Assessing Federal Policies on the Inclusion of Women, Racial and Ethnic Minorities, People of Diverse Ages, People with Disabilities, and Sexual Minorities in Clinical Trials and Clinical Research

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Over the latter half of the 20th century, randomized controlled trials (RCTs) came to be regarded as the gold standard in evidence-based medicine to determine the safety and efficacy of investigational medical therapies. Initially, the results from RCTs were largely considered to be generalizable to all patient populations.(Bothwell, Greene et al. 2016) Over the past few decades, growing evidence surfaced to challenge that assumption.(Beglinger 2008) Specifically, research has demonstrated that women,(Garcia, Mulvagh et al. 2016) pregnant women, children,(Kurz and Nakamura 2002) older adults,(Beglinger 2008) and racial and ethnic minorities(Ramamoorthy, Pacanowski et al. 2015) can have distinct physiologies, disease presentations, or health circumstances that affect how they will respond to an investigational drug. Such differences contribute to variable therapeutic responses and necessitate targeted efficacy and safety evaluation. For instance, it appears that men are more likely to respond to tricyclic antidepressants and women to selective serotonin reuptake inhibitors as treatments for depression.(Kornstein, Schatzberg et al. 2000, Baca, Garcia-Garcia et al. 2004, Bano, Akhter et al. 2004) Reduced renal and hepatic clearance in older adults increases the risk of harms from drugs such as anticoagulants and psychotropic agents.(Shepherd, Hewick et al. 1977, Maixner, Mellow et al. 1999) Biological differences are further compounded by nonbiological risk factors—including socioeconomic status, environmental factors, educational attainment, behavioral characteristics, structural racism, and access to health care—that affect each population and demand nuanced analysis and interpretation of population-specific data in clinical trials.(Rogers and Lange 2013)

Frequently adopted by clinicians across different specialties, health care algorithms often include race and ethnicity as input variables to influence clinical decision making.(Schmidt and Waikar 2021) As socially constructed concepts, using race/ethnicity as single variable proxies for genetic predisposition and socioeconomic inequities may have unwanted effects and perpetuate health and health care disparities without careful examination and nuanced interpretation of statistical evidence.(Agency for Healthcare Research and Quality 2021) For example, HIV researchers observed an increased hazard of virologic failure in response to antiretroviral therapy for black patients compared to white patients,(Ribaudo, Smith et al. 2013) which was later substantiated by genetic polymorphisms that were more common in black patients and resulted in higher concentrations of a certain antiretroviral (efavirenz).(Soeria-Atmadja, Österberg et al. 2017) However, the debate continues regarding first-line choice of anti-hypertensive medications: while monotherapy trials have indicated that black patients may have a reduced blood pressure response with angiotensin converting enzyme inhibitors or angiotensin receptor blockers compared with

white patients,(Thomas, Booth III et al. 2018) genetic analysis has found no association between West African ancestry proportion and response to antihypertensive medication, suggesting that the effect is mediated by nonbiological factors.(Rao, Segar et al. 2021)

People with intellectual and physical disabilities sometimes experience biological differences that alter drug metabolism and thus necessitate additional attention regarding dosing, toxicity, and efficacy of certain pharmacological agents. For example, children with Down syndrome not only have a multifold risk of developing acute leukemia, but they also experience a much higher incidence of treatment-related toxicities when treated with standard pediatric leukemia regimens relative to children without Down syndrome.(Hefti and Blanco 2016) As another example, post-spinal cord injury patients encounter autonomic nervous system failure and changes in their global homeostasis, which lead to altered drug pharmacokinetics throughout the acute, subacute, and, in most cases, chronic phases of their condition.(Mestre, Alkon et al. 2011)

In recent years, while numerous federal policies have promoted the inclusion of women, racial and ethnic minorities, and people of diverse ages in clinical trials and clinical research, these groups remain underrepresented.(Oh, Galanter et al. 2015) Although women's overall representation in trials has increased substantially, other important gaps remain, such as regarding treatment during pregnancy.(Geller, Koch et al. 2011, Vitale, Fini et al. 2017, Scott, Unger et al. 2018) People with disabilities and sexual minorities also remain frequently overlooked.

