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# Plans and Enrollment Often Fell Short for Underrepresented Groups in a Sample of NIH-Funded Clinical Trials

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# Plans and Enrollment Often Fell Short for Underrepresented Groups in a Sample of NIH-Funded Clinical Trials

## Why OIG Did This Review

- Underrepresented racial groups, ethnic groups, and females are disproportionately burdened by many diseases yet have historically been underrepresented in medical research.
- This underrepresentation can exacerbate preexisting health disparities.
- A recent National Academies of Science report highlighted the increasingly diverse U.S. population while emphasizing the urgency of improving diverse representation in clinical research to combat health disparities.

## What OIG Found

Researchers in our sample often fell short in enrolling underrepresented groups in NIH-funded clinical trials and in meeting NIH's requirements for inclusion enrollment plans.

- Two-thirds of the clinical trials in our sample had inclusive enrollment plans, but one-third did not plan to include all racial and ethnic groups.
- Slightly more than half of clinical trials in our sample were missing required information that would explain the planned target population.
- Most completed clinical trials in our sample missed planned enrollment targets for underrepresented groups.
- NIH monitors clinical trial enrollment but has had limited success spurring improvement.

## What OIG Recommends

OIG recommends that NIH:

1. Hold researchers accountable for clearly describing the rationale for planned study population, as required by NIH policy.
2. Develop additional ways of supporting researchers in meeting inclusion enrollment targets.
3. Promptly take steps to align NIH's demographic data collection and reporting with the revised OMB requirements and obtain more precise clinical trial inclusion enrollment data.

NIH concurred with all three recommendations.

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# BACKGROUND

## OBJECTIVES

1. To determine the extent to which grantee institutions meet inclusion enrollment targets in NIH-funded clinical trials.
2. To determine how NIH monitors and holds grantee institutions accountable for inclusive enrollment of human subjects in NIH-funded clinical trials.

## Rationale

A longstanding concern in clinical research has been the underrepresentation of racial groups, ethnic groups, and females.[1, 2, 3] Diverse representation in clinical trials is important because the efficacy and safety of an intervention may differ among members of different racial and ethnic groups and between males and females. Underrepresentation of these groups in medical research potentially exacerbates preexisting health disparities.[4, 5]

The lack of inclusion of racial groups, ethnic groups, and females within clinical trials has been caused by many factors. Common hurdles for diverse enrollment include increased costs (e.g., providing translated informed consent for patients with limited English proficiency or pregnancy tests for females), lack of outreach to diverse communities about local clinical trials, and implicit biases, among other barriers.[6] Clinical trial recruitment is already considered challenging without these issues.[7]

The National Academies of Science released a 2022 report focused on diversity in clinical trials. Among the report's many findings, it highlighted the increasingly diverse U.S. population while emphasizing 1) the urgency of improving diverse representation in clinical research to combat health disparities found among underrepresented populations and 2) that improving diversity will require a significant investment of time and money.[8]

The National Institutes of Health (NIH) is the largest public funder of biomedical research in the world, spending about $38 billion annually on research, including clinical trials, to achieve its mission to enhance health; lengthen life; and reduce illness and disability.[9] The NIH-Wide Diversity, Equity, Inclusion, and Accessibility (DEIA) Strategic Plan highlights the agency's commitment to conducting and supporting research that includes and benefits all, especially groups that have been historically underrepresented.[10] Further emphasizing the importance of diversity in clinical trials, a recent meeting of the Advisory Committee to the NIH Director included a

recommendation that NIH "establish policies that elevate diversity, equity, and inclusion in the recruitment and retention of participants in clinical research."[11]

## Background

Clinical trials are research studies in which one or more human subjects are prospectively assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.[12] An intervention may include medical products (e.g., drug, biologic, or device) but could also include surgical techniques, strategies to change health-related behavior, and diagnostics.[13]

Clinical trials are conducted in phases to incrementally learn more about an intervention. Phase 1 evaluates small groups of people to assess whether a new medical intervention is safe. Phase 2 evaluates a larger group of people to determine the efficacy of the medical intervention. Phase 3 evaluates the safety and efficacy of a medical intervention within a larger population.[14]

### Disparities in Clinical Trial Enrollment Based on Race, Ethnicity, and Sex[15]

The efficacy and safety of an intervention may differ among members of different racial and ethnic groups and between males and females.[16] To produce scientifically generalizable research, clinical trial enrollment should reflect the demographic composition of the general public, those affected by the disease under study, or those for whom the medical product is intended.[17, 18]

**Race and Ethnicity:** Differences exist in the prevalence of diseases that affect racial and ethnic groups, including chronic conditions (e.g., type 2 diabetes, cardiovascular diseases), infectious diseases (e.g., HIV/AIDS, STDs), and different types of cancer (e.g., colon, prostate, cervix, lung).[19, 20] However, clinical trial populations do not always accurately reflect the disease burdens of the populations most affected by them. Racial and ethnic groups, particularly Black Americans, were underrepresented in recent COVID-19 vaccine clinical trials.[21] An analysis of drug trials conducted in 2018 showed that Black Americans comprised 13 percent of the population but only 5 percent of clinical trial participants. Hispanic representation is more disparate, as Hispanics comprised 18 percent of the U.S. population but less than 1 percent of trial participants.[22]

**Sex:** Despite well-known sex-based differences in response to many drugs, females have historically been underrepresented in clinical trials. Historically, factors driving this underrepresentation include NIH and Food and Drug Administration (FDA) policies intended to safeguard females with child-bearing potential during the early phases of clinical trials, as well as perceived costs and complexities.[23, 24] Multiple studies have shown that females are at greater risk of having an adverse drug reaction.[25] For example, one analysis of vaccines administered during the first month of COVID-19 vaccination found more than 75 percent of adverse events related to the COVID-19 vaccine involved females.[26]

### NIH Policy and Processes Related to Diversity within Clinical Trials

Headed by the Office of the Director, NIH consists of 27 institutes and centers that are focused on specialty areas (e.g., the National Cancer Institute and National Heart, Lung, and Blood Institute).[27] NIH's mission is "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability."[28] NIH accomplishes this mission, in large part, by annually funding over $38 billion in extramural research, including about $6 billion for clinical trials, through its grant-making process.[29, 30]

The 1993 NIH Revitalization Act required that NIH ensure that members of underrepresented racial/ethnic groups and females are included in clinical research.[31] The law provides for exceptions to this requirement when inclusion of underrepresented racial/ethnic groups and females in clinical research would be "inappropriate" 1) for the health of the subjects, 2) for the purpose of the research, or 3) under other circumstances prescribed by the Director of NIH.[32]

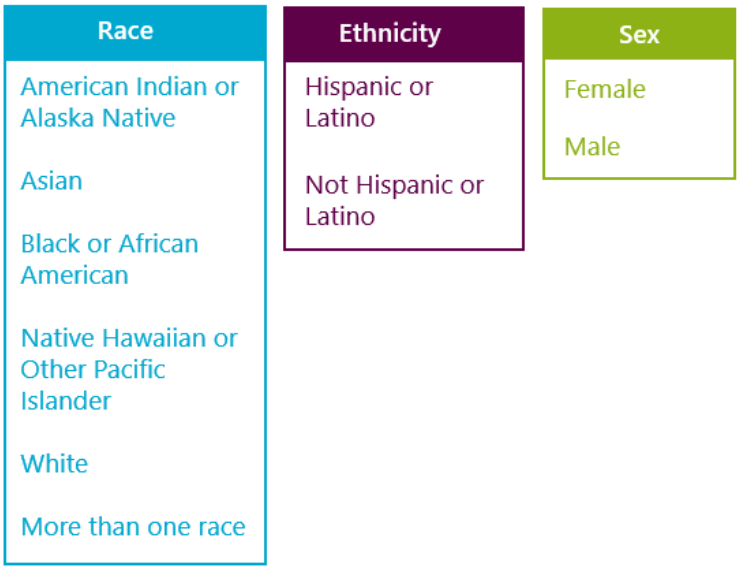
### Clinical Research Inclusion Enrollment Plans and NIH Peer Review Process

NIH requires principal investigators (hereinafter researchers) who apply for clinical research funding on behalf of grantee institutions to submit inclusion enrollment plans (hereinafter inclusion plans) as part of their applications.[33] This inclusion plan must include a numerical breakdown of targeted participant demographics by race and ethnicity, as well as by sex.[34]

NIH defines racial and ethnic categories as "a readily identifiable subset of the U.S. population distinguished by either racial, ethnic, and/or cultural heritage."[35] Reporting of inclusion data should follow the Office of Management and Budget Statistical Policy Directive 15 (OMB SPD 15).[36] OMB issued revised SPD 15 standards in March 2024.[37] An inclusion enrollment report must also include a breakdown of sex, which must be reported as male or female.[38] See Exhibit 1 below for details on the OMB SPD 15 standards in place at the time of this review.

