors have a harder time implementing their ideas, as it isn't clear how to quantify their objectives or results.
- The public, including advocates and media, have a harder time holding sponsors accountable, as they lack the data to understand who is falling behind.

2.5.1 Solution 13: Create transparent, REAL benchmarks.

PROCESS

Today, lack of transparency is the primary barrier. Industry cannot manage what it cannot measure. As a governing body, the FDA could consider publishing benchmarks for diverse recruitment. REAL benchmarks will help achieve goals in a sustainable way:

In addition to implementing REAL benchmarks, a cross-departmental task force between and among units of the FDA, NIH, HHS, and other regulating bodies should develop, enforce, and report on better data collection and tracking systems.[53]

REAL	Definition	Implementation
Responsive	Benchmarks are responsive if they are based on real-world data and consistently updated over time.	Populations with high rates of morbidity should be appropriately represented in diagnostic trials. Populations with high rates of mortality should be overrepresented in interventional clinical trials.
Explicit	Benchmarks are explicit if they define the methodology by which a given metric must be calculated.	Create a formula to determine the proportion of people within each demographic that should be participating. For interventional studies this formula should be based on mortality rates within the group. For observational or diagnostic trials, the formula should be based on morbidity rates.
Actionable	Benchmarks are actionable if there is clear evidence that some programs run by sponsors can impact the underlying metric.	Documentation should include actions and instructions drawn from examples that have worked in the past.
Legible	Benchmarks are legible if the data used to create the benchmark is publicly available, making the measure externally verifiable.	The database should be more explicit and accessible to ensure all stakeholders and clinical trials are being held to the same standards.

2.5.2 Barrier: Lack of quantifiable economic incentives.

> "Industry is more motivated to do diverse trials in phase IV because they know that there's a market for the drug, so they are willing to invest the money at that point. Without quantifiable financial incentives I can't see anyone changing how they design trials pre-approval."
>
> -Chief Medical Officer of a global midsize biopharma

While benchmarks provide encouraging levels of transparency, industry-wide change is unlikely without the proper incentive structures:

1. Sponsors would rather avoid the cost and risk of investing in diverse recruitment in pivotal phase 3 trials before approval.
2. Public companies have a fiduciary duty to maximize shareholder value. Without explicit financial incentives, markets are unlikely to support investment in diverse recruitment.

2.5.2 Solution 14: Explore systemic, quantifiable economic incentives.

TOOLS

Financial incentives need to be designed thoughtfully. The FDA is already providing guidelines around diversity in clinical research. In tandem with introducing REAL benchmarks, the next step is to evaluate various incentives:

Positive Incentives	Negative Incentives
For submissions with sufficiently-diverse patient populations: • Expedite review and approval processes. • Approve positive claims in advertising • Prolong market exclusivity • Provide tax credits for research and development. • Offer exemption from some FDA fees. • Expedite CMS coverage decisions for representative research.	For submissions with insufficiently diverse patient populations: • Mandate post-market testing in a more representative population. • Introduce mandatory disclaimers • Refuse to file applications that do not meet predefined levels of representativeness.

3.0 To Conclude...

> "Sometimes we're expecting the world, but a lot of times it's these really small changes that make the biggest difference. Representation in research is not a one size fits all. It's not a sprint, it's a marathon. It's a mind shift across the industry."
>
> -Associate Director, Patient Diversity at a major CRO

In summary, every player in the clinical trial ecosystem has a role to play in improving the representativeness of patient populations. Literature review, quantitative analysis, and interviews have all pointed to the following 5 key areas of improvement, summarized below by stakeholder type:

- Sites must build more diverse research teams, implement implicit bias training, invest in a community presence, broaden their recruitment channels, and prioritize channels that reach underserved communities.

- Sponsors and CROs must allocate a budget for diverse enrollment activities, outline explicit KPIs for representative enrollment and reward sites and research teams that meet these targets. Site selection should prioritize those within a diverse community and sponsors must facilitate inter-site collaboration, to ease with patient transfer. At the level of trial design, there should be a structural shift to support more accessible protocol designs.

- Finally, regulators must give these shifts direction and impetus by exploring REAL benchmarks as well as incentives.

With a concerted effort at all levels of research and across all treatment areas, representative research can become standard practice instead of a distant future goal.

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Appendix I: Defining race and ethnicity

Figure 7 outlines the racial and ethnic subgroups that fall into the broader categories specified by the OMB. In 2011 the Department of Health and Human Services (HHS) published new definitions of race and ethnicity that were designed to capture the US population in greater detail (Figure 8).[54] These revised definitions of race and ethnicity don't even apply to all HHS data sets, let alone data from federal agencies, academic institutions, or private institutions, unless they voluntarily adopt them.[8]

Even more comprehensive definitions have since been published, which include as many as 900 classifications of race and ethnicity, but these definitions are not commonly used.[54] As such, it's clear that there isn't even a consensus on definitions of race and ethnicity, which leads to inconsistencies in recorded data and incomplete data sets, thereby impeding researchers' ability to monitor health disparities.[55] Their effects are amplified in smaller populations like American Indians and Alaska Natives.[54]