An FDA summary report of 2015-2019 drug trials shows that non-Hispanic whites compose 78% of participants enrolled in US trial sites,(Food and Drug Administration 2020) despite the fact that they make up 61% of the country's population.(Ortman and Guarneri 2009) Although Congress has created incentives for manufacturers to test their drugs in children, an overwhelming number of drugs still have no information in the labeling to guide pediatric use.(DRUGS and MMM 2014) A substantial share of modern clinical trials explicitly exclude older adults or use enrollment criteria that could disproportionately impact older adults, for example by excluding potential participants on inability to give informed consent, cognitive impairment, functional limitations, or decreased life expectancy.(Zulman, Sussman et al. 2011) The continued lack of representation is seen across numerous fields of medical research: different studies have found that minorities and women remain underrepresented in oncology,(Chen Jr, Lara et al. 2014, Reihl, Patil et al. 2021) cardiovascular,(Kim, Carrigan et al. 2008) ophthalmology,(Berkowitz, Groth et al. 2021) and

surgical trials.(Kalliainen, Wisecarver et al. 2018) Further, when clinical trials do include underrepresented populations, subgroup-specific analyses and results are oftentimes missing or poorly executed.(Assmann, Pocock et al. 2000, Wang, Lagakos et al. 2007)

As challenges remain for trial inclusivity, policymakers in recent years have described the need for more effective inclusion of diverse populations in clinical research and have established important policies to advance trial diversity. In this review, we conducted a broad assessment of existing trial enrollment policies and their benefits and limitations. We examined major federal policies designed to improve the inclusion of women, racial and ethnic minorities, people of diverse ages, people with disabilities, and sexual minorities in clinical trials and describe their broad impact. Our goal was to provide a landscape of current federal policies, pertinent information on how they were developed and have evolved over time, and evidence of their impact on research inclusivity. We identify holes and loopholes in the system and identify targeted recommendations for improvements. We ask: what has worked for some groups or in some settings that can be applied to other areas?

Methods

We consulted available published literature and searched HHS policies on Regulations.gov using the search terms in Appendix A to identify federal policies to improve the inclusion of women, racial and ethnic minorities, people of diverse ages, people with disabilities, and sexual minorities in clinical trials. We searched PubMed for peer-reviewed studies evaluating the outcomes of current policies, as well as editorials or other papers describing areas for improvements. Finally, we conducted some interviews with key informants on policy efficacy.

Historically, the terms “sex” and “gender” have been used interchangeably in many policies; in this report, these terms are used in accordance with the source material referenced.

Results

Over many decades, federal policies have emerged related to the inclusion of women, racial and ethnic minorities, and people of diverse ages in clinical trials and clinical research. The history of trial diversity polices is deeply embedded in the broader historical context of work toward equity and inclusion. A review of this history shows how much remains to be done.

Early History

Race

The 1964 Civil Rights Act was perhaps the earliest occasion when legislators or regulators set policies on racial diversity in clinical research. In compliance with the law, in 1965, National Institutes of Health (NIH) General Clinical Research Centers added new notices to grant applications warning that racial discrimination was illegal. Eventually, all domestic US grant applicants to the Department of Health and Human Services (HHS) had to file with the HHS Office of Civil Rights an Assurance of Compliance with Title 6 of the 1964 Civil Rights Act, which prohibits discrimination based on race, color, religion, national origin, or sex in services and establishments that receive federal funding, including hospitals and medical facilities.(1964)

Since that time, enforcement of Title 6 has been partial and inconsistent, and racial and ethnic minorities have continued to experience inadequate treatment in clinical care and research at both federal and state levels.(Yearby 1964) National attention was drawn to problems of racism in research in 1972 with the revelation of the 40-year Tuskegee Syphilis Study conducted by the US Public Health Service (PHS) observing the progression of syphilis among untreated low-income African-American men long after treatment had become available.(Brandt 1978) In response, Congress passed the 1974 National Research Act, which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.(Vargesson 2015) The Commission published the Belmont Report, which laid the groundwork of principles and guidelines for research involving human subjects, identifying three basic ethical principles for human subject experimentation: respect for persons, beneficence, and justice. The report pointed out that "the selection of research subjects needs to be scrutinized to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied."(Biomedical and Research 1978)

Sex and Gender

In the mid-twentieth century, alongside growing awareness of the value of protecting vulnerable populations, many began to draw attention to a long-held bias in the field of clinical research: the

"male norm," as later summarized in a 1994 report by the Institute of Medicine.(Mastroianni, Faden et al. 1994) Healthy, young or middle-age males, frequently of the Caucasian race, were considered to be the "norm" study population; by contrast, females were thought to confound trial results with their fluctuating hormone levels and reproductive potentials.(Pardue and Wizemann 2001, Pinn 2003) When news broke from Europe and Canada in the early 1960s that widespread maternal exposure to the sedative thalidomide during pregnancy led to fetal death and birth defects, policymakers took the stance that pregnant women were a "vulnerable population" who should be shielded from the potential reproductive adverse effects of drug exposures in trials.(Vargesson 2015) In response to the tragedy, the US Congress passed the Kefauver-Harris Amendments in 1962 to strengthen the authority of the Food and Drug Administration (FDA) in overseeing drug development and pre-market evaluation.(Amendments 1962) Some years later in 1977, the FDA created a guideline, "General considerations for the clinical evaluations of drugs" that banned women of childbearing potential from Phase 1 and early Phase