**Exhibit 1: Racial, ethnic, and sex categories that must be included in NIH's inclusion plans as of June 2023[39]**

Note: Although "more than one race" is not an OMB racial category, the SPD-15 Directive allows for individuals to select more than one of the racial categories. In FY 2015, NIH began to collect this category for new planned enrollments.



NIH requires the inclusion plan to include scientific or ethical justification for any exclusions of any group, if applicable. Justifications for excluding a group include evidence from prior studies that supports no significant differences of clinical or public health importance in intervention effect based on race, ethnicity, sex, and/or relevant cross-demographic comparisons.[40] Cost is not an allowable justification to exclude a group.[41]

NIH's peer review is the process by which scientists outside of and within NIH evaluate grant applications for scientific and technical merit, among other factors such as inclusion plans.[42] Grant applications undergo two levels of peer review: the initial scientific review and review by an advisory council. In the first level of peer review, non-NIH experts assess clinical research applications based on scored review criteria as well as consideration of additional items, including inclusion of racial groups, ethnic groups, and females.[43] At the second level of peer review, an advisory council composed of expert members who are independent of NIH evaluate a grant application's acceptability.[44]

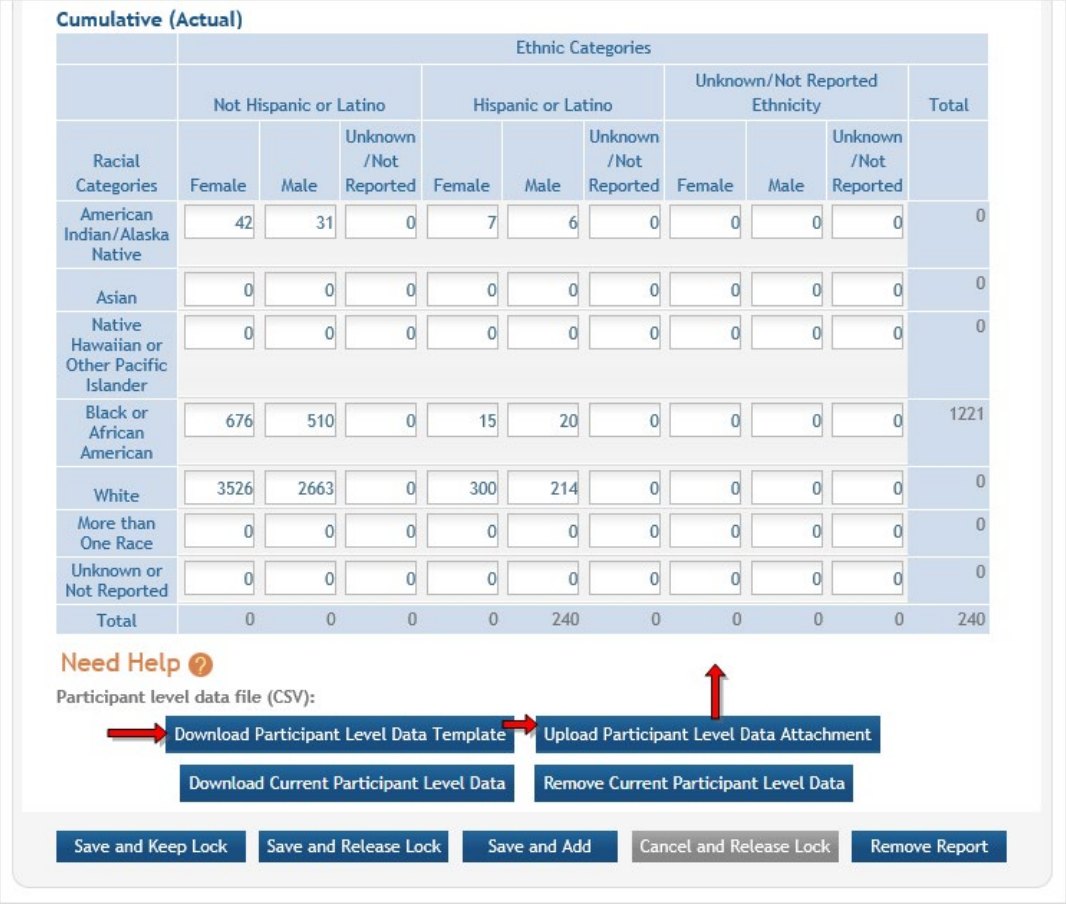
For Phase III clinical trials, peer reviewers assess inclusion plans to conduct analyses of intervention effects based on race, ethnicity, sex, and/or relevant cross-demographic comparisons. Depending on the context of the scientific question and the study design, the grant applicant may indicate that including a diverse population is not necessary to make the research scientifically generalizable. In these instances, the grant applicant must provide justification.[45] Ultimately, the peer reviewers determine each application as having either acceptable or unacceptable inclusion plans.[46]

NIH policy states it bars grant applications from funding in cases in which peer reviewers determine that an application does not adequately address inclusion or exclusion of gender and minorities.[47] In these instances, NIH program officers, who are NIH staff scientists who administer grant portfolios, help the applicant to resolve the problems.[48] Grant applicants must then provide additional information or adjust their research plans before NIH will agree to fund their grants.[49]

### Post-Award Review and Monitoring

NIH program officers monitor progress made by grantee institutions toward meeting the approved inclusion plan.[50, 51] NIH requires grantee institutions to submit annual progress reports which include an inclusion enrollment report (IER) that shows participant demographics by race, ethnicity, and sex.[52] Grantee institutions generally update IERs annually; however, in some circumstances, depending on reporting requirements, they may update an IER more than once in a given year.[53] See Exhibit 2 for a sample cumulative enrollment table within an IER.

### Exhibit 2: Sample IER Table



**Cumulative (Actual)**

| | Ethnic Categories | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Not Hispanic or Latino | | | Hispanic or Latino | | | Unknown/Not Reported Ethnicity | | | Total |
| Racial Categories | Female | Male | Unknown /Not Reported | Female | Male | Unknown /Not Reported | Female | Male | Unknown /Not Reported | |
| American Indian/Alaska Native | 42 | 31 | 0 | 7 | 6 | 0 | 0 | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Black or African American | 676 | 510 | 0 | 15 | 20 | 0 | 0 | 0 | 0 | 1221 |
| White | 3526 | 2663 | 0 | 300 | 214 | 0 | 0 | 0 | 0 | 0 |
| More than One Race | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 0 | 0 | 0 | 0 | 240 | 0 | 0 | 0 | 0 | 240 |



Source: era.nih.gov.

For Phase III clinical trials, NIH program officers should monitor the requirement for analysis of intervention effects by race, ethnicity, and sex. If the enrollment is not on target with the initial inclusion plan, the program officer is tasked with asking the grantee institution to address the problem.[54] If enrollment problems persist, the program officer will request and monitor a corrective action plan. If the grantee institution fails to make progress following the corrective action, the program officer may take administrative steps that include suspending and terminating the study.[55]

## Related Work

The Government Accountability Office (GAO) released a 2022 report that described the extent to which Federal agencies conducting cancer research and other non-Federal cancer research centers have taken steps to facilitate a diverse study population and lower barriers to participation in trials. That report identified a range of actions and practices, such as research collaborations and data standardization, among others that Federal agencies, including NIH, and non-Federal cancer centers have worked on.[56] Additionally, a 2015 GAO report found aggregated NIH-funded clinical research included more women than men for fiscal years 2005-2014. GAO also found that NIH does not routinely examine more detailed enrollment data, such

as enrollment data organized by the disease and condition being studied. As a result, GAO concluded that NIH was limited in its ability to identify whether women are sufficiently represented in studies in specific disease areas or condition areas.[57] Additionally, starting with 2018 data, NIH posts inclusion enrollment details by disease category, which gives NIH staff and external investigators the ability to evaluate inclusion by disease/condition.