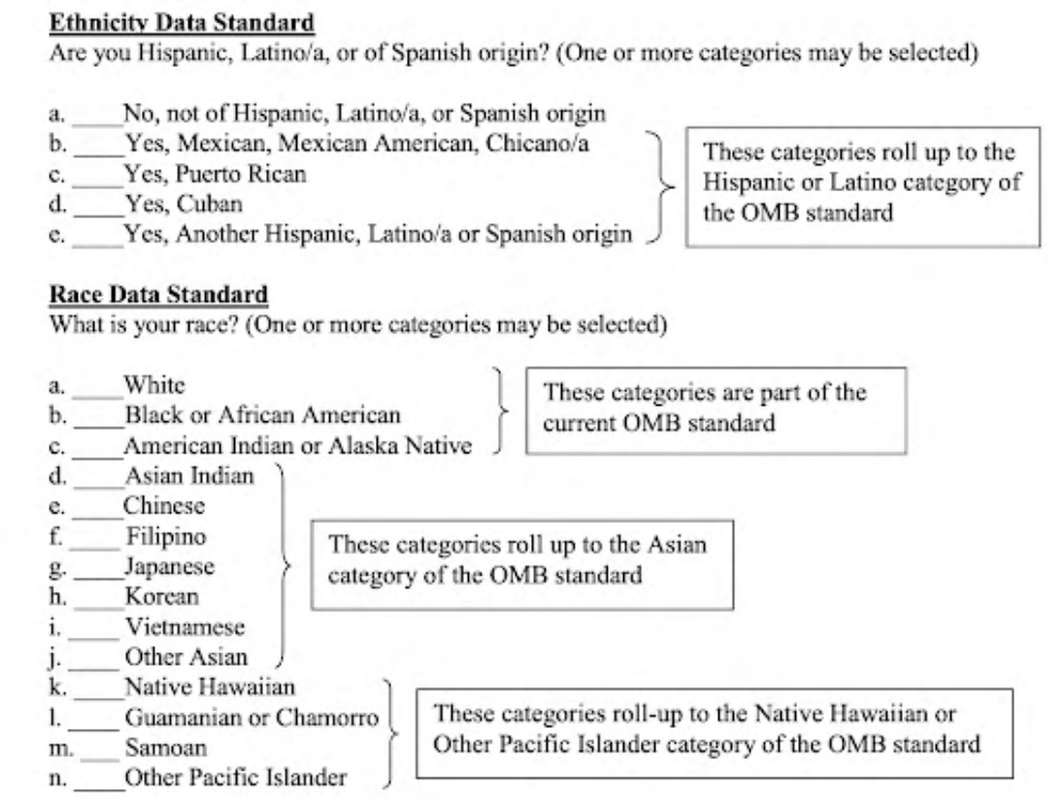

Figure 7: Illustration of the racial and ethnic groups that are rolled up into OMB categorizations.[37,56]

Table 1: Comparison of OMB 1997 and HHS 2011 Race and Ethnicity Collection Standards

	OMB 1997	HHS 2011
Race*	White	White
	Black or African American	Black or African American
	American Indian or Alaska Native	American Indian or Alaska Native
	Asian	Asian Indian Chinese Filipino Japanese Korean Vietnamese Other Asian
	Native Hawaiian or Other Pacific Islander	Native Hawaiian Guamanian or Chamorro Samoan Other Pacific Islander
Ethnicity*	Not Hispanic or Latino	No, not of Hispanic, Latino/a, or Spanish origin
	Hispanic or Latino	Yes, Mexican, Mexican American, Chicano/a Yes, Puerto Rican Yes, Cuban Yes, Another Hispanic, Latino/a or Spanish origin

* OMB 1997 and HHS 2011 permit the reporting of more than one race; HHS 2011 also permits people to select one or more ethnicity.

Figure 8: Race and ethnicity categories as per HHS 2011 novel definitions.54

Appendix II: Timeline of FDA mandates

Over the past 2 decades the FDA has issued a myriad of non-binding guidelines on the necessity of diversity in clinical trials and methods to increase participation from underserved, under-represented populations.

Year	Event	Description
1993	National Institute of Health Revitalization Act	General call to improve the number of women and members of racial minorities in NIH-funded clinical trials.[22]
2007	Food and Drug Administration Amendments Act (FDAAA) Section 801	Mandated age and gender reporting of participants in certain phase II-IV trials. Information regarding race and ethnicity of participants only needs to be reported if it was collected under the research protocol.[22,49,50]
2012	FDA Safety and Innovation Act (FDASIA) Section 907	Required the FDA to assess whether demographic subgroups (sex, age, race and ethnicity) are represented in research. Also required an assessment of data on the safety and efficacy of these products within subgroups.[48]
2013	FDA Action plan in response to FDASIA	3 priority areas: improving the quality of demographic data; identifying barriers to participation and developing strategies to increase enrollment; and increasing publically available data on demographic subgroups.[48]
2016	FDA issue: Collection of Race and Ethnicity Data in Clinical Trials	Call for phase III trials to adjust their primary research questions to account for potential differences in drug performance, if previous evidence has indicated different responses based on sex or race/ethnicity.
2022	FDA issue: Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry	Call for every trial to submit an operational plan to increase racial/ethnic diversity. This plan should include specific design features to support analysis of racial/ethnic-based differences in performance if previous evidence deems this relevant.[47]

Power