## Methodology

### Scope

Our review focused on a random sample of 30 NIH-funded Phase III clinical trials. We selected the sample from a population of 156 Phase III clinical trials that had IER enrollment data for FY 2020 and had at least 50-percent actual enrollment. Our sample was spread across eight institutes. See Appendix A for a breakdown of clinical trials by institute.

We selected Phase III clinical trials because they generally enroll larger populations of human subjects and NIH has long established structured data about them. Our review of IERs assessed enrollment for FY 2016–2020. We chose to start with FY 2016 data because NIH had different inclusion reporting requirements before then and maintained IERs in a different database. We chose 2020 as the end year because it was the most recent year with complete data at the time.

### Analysis of Clinical Trial Enrollment Data

For our sample of 30 clinical trials, we reviewed 5 years of IER data (FYs 2016–2020) from NIH's Human Subjects System. The data include a breakdown of planned and actual human subject enrollees by race, ethnicity, and sex that we used to determine if trials missed or met their enrollment targets. We note that not all 30 clinical trials had new IER data for each year because some started later than 2016 and some ended earlier than 2020. We did not set out to determine whether differences we saw between planned and actual enrollment affected the results of the research.

For our analysis of completed trials missing enrollment targets for underrepresented groups, we excluded five clinical trials that ended early. Data safety monitoring boards (DSMBs), advisory committees of experts responsible for reviewing ongoing clinical trial data for safety and merits, ended three of these five clinical trials early because the researchers had already achieved their research objectives. For the other two trials, the researchers ended accrual of human subjects early because they struggled to recruit during the COVID-19 pandemic. Because these trials, and potentially their recruitment, ended early, it would not be appropriate to include their enrollment data in analysis of whether trials met their enrollment targets.

### Document Review

NIH maintains all records related to grant oversight within its Electronic Records Administration (eRA) data system. This system includes initial and updated inclusion

plans, IERs, and related documents such as program officers' notes. In some instances, correspondence between the program officer and grantee institution may be stored outside eRA, such as in emails or phone call notes.

For the 30 clinical trials in our sample, we requested and analyzed the following documents from their respective grant records:

- The original inclusion plan and planned enrollment table with each grant application, as well as any narrative in the application that supported how the planned enrollment table was determined (i.e., rationale), such as analysis or reference to disease burden and recruitment strategies;
- Documentation of any changes to the original inclusion plans after initial approval; and
- Any documentation of oversight by NIH program officers related to diversity and inclusion enrollment.

**Interviews**

We conducted structured interviews with 17 of 19 NIH program officers who were responsible for monitoring the 30 clinical trials in our sample. Two program officers were unavailable for interviews. We asked program officers questions about the peer review process, how they monitor enrollment of clinical trial subjects, and the challenges they face. We spoke with additional NIH staff about their policies and procedures related to inclusion enrollment data and their data systems.

For further context, we also spoke with eight researchers who conducted clinical trials within our sample. We asked these researchers about 1) the design and submission of their inclusion plans during the grant application review process; 2) meeting the inclusion plan's targets, as well as NIH's monitoring of this effort; and 3) challenges the researchers face throughout this effort.

## Standards

We conducted this study in accordance with the Quality Standards for Inspection and Evaluation issued by the Council of the Inspectors General on Integrity and Efficiency.

## Limitations

Our findings are not generalizable and apply to our sample of 30 Phase III clinical trials. We did not independently verify the clinical trial enrollment data we received from NIH. A number of trials had some participants that did not report race, sex, or ethnicity. We did not assess the impact of unknown values on whether trials met targets.

# FINDINGS

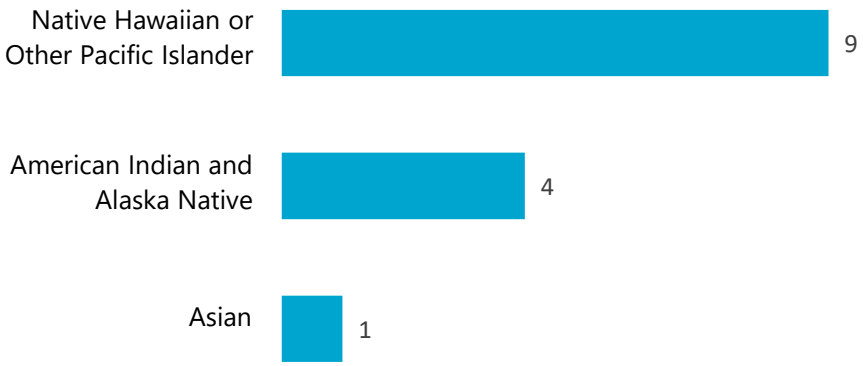
## Two-thirds of the clinical trials in our sample had inclusive enrollment plans, but one-third did not plan to include all racial and ethnic groups

Among the clinical trials in our sample, 18 of 30 included all underrepresented racial, ethnic, and sex groups in their inclusion plans. Across these 18 trials, researchers considered a diverse and representative participant group. An additional two clinical trials were focused on Black or African Americans, and by nature of the research approved, did not include other underrepresented racial groups within the application.

In contrast, 10 of 30 trials did not plan to include at least 1 underrepresented racial group from the planned enrollment population. This means that in 10 instances, NIH approved clinical trials in which the researchers submitted inclusion plans to NIH that did not include all underrepresented racial groups. Across the 10 trials, researchers left out underrepresented racial groups from plans in 14 instances. For example, researchers did not plan to include "Native Hawaiian or Other Pacific Islanders" in nine occurrences. The racial category "American Indian and Alaska Natives" was the population second most often not included in planned enrollment targets. See Exhibit 3 for details on groups trials did not plan to include.

Although these 10 clinical trials did not include every demographic group, NIH guidance states that it does not expect every study will include both sexes; all racial and ethnic groups and subgroups; and all age groups. Rather, inclusion of sex/gender, race, ethnicity, and age should be guided by the scientific aims of the study.

**Exhibit 3: Racial groups that clinical trials did not plan to include (total instances = 14 across 10 trials)**



## Slightly more than half of clinical trials in our sample were missing required information that would explain the planned target population

Of 30 clinical trials in our sample, 17 provided little to no explanation for how they determined their inclusion enrollment targets. When researchers apply for grant funds, NIH requires the researchers to submit an inclusion plan that describes and fully justifies the intended clinical trial population. However, inclusion plans from our sample often included a limited basis for how the researchers set enrollment targets for underrepresented groups. For example, the inclusion plan for one clinical trial simply described that it would enroll women and members of underrepresented groups without any additional details. When we asked about this inclusion plan, the researcher explained that he selected additional sites to assist with enrollment but "guessed at what final enrollment would be based on race and gender." For another clinical trial, the inclusion plan stated, "We will oversample practices with high percent (sic) black and Hispanic families," without any other specificity. These shortfalls we saw in our review of inclusion plans raise concerns about NIH's peer review process and the extent to which this section of the grant application is thoroughly analyzed. See Exhibit 4 for examples of inclusion plans that provide less robust rationales for establishing enrollment targets.

**NIH guidance:**

Applicants should describe and fully justify the distribution of individuals who will be included in the research.

**Exhibit 4: Examples of inclusion plans with less robust rationales**

1. "Children will be entered in the proposed study without regard to gender. It is anticipated that enrollees will be divided approximately equally between boys and girls. Children will be entered in the proposed study without regard to race or ethnicity."
2. "Women and minorities will be included in the pilot study and intervention phase of the proposed study to the same extent that both exist in the population of patients cared for at the three participating facilities."
3. "[The trial's] investigators are committed to recruiting a representative number of women and minorities to the study to reflect the prevalence of disease in the US population… Investigators have pre-specified recruitment goals: 40% for women and 12% for minorities. Having these recruitment goals helps to motivate centers at every stage of the trial…"

Generally, NIH requires that researchers strongly consider the population in which they are recruiting and assess whether targets are scientifically appropriate to allow for analysis by sex, race, and ethnic groups. Even if previous research suggests there

is no difference between groups, researchers should still describe the intended recruitment breakdown with justifications grounded in science. For example, it is not enough to base population targets solely on site-level or local demographic data. In less diverse geographic areas, this approach may fail to include underrepresented racial groups. Rather, researchers should base their plans on scientific or ethical factors, per NIH policy.

We saw more robust rationales for planned enrollment targets in 13 of 30 clinical trials in our sample. These 13 clinical trials provided analysis of disease burden combined with demographic data to explain the approach taken. These rationales explained the logic for setting targets at the proposed levels, based on data from previous clinical trial recruitment results or U.S. Census data. For example, 6 of these 13 clinical trials provided rationales that clearly tied the planned enrollments to previous clinical trial network recruitment. These trials tended to have more comprehensive plans because clinical trial networks are well-established national collaborations between groups of researchers and research institutions. In addition, the clinical trial networks associated with our sampled trials often had data and prior experience achieving diverse enrollment to inform their recruitment targets. See Exhibit 5 for additional examples of sufficient rationales.

**Exhibit 5: Examples of inclusion plans with more robust rationales**

1. "Our sample of approximately 588 complex patients enrolled in the…(program) will be representative of the race/ethnic distribution of the primary care population. Based on 2010 (program) data, we estimate that approximately 30% of participants will be White, 20% Hispanic, 19% African American, 24% Asian/Pacific Islander, and 2% Native American."
2. "While the exact demographic break-down of (residential care facilities) residents has not been published, our previous studies of persons with schizophrenia who live in (residential care facilities) have shown a highly diverse population: 34% female, 54% Caucasian, 16% African-American, 21% Hispanic, and 9% as other race."
3. "According to 2012 Census Data, 50.5% of Oklahoma City residents are female. We expect that the proportion of female participants will likely be somewhat larger given our previous studies with smokers (55-62% female). According to 2012 United States Census data, the racial composition of individuals living in Oklahoma City is 62.7% White, 14.4% Black or African American, 3.5% Asian, 5.0% American Indian/Alaska Native, 0.1% Native Hawaiian/Other Pacific Islander, and 14.3% two or more races. The ethnic composition of individuals living in Oklahoma City is 8.9% Hispanic/Latino and 91.1% Non-Hispanic/Latino."

Finally, the two trials in our sample that were focused exclusively on the Black or African American population, a historically underrepresented group within clinical research, also included robust rationales. They provided context that the study populations are disproportionately affected yet disparately experience the worst outcomes for the disease under study.

"Black men constitute the race/ethnic/gender group in the U.S. with the highest rates and greatest severity of premature hypertension and target organ damage and the lowest rates of hypertension awareness, treatment, and control. This research program seeks to reduce this major racial/gender disparity."

*- Language justifying the enrollment plan for a clinical trial focused on Black or African American males*

## Most completed clinical trials in our sample missed planned enrollment targets for underrepresented groups

Of the 12 clinical trials in our sample that had completed their recruiting (hereinafter completed clinical trials), 10 recruited fewer participants from one or more underrepresented groups than originally planned.[58] Completed clinical trials most commonly recruited fewer Black or African American; American Indian and Alaska Native; and Asian participants than originally planned. Additionally, clinical trials missed targets for female participants more often than they did for male participants.

The extent to which these 10 clinical trials missed their targets varied.[59] Some trials missed targets by 15 percent or less of the total planned for the underrepresented group. For example, one clinical trial had a planned target of 75 Asian Americans but enrolled 68 (a 9-percent difference). Other clinical trials missed targets by significant amounts. For example, another clinical trial had planned to enroll 144 Black Americans however enrolled only 74 (a 49-percent difference).

It is possible for a trial to miss numerical targets for underrepresented groups and still achieve planned diversity if the trial's distribution of enrollees among groups does not shift between planned and actual enrollment, for example if a trial under- or over-recruited equally across all groups. This was not the case in the 10 trials that missed targets. In each of these 10 trials, the trial population was less diverse than planned because the percentage of the study population made up by underrepresented groups fell between planned and actual enrollment. In some cases, the share of the trial's population made up by underrepresented racial groups; the share of females; and/or the share of Hispanic or Latino people fell by a few percentage points or less. In other cases, the share of the trial population made up of underrepresented groups fell between planned and actual enrollment by as much as 10 to 35

percentage points. It is unknown whether the difference in the original target and actual enrollment affected the generalizability of results or the ability of the researchers to perform subgroup analyses. See Appendices B and C for more details on the magnitude by which completed clinical trials missed their target enrollment(s) and the extent to which trials enrolled a diverse population.

Yet, all the clinical trials in our sample also met or exceeded planned enrollment for one or more underrepresented groups. For Native Hawaiian or Other Pacific Islander human subjects, clinical trials met or exceed enrollment targets as often as they missed targets. For Hispanic or Latino human subjects, clinical trials met or exceed enrollment targets in more instances than they missed targets.

See Exhibit 6 for more information on the numbers of completed clinical trials that 1) planned to enroll human subjects of each demographic group, 2) missed enrollment targets, and 3) met or exceeded enrollment targets.

**Exhibit 6: The number of completed clinical trials with planned inclusion that missed, met, or exceeded enrollment targets for each group**

| | Trials with planned inclusion (Total trials: 12) | Missed enrollment target | Met or exceeded enrollment target |
|---|---|---|---|
| American Indian or Alaska Native | 10 | 6 | 4 |
| Asian | 12 | 7 | 5 |
| Black or African American | 12 | 7 | 5 |
| Native Hawaiian or Other Pacific Islander | 8 | 4 | 4 |
| White | 12 | 4 | 8 |
| Female | 12 | 6 | 6 |
| Male | 12 | 3 | 9 |
| Hispanic or Latino | 12 | 3 | 9 |
| Not Hispanic or Latino | 12 | 8 | 4 |

## NIH monitors clinical trial enrollment but has had limited success spurring improvement

Program officers we spoke with during our review acknowledged the importance of enrolling underrepresented groups in clinical trials. NIH program officers, who may oversee up to 50 clinical trial sites at a time, told us diverse recruitment is a priority, but they reported that they have other competing priorities. Although researchers highlighted the importance of including underrepresented groups in clinical trials, they reported challenges in recruiting these groups. Furthermore, the NIH-Wide DEIA Strategic Plan emphasizes that the agency is committed to conducting and supporting research that includes and benefits all, especially groups that have been historically underrepresented.[60] Nevertheless, enrollment for these underrepresented groups still may lag.

### Program officers use a range of information to provide insights on recruiting underrepresented groups

Program officers rely on annual progress reports, which include inclusion enrollment data as well as other data sources, to monitor clinical trial recruitment progress. In addition to the annual inclusion enrollment data, NIH program officers reported using other, timelier data sources to monitor clinical trial progress, including the progress made toward enrollment targets for underrepresented groups. For example, program officers often reported using data safety monitoring board (DSMB) data on recruitment, which are typically available at least twice a year. Others reported having access to a clinical trial dashboard populated by trial sites to monitor enrollment over time.

DSMBs are advisory committees of experts responsible for reviewing ongoing clinical trial data. In addition to monitoring the safety and merits of ongoing clinical trials, DSMBs work to ensure compliance with goals for recruitment and retention, including those related to the participation of underrepresented groups.

Clinical trials funded through cooperative agreements, which represent most of the grants in our sample, generally have additional systems monitoring clinical trial progress, including the progress made toward human subject inclusion targets. For example, the National Cancer Institute (NCI) has multiple clinical trial networks and provides them with infrastructure support for coordination and data collection. One program officer from NCI stated that she has access to enrollment data on a "24-hour basis." Likewise, a program officer from the National Institute of Neurological Disorders and Stroke described a system the institute used that provided enrollment data, including diversity data, in real time.

Timely monitoring of recruitment data helps NIH flag clinical trials that appear to be behind schedule for meeting their inclusion targets. When NIH can identify shortfalls

in recruitment early on, it is better able to assist researchers to take steps to improve inclusion. Several program officers commented that the earlier they notify a researcher about recruitment concerns, the more likely the concerns will be addressed. Program officers reported that they generally correspond with researchers through email and phone calls to discuss these concerns and plan the next course of action.

**Exhibit 7: Program officers' notes regarding clinical trials not meeting their targets**

**Example of email between program officer and researcher about underperforming clinical trial:**

"Low inclusion of women: (your study) was flagged due to low inclusion of women (43%). It would be preferable that you enroll 51% of women, unless you have an exceptionally strong justification, and I mean exceptional that we can present to the (Institute)."

**Example of summary of underperforming clinical trial:**

"[M]inority recruitment is very low with 1% Black/African American, 3% Hispanic/Latino, and 1% Asian… [It is recommended] that minority recruitment be a major focus for the last 60 plus subjects that will be enrolled into the study. The study team should focus on sites in areas with access to minority populations to increase minority recruitment for the reminder (sic) of the study enrollment period."

## NIH and researchers have had limited success in using research and administrative flexibilities to overcome the challenges of lagging enrollment

When under-enrollment persists, NIH and researchers have had limited success addressing the problem. To improve enrollment of underrepresented groups, NIH has offered researchers flexibilities related to 1) the way the research was conducted or 2) administrative options. For example, NIH has provided researchers the ability to alter their research plans by adjusting the number of human subjects in the clinical trial or changing the study design. Among the administrative options, NIH provided no-cost extensions, which allowed more time for enrollment but not additional funds to recruit during the extension. In some situations, NIH has also used administrative supplements, which can provide more funding for unforeseen increased costs.

Researchers sometimes reported encountering difficulties pursuing new recruitment strategies even with the flexibilities provided. Some researchers reported that when sites underperformed and failed to meet inclusion targets, they took measures to improve site performance, often with NIH's support. For example, researchers increased monitoring of recruitment data, dropped poorly performing sites, and added new sites. However, even though NIH's flexibility allowed for site changes,

some sites continued to struggle, and the clinical trials were unable to achieve planned enrollment targets for underrepresented groups.

### Exhibit 8: Examples of flexibility options NIH offered to researchers to improve enrollment of underrepresented groups

**1) Flexibilities in the way research is conducted**

- Adding or dropping clinical trial sites;
- Adjusting the number of human subjects; and
- Changing study design (e.g., change protocols or adjust or drop study questions)

**2) Administrative flexibilities**

- No-cost extension (extension of time for a trial without provision of additional funds; trials can continue to enroll subjects during this time); and
- Administrative supplements, i.e., funded adjustments (additional funding to meet unforeseen increased costs that are within the scope of the approved project)

Researchers also reported that NIH offered no-cost extensions when their enrollment of underrepresented groups lagged. Although this allowed for extended time periods to recruit, it did not include additional funding to cover additional costs that the trials incur when recruitment is extended. A part of a trial's budget is dedicated to recruitment, and extending that has a cascading effect on the whole trial's schedule and budget. See Exhibit 9 below for examples.

### Exhibit 9: Instances in which clinical trials experienced unexpected delays or expenses

**Example 1:** One researcher described the challenges with money and time presented for meeting enrollment targets, especially when the two challenges are both pressing. In this case, the trial required custom software prior to recruitment. The software developer was 9 months late delivering the custom software, resulting in an idle period that exacerbated pressures on the trial's budget and timeline. Additionally, once recruitment started, the trial faced many COVID-19-related recruitment challenges, including the researcher not being allowed to recruit for non-COVID-19-related studies at the site they planned to recruit from. The researcher still could not meet recruitment targets despite changing the protocol to make enrollment easier by dropping one part of their analysis and reducing enrollment targets.

**Example 2:** Due to COVID-19 and poorly performing sites, a trial struggled to meet planned enrollment targets for underrepresented groups. To improve enrollment, the trial not only dropped poorly performing sites in order to devote more resources to other sites, but relied on devoting more time to recruitment through multiple no-cost extensions. However, paying for recruitment expenses, including staff, during those no-cost extensions proved challenging.

## Data limitations may hinder NIH's ability to ensure and accurately report clinical trial diversity

We observed within our sample data limitations that could affect meeting planned targets for underrepresented populations. One data limitation was with the number of enrollees with no listed race and ethnicity. NIH guidance allows human subjects to self-report in the "Unknown" category if they do not identify with the other OMB SPD 15 categories.[61, 62] Also, almost 5 percent of enrolled human subjects in our sample were classified as the race category "Unknown" in NIH's Human Subjects System database. Additionally, 2 percent of enrolled human subjects were classified in the ethnicity category "Unknown" in NIH's database. Because the OMB SPD 15 categories in place during this review were created in 1977, they likely do not reflect the current demographics of the U.S. For example, the most recent American Community Survey classified almost 6 percent of the U.S. population as "some other race" not listed in the OMB SPD 15 standards.

# CONCLUSION AND RECOMMENDATIONS

National attention to pervasive health disparities has increased in recent years, and by extension, so has the urgency of increasing diversity in clinical trials. Recognizing the need for change, Federal agencies that fund or regulate clinical trials; research institutions; industry; and other interested parties have raised awareness about underrepresentation in clinical research and taken steps to improve diversity. The 2023 NIH-Wide DEIA Strategic Plan called for further research into health disparities and committing to supporting research that includes and benefits all. Congress recently passed a law requiring diversity plans within certain FDA-regulated clinical trials.

With the goal of improving diversity of clinical trial participants, NIH requires that researchers provide robust enrollment plans that include enrollment targets by sex, race, and ethnicity along with well-supported justifications for enrollment targets and for exclusion of any underrepresented groups. Although NIH does not require that every racial and ethnic group be included in every clinical trial, researchers in our sample often planned to enroll certain racial and ethnic groups but not others without providing a clear rationale for doing so.

NIH takes steps to support researchers with lagging enrollment, but the steps have not always been effective in overcoming enrollment challenges. This is significant given that most completed trials in our sample failed to meet one or more enrollment targets. Not meeting enrollment targets, as well as not committing to include certain groups in inclusion enrollment plans, risks fewer members of underrepresented groups participating in NIH-funded research. This may result in research that does not accurately reflect either disease burdens or the general population, making it difficult to produce generalizable results.

Given that the U.S. population continues to diversify and that calls for ensuring other underrepresented groups, such as individuals with disabilities, are included in clinical trials, the shortcomings we observed in this review become more concerning. To that end, we recommend that NIH:

## Hold researchers accountable for clearly describing the rationale for planned study population, as required by NIH policy

During peer review, before funding decisions, NIH should ensure that plans justify and clearly describe the rationale for the planned study population. Having a diverse clinical trial study population requires planning on the part of researchers and NIH. Therefore, ensuring that each plan fully describes the basis for its planned study population would demonstrate that NIH takes this requirement seriously and is holding researchers accountable.

It may be reasonable that not all racial and ethnic groups and both sexes are included in every study. However, NIH should err on the side of transparency in ensuring that these decisions are explained by researchers. Such transparency could bolster confidence in clinical research by demonstrating that, when underrepresented groups are not included, it is scientifically or ethically justified.

## Develop additional ways of supporting researchers in meeting inclusion enrollment targets

The 1993 NIH Revitalization Act requires that NIH ensure that underrepresented groups are included in clinical research and states that cost is not a permissible reason to exclude racial groups, ethnic groups, and females. However, we found that, despite taking action, NIH had limited success spurring improvement when the clinical trials in our sample struggled to meet inclusion enrollment targets.

Therefore, as NIH carries out efforts related to its new DEIA Strategic Plan, we urge NIH to consider the ways it can more comprehensively support researchers meeting inclusion enrollment targets. For example, NIH could identify opportunities improving researchers' ability to develop realistic and viable recruitment strategies early in the research planning phases. NIH could also examine policies and procedures governing how it works with researchers once trials are under way. For example, in addition to the current flexibilities it offers, NIH could work with researchers to expand the number and variety of approaches it can take when researchers struggle to meet recruitment goals for underrepresented groups. In these efforts, NIH could leverage Departmental resources, such as the Office of Human Research Protections, which has experience providing workshops to institutional review boards and researchers that cover recruiting underrepresented groups.

Finally, if NIH determines that changes to HHS grants policy may be required to effectively support researchers in meeting inclusion enrollment targets, it should raise that issue within the Department.

## Promptly take steps to align NIH's demographic data collection and reporting with the revised OMB requirements and obtain more precise clinical trial inclusion enrollment data

In March 2024, OMB completed a revision of its Statistical Policy Directive 15 to improve the quality and usefulness of Federal race and ethnicity data. To obtain the most accurate and precise demographic data regarding enrollment within NIH-funded clinical trials, NIH should promptly create an Agency Action Plan by September 2025, as required by OMB. By doing so, NIH may be able to capture the demographic information of a changing U.S. population more accurately and, perhaps, minimize reporting human subjects as ''unknown."

We recognize that updating its race and ethnicity requirements may be a complicated process, involving revising guidance and changes to information systems. However, to obtain more precise clinical trial inclusion enrollment data, we encourage NIH to have its Agency Action Plan ready by the September 2025 deadline and execute its plan in a timely manner.

# AGENCY COMMENTS AND OIG RESPONSE

NIH concurred with all three of our recommendations.

First, NIH agreed with our recommendation that it hold researchers accountable for clearly describing the rationale for planned study populations, as required by NIH policy. NIH stated that it had determined that all the clinical trials in our sample had planned study populations that were scientifically acceptable, despite our finding that clinical trials in our sample were often missing required information that would explain the planned target population. NIH added that its ongoing peer review reform effort will help focus peer review on the scientific and technical merit of proposed research projects. It concluded that changes related to this effort will better focus applicants and reviewers on inclusion so that the rationale for the planned study population is clearly explained. OIG looks forward to reviewing the NIH policy and guidance that result from NIH's reform effort and how they will increase accountability for clearly describing the rationale for planned study populations.

Second, NIH concurred with our recommendation that it develop additional ways of supporting researchers in meeting inclusion enrollment targets. NIH highlighted the importance of its existing annual monitoring of clinical trial progress; the resources it makes available to researchers to help plan for and achieve diverse enrollment; and activities conducted by the institutes to support diverse participation in clinical trials. NIH added that it is creating new training for program officers and researchers to spur recruitment of underrepresented groups. OIG acknowledges NIH's existing efforts and its forthcoming training. In NIH's Final Management Decision, OIG encourages NIH to consider additional action that can more comprehensively support researchers meeting inclusion enrollment targets.

Third, NIH concurred with our recommendation that it promptly take steps to align its demographic data collection and reporting with the revised OMB requirements and obtain more precise clinical trial inclusion enrollment data. We note that OIG issued our draft report to NIH on March 12, 2024, just prior to OMB publishing its revisions to Statistical Policy Directive No. 15 on March 28, 2024. We have updated our recommendation in the final report to account for OMB's revised Directive. NIH reported that it is currently assessing changes it needs to make, and will submit an Action Plan, as required by OMB, by the September 2025 deadline. OIG understands that NIH is taking steps to implement this recommendation and looks forward to reviewing NIH's Action Plan and other materials.

For the full text of NIH's comments, see Appendix D.

# APPENDICES

## Appendix A: Breakdown of Sample of 30 Clinical Trials by Institute

| Institute | Acronym | Clinical trials per institute |
|---|---|---|
| National Cancer Institute | NCI | 11 |
| National Heart, Lung, and Blood Institute | NHLBI | 6 |
| National Institute of Neurological Disorders and Stroke | NINDS | 4 |
| National Eye Institute | NEI | 3 |
| National Institute of Allergy and Infectious Disease | NIAID | 3 |
| National Institute on Drug Abuse | NIDA | 1 |
| National Institute of Diabetes and Digestive and Kidney Disease | NIDDK | 1 |
| National Institute of Mental Health | NIMH | 1 |
| **Total** | | **30** |

Source: OIG analysis, 2023

## Appendix B: Detail on Magnitude of Under-Enrollment for Each Demographic Group Among the 12 Completed Clinical Trials

| | Total trials with planned inclusion | Missed enrollment target | Under by 10% or more | Under by 15% or more | Under by 20% or more |
|---|---|---|---|---|---|
| American Indian or Alaska Native | 10 | 6 | 5 | 5 | 4 |
| Asian | 12 | 6 | 6 | 6 | 6 |
| Black | 12 | 7 | 5 | 5 | 5 |
| Native Hawaiian or Other Pacific Islander | 8 | 4 | 2 | 2 | 2 |
| White | 12 | 4 | 3 | 3 | 3 |
| Female | 12 | 6 | 4 | 4 | 2 |
| Male | 12 | 3 | 2 | 2 | 2 |
| Hispanic or Latino | 12 | 3 | 1 | 1 | 1 |
| Not Hispanic or Latino | 12 | 8 | 3 | 3 | 3 |

# Appendix C: Detail on Enrollment of Each Demographic Group for the 12 Completed Clinical Trials

**Detail on Planned and Actual Enrollment of Each Racial Group for the 12 Completed Clinical Trials**

| Trial | | American Indian or Alaska Native | Asian | Black or African American | Native Hawaiian or Other Pacific Islander | White | More than one | Total* |
|---|---|---|---|---|---|---|---|---|
| 1 | Planned | 142 | 174 | 1013 | 26 | 3317 | 328 | 5000 |
| | Actual | 141 | 184 | 1001 | 28 | 3319 | 306 | 5047 |
| | % difference | -1% | +5 | -1% | +7% | 0% | -7% | +1% |
| 2 | Planned | 12 | 75 | 227 | 7 | 1579 | 0 | 1900 |
| | Actual | 6 | 68 | 128 | 10 | 1645 | 5 | 1938 |
| | % difference | -50% | -9% | -44% | +43% | +4% | n/a | +2% |
| 3 | Planned | 8 | 12 | 122 | 8 | 536 | 16 | 702 |
| | Actual | 2 | 12 | 117 | 4 | 535 | 9 | 702 |
| | % difference | -75% | 0% | -4% | -50% | 0% | -44% | 0% |
| 4 | Planned | 2 | 8 | 106 | 4 | 508 | 32 | 660 |
| | Actual | 2 | 8 | 106 | 4 | 508 | 32 | 660 |
| | % difference | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| 5 | Planned | 12 | 185 | 144 | 20 | 227 | 0 | 588 |
| | Actual | 26 | 122 | 74 | 18 | 284 | 31 | 647 |
| | % difference | +117% | -34% | -49% | -10% | +25% | n/a | +10% |
| 6 | Planned | 6 | 5 | 261 | 2 | 299 | 4 | 577 |
| | Actual | 5 | 4 | 199 | 2 | 228 | 3 | 464 |
| | % difference | -17% | -20% | -24% | 0% | -24% | -25% | -20% |
| 7 | Planned | 17 | 45 | 96 | 7 | 289 | 46 | 500 |
| | Actual | 4 | 33 | 66 | 6 | 356 | 6 | 501 |
| | % difference | -76% | -27% | -31% | -14% | +23% | -87% | 0% |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 8 | Planned | 2 | 22 | 32 | 0 | 260 | 0 | 316 |
| | Actual | 2 | 11 | 33 | 0 | 164 | 20 | 328 |
| | % difference | 0% | -50% | +3% | n/a | -37% | n/a | +4% |
| 9 | Planned | 2 | 10 | 34 | 4 | 174 | 8 | 232 |
| | Actual | 2 | 10 | 9 | 0 | 254 | 12 | 291 |
| | % difference | 0% | 0% | -74% | -100% | +46% | +50% | +25% |
| 10 | Planned | 3 | 5 | 20 | 0 | 114 | 0 | 139 |
| | Actual | 2 | 4 | 26 | 1 | 88 | 3 | 144 |
| | % difference | -33% | -20% | +30% | n/a | -32% | n/a | -9% |
| 11 | Planned | 0 | 5 | 7 | 0 | 66 | 2 | 80 |
| | Actual | 0 | 5 | 7 | 0 | 66 | 2 | 80 |
| | % difference | n/a | 0% | 0% | n/a | 0% | 0% | 0% |
| 12 ** | Planned | 0 | 1 | 4 | 0 | 2 | 1 | 8 |
| | Actual | 0 | 0 | 4 | 0 | 2 | 0 | 10 |
| | % difference | n/a | -100% | 0% | n/a | 0% | -100% | 25% |

*Some participants are reported as unknown.

**Participants from the trial site were enrolled in a multi-site clinical trial. The clinical trial was conducted at over 80 sites; however, only one site was randomized into our sample. The enrollment data from the single site may not be representative of the overall trial participant demographics.

## Detail on Planned and Actual Distribution of Enrollment Among Racial Groups for the 12 Completed Clinical Trials

| Trial | | American Indian or Alaska Native | Asian | Black or African American | Native Hawaiian or Other Pacific Islander | White | More than one | Total* |
|---|---|---|---|---|---|---|---|---|
| 1 | % of planned trial population | 3% | 3% | 20% | 1% | 66% | 7% | 100% |
| | % of enrolled trial population | 3% | 4% | 20% | 1% | 66% | 6% | 99% |
| 2 | % of planned trial population | 1% | 4% | 12% | 0% | 83% | 0% | 100% |
| | % of enrolled trial population | 0% | 4% | 7% | 1% | 85% | 0% | 96% |
| 3 | % of planned trial population | 1% | 2% | 17% | 1% | 76% | 2% | 100%*** |
| | % of enrolled trial population | 0% | 2% | 17% | 1% | 76% | 1% | 97% |
| 4 | % of planned trial population | 0% | 1% | 16% | 1% | 77% | 5% | 100% |
| | % of enrolled trial population | 0% | 1% | 16% | 1% | 77% | 5% | 100% |
| 5 | % of planned trial population | 2% | 31% | 24% | 3% | 39% | 0% | 100% |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | % of enrolled trial population | 4% | 19% | 11% | 3% | 44% | 5% | 86% |
| 6 | % of planned trial population | 1% | 1% | 45% | 0% | 52% | 1% | 100% |
| | % of enrolled trial population | 1% | 1% | 43% | 0% | 49% | 1% | 95% |
| 7 | % of planned trial population | 3% | 9% | 19% | 1% | 58% | 9% | 100% |
| | % of enrolled trial population | 1% | 7% | 13% | 1% | 71% | 1% | 94% |
| 8 | % of planned trial population | 1% | 7% | 10% | n/a | 82% | 0% | 100% |
| | % of enrolled trial population | 1% | 3% | 10% | n/a | 50% | 6% | 70% |
| 9 | % of planned trial population | 1% | 4% | 15% | 2% | 75% | 3% | 100% |
| | % of enrolled trial population | 1% | 3% | 3% | 0% | 87% | 4% | 99% |
| 10 | % of planned trial population | 2% | 3% | 13% | 0% | 82% | 0% | 100% |
| | % of enrolled trial population | 1% | 3% | 18% | 1% | 61% | 2% | 86% |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 11 | % of planned trial population | n/a | 6% | 9% | n/a | 83% | 3% | 100% |
| | % of enrolled trial population | n/a | 6% | 9% | n/a | 83% | 3% | 100%*** |
| 12 | % of planned trial population | n/a | 13% | 50% | n/a | 25% | 13% | 100% |
| ** | % of enrolled trial population | n/a | 0% | 40% | n/a | 20% | 0% | 60% |

*Summation of rows will not necessarily add up to 100, as percentages are rounded to the ones place, and some participants are reported as unknown.

**Participants from the trial site were enrolled in a multi-site clinical trial. The clinical trial was conducted at over 80 sites; however, only one site was randomized into our sample. The enrollment data from the single site may not be representative of the overall trial participant demographics.

***100% when rounded to the hundredths place.

## Detail on Planned and Actual Enrollment of Sex and Ethnic Groups for the 12 Completed Clinical Trials

| Trial | | Female | Male | Hispanic or Latino | Not Hispanic or Latino | Total* |
|---|---|---|---|---|---|---|
| 1 | Planned | 1853 | 3147 | 931 | 4069 | 5000 |
| | Actual | 1837 | 3210 | 929 | 4077 | 5047 |
| | % difference | -1% | +2% | 0% | 0% | +1% |
| 2 | Planned | 1889 | 11 | 131 | 1769 | 1900 |
| | Actual | 1926 | 12 | 188 | 1701 | 1938 |
| | % difference | +2% | +9% | +44% | -4% | +2% |
| 3 | Planned | 351 | 351 | 86 | 616 | 702 |
| | Actual | 266 | 436 | 91 | 607 | 702 |
| | % difference | -24% | +24% | +6% | -1% | 0% |
| 4 | Planned | 307 | 353 | 103 | 557 | 660 |
| | Actual | 309 | 351 | 103 | 548 | 660 |
| | % difference | +1% | -1% | 0% | -2% | 0% |
| 5 | Planned | 318 | 270 | 116 | 472 | 588 |
| | Actual | 361 | 286 | 194 | 453 | 647 |
| | % difference | +14% | +6% | +67% | -4% | +10% |
| 6 | Planned | 117 | 460 | 101 | 476 | 577 |
| | Actual | 97 | 367 | 96 | 362 | 464 |
| | % difference | -17% | -20% | -5% | -24% | -20% |
| 7 | Planned | 238 | 262 | 116 | 384 | 500 |
| | Actual | 226 | 275 | 122 | 368 | 501* |
| | % difference | -5% | +5% | +5% | -4% | 0% |
| 8 | Planned | 158 | 158 | 44 | 272 | 316 |
| | Actual | 129 | 121 | 100 | 150 | 328 |
| | % difference | -18% | -23% | +127% | -45% | +4% |
| 9 | Planned | 116 | 116 | 42 | 190 | 232 |
| | Actual | 146 | 145 | 31 | 258 | 291 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | % difference | +26% | +25% | -26% | +36% | +25% |
| 10 | Planned | 94 | 64 | 35 | 123 | 158 |
| | Actual | 71 | 73 | 46 | 85 | 144 |
| | % difference | -24% | +14% | +31% | -31% | -9% |
| 11 | Planned | 58 | 22 | 5 | 75 | 80 |
| | Actual | 58 | 22 | 5 | 75 | 80 |
| | % difference | 0% | 0% | 0% | 0% | 0% |
| 12** | Planned | 2 | 6 | 2 | 6 | 8 |
| | Actual | 4 | 6 | 4 | 6 | 10 |
| | % difference | +100% | 0% | +100% | 0% | +25% |

*Some participants are reported as unknown.

**Participants from the trial site were enrolled in a multi-site clinical trial. The clinical trial was conducted at over 80 sites; however, only one site was randomized into our sample. The enrollment data from the single site may not be representative of the overall trial participant demographics.

## Detail on Planned and Actual Distribution of Enrollment Between Sex and Ethnic Groups for the 12 Completed Clinical Trials

| Trial | | Female | Male | Hispanic or Latino | Not Hispanic or Latino |
|---|---|---|---|---|---|
| 1 | % of planned trial population | 37% | 63% | 19% | 81% |
| | % of enrolled trial population | 36% | 64% | 18%* | 81%* |
| 2 | % of planned trial population | 99% | 1% | 7% | 93% |
| | % of enrolled trial population | 99% | 1% | 10%* | 88%* |
| 3 | % of planned trial population | 50% | 50% | 12% | 88% |
| | % of enrolled trial population | 38% | 62% | 13%* | 86%* |
| 4 | % of planned trial population | 47% | 53% | 16% | 84% |
| | % of enrolled trial population | 47% | 53% | 16%* | 83%* |
| 5 | % of planned trial population | 54% | 46% | 20% | 80% |
| | % of enrolled trial population | 56% | 44% | 30% | 70% |
| 6 | % of planned trial population | 20% | 80% | 18%* | 83%* |
| | % of enrolled trial population | 21% | 79% | 21%* | 78%* |
| 7 | % of planned trial population | 48% | 52% | 23% | 77% |
| | % of enrolled trial population | 45% | 55% | 25%* | 73%* |

| | | | | | |
|---|---|---|---|---|---|
| 8 | % of planned trial population | 50% | 50% | 14% | 86% |
| | % of enrolled trial population | 42%* | 39%* | 30%* | 46%* |
| 9 | % of planned trial population | 50% | 50% | 18% | 82% |
| | % of enrolled trial population | 50% | 50% | 11% | 89% |
| 10 | % of planned trial population | 59% | 41% | 22% | 78% |
| | % of enrolled trial population | 49% | 51% | 32%* | 59%* |
| 11 | % of planned trial population | 73%* | 28%* | 6% | 94% |
| | % of enrolled trial population | 73%* | 28%* | 6% | 94% |
| 12** | % of planned trial population | 25% | 75% | 25% | 75% |
| | % of enrolled trial population | 40% | 60% | 40% | 60% |

*Summation of rows will not necessarily add up to 100 within binary grouping, as percentages are rounded to the ones place, and some participants are reported as unknown.

**Participants from the trial site were enrolled in a multi-site clinical trial. The clinical trial was conducted at over 80 sites; however, only one site was randomized into our sample. The enrollment data from the single site may not be representative of the overall trial participant demographics.

## Appendix D: Agency Comments

NIH official comments are on the next page.

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

**DATE:** April 12, 2024

**TO:** Ann Maxwell
Deputy Inspector General for Inspection and Evaluations, HHS

**FROM:** Principal Deputy Director, National Institutes of Health

**SUBJECT:** NIH Comments on Draft Report, "*NIH-Funded Clinical Trials: Plans and Enrollment Often Fell Short for Underrepresented Groups*" (OEI-01-21-00320)

Attached are the National Institutes of Health's (NIH) comments on the draft Office of Inspector General's (OIG) report, "*NIH-Funded Clinical Trials: Plans and Enrollment Often Fell Short for Underrepresented Groups*" (OEI-01-21-00320).

NIH appreciates the review conducted by OIG and the opportunity to provide comments on this draft report. If you have questions or concerns, please contact Tiffany Brown in the Office of Management Assessment at 301-496-2464.

Lawrence A Tabak, D.D.S., Ph.D.

Attachments

The National Institutes of Health (NIH) appreciates the review conducted by OIG and the opportunity to provide clarifications on this draft report. NIH respectfully submits the following general comments.

**OIG Recommendation 1:**
We recommend that NIH hold researchers accountable for clearly describing the rationale for planned study population, as required by NIH policy.

**NIH Response:**
NIH concurs with OIG's recommendation regarding holding researchers accountable for clearly describing the rationale for the planned study population.

NIH considers inclusive enrollment plans to be plans that are appropriate in the context of the science, which may not in all cases include every demographic group. NIH requires applicants to submit inclusion plans and estimated planned enrollment based on the scientific question to be answered by the study, the disease or condition being studied, the population at risk for or affected by the disease or condition, and the proposed study design. NIH's Guidelines for the Review of Inclusion on the Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research explain that NIH does not expect every study to include participants from every racial or ethnic group, sex or gender, and age group. NIH requires exclusions (i.e. groups who are ineligible for the study) based on sex or gender, race, ethnicity, or age to be explained in the application, but NIH does not require justification if every demographic group is not expected to be enrolled in a study but may be enrolled if they agree to participate. For the trials OIG reviewed, NIH determined the proposed population to be scientifically acceptable prior to award.

NIH recognizes the value of robust inclusion plans and continues to make efforts to improve those plans. Through NIH's peer review process, experts with relevant expertise in the scientific discipline of the proposed science evaluate the acceptability of the inclusion plans and those with unacceptable plans cannot be funded until concerns are resolved. In October 2023, NIH announced a Simplified Review Framework for NIH Research Project Grant Applications (NOT-OD-24-010) to better focus peer reviewers on the key questions needed to assess the scientific and technical merit of proposed research projects. Included in this change is a focus on whether the study results will be generalizable and whether the sample is appropriate and sufficiently diverse to address the proposed question(s). NIH expects this change to better focus applicants and reviewers on inclusion so that the rationale for the planned study population is clearly explained and inclusion is considered in the application's overall impact score. In addition, applications with inclusion plans found unacceptable by peer review will not be funded until any concerns are resolved.

**OIG Recommendation 2:**
We recommend that NIH develop additional ways of supporting researchers in meeting inclusion enrollment targets.

**NIH Response:**
NIH concurs with OIG's recommendation regarding supporting researchers in meeting inclusion enrollment targets.

NIH remains committed to supporting sound science that informs clinical practice and is generalizable across populations and recognizes that ongoing and consistent monitoring facilitates progress and accountability. NIH program staff receive regular updates on trial enrollment and use a number of strategies to address concerns. NIH program officers evaluate enrollment progress at least annually to ensure enrollment is appropriately diverse to answer the scientific question(s) proposed in the application.

NIH provides a number of resources to help researchers design trials to encourage diverse enrollment and meet their planned enrollment goals. For example, NIH provides training, podcasts, tip sheets, toolkits, fact sheets, sample flyers, videos and other resources to help investigators enroll diverse populations. A resource list is available on the NIH Inclusion of Women and Minorities website at https://grants.nih.gov/sites/default/files/Resources_Recruitment_and_Retention_WM%2CIAL_final508c.pdf. In Spring 2024, NIH will provide an enhanced training for NIH program staff which covers tools and strategies for reviewing enrollment targets. In addition, NIH is developing a podcast to educate applicants and recipients about allowable costs, such as transportation and childcare, to facilitate inclusion of participants in clinical research. NIH will review and update trainings, communications, and guidance to facilitate participant inclusion and support researchers in meeting inclusion enrollment targets.

NIH Institutes and Centers support a range of strategies to support diverse participation and emphasize community engagement strategies in developing and executing trials. For example, the National Center for Advancing Translational Sciences (NCATS) Clinical and Translational Science Awards (CTSA) leverages the strength of over 60 academic medical centers to engage participants and communities and promote the integration of underserved populations in translational research across the human lifespan. In addition, the NIH Community Engagement Alliance (CEAL) leverages community organizations that have a direct line to the communities and individuals hardest hit by COVID-19 and is expanding into a research network to address additional areas where health disparities exist to build trust in science and research, ensure inclusion across the research continuum, advance community-driven solutions addressing health inequities, and strengthen community-engaged research. NIH plans to continue these efforts to support researchers in meeting their inclusion enrollment targets.

**OIG Recommendation 3:**
When OMB updates its demographic groups, NIH should promptly take steps to update its own demographic groups to obtain more precise clinical trial inclusion enrollment data.

**NIH Response:**
NIH concurs with OIG's finding and corresponding recommendation regarding promptly taking steps to update its own demographic groups to obtain more precise clinical trial inclusion enrollment data.

On March 28, 2024, OMB published a set of revisions to Statistical Policy Directive No. 15: *Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity*. NIH is reviewing changes needed to agency forms, systems, guidance, communications, and training. By the September 2025 deadline, NIH will submit an Action Plan detailing plans for those changes and will implement necessary changes.

# ACKNOWLEDGMENTS AND CONTACT

## Acknowledgments

Chris Galvin served as the team leader for this study. Others in the Office of Evaluation and Inspections who conducted the study include Jac Carreiro, Anna Lin, and Rachel Pavia. Office of Evaluation and Inspections headquarters staff who provided support include Joe Chiarenzelli, Rob Gibbons, Althea Hosein, and Sarah Swisher.

This report was prepared under the direction of Joyce Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office, and Ken Price, Deputy Regional Inspector General.

## Contact

To obtain additional information concerning this report, contact the Office of Public Affairs at Public.Affairs@oig.hhs.gov. OIG reports and other information can be found on the OIG website at oig.hhs.gov.

Office of Inspector General
U.S. Department of Health and Human Services
330 Independence Avenue, SW
Washington, DC 20201

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**The Office of Audit Services.** OAS provides auditing services for HHS, either by conducting audits with its own audit resources or by overseeing audit work done by others. The audits examine the performance of HHS programs, funding recipients, and contractors in carrying out their respective responsibilities and provide independent assessments of HHS programs and operations to reduce waste, abuse, and mismanagement.

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**The Office of Investigations.** OI's criminal, civil, and administrative investigations of fraud and misconduct related to HHS programs and operations often lead to criminal convictions, administrative sanctions, and civil monetary penalties. OI's nationwide network of investigators collaborates with the Department of Justice and other Federal, State, and local law enforcement authorities. OI works with public health entities to minimize adverse patient impacts following enforcement operations. OI also provides security and protection for the Secretary and other senior HHS officials.

**The Office of Counsel to the Inspector General.** OCIG provides legal advice to OIG on HHS programs and OIG's internal operations. The law office also imposes exclusions and civil monetary penalties, monitors Corporate Integrity Agreements, and represents HHS's interests in False Claims Act cases. In addition, OCIG publishes advisory opinions, compliance program guidance documents, fraud alerts, and other resources regarding compliance considerations, the anti-kickback statute, and other OIG enforcement authorities.

# ENDNOTES

[1] In 2011, Black Americans comprised 12% of the population but only 5% of clinical trial participants. Hispanic representation is more disparate, as Hispanics comprised 16% of the U.S. population, but only 1% of trial participants. The Society for Women's Health Research, United States Food and Drug Administration Office of Women's Health. *Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities in Clinical Trials*. Page ii. September 22-23, 2011. Accessed at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3432572/ on June 20, 2023.

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[14] *Ibid.*

[15] NIH policy typically uses the phrase "sex or gender"; however, we elected to use the phrase "sex" to describe the demographic data. OEI language guidance refers to "sex" as a person's biological sex assignment assigned at birth whereas "gender" refers to the attitudes, feelings, and behaviors that a given culture associated with a person's biological sex. For our reporting purposes, the use of "sex" is more appropriate.

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[36] *Ibid.*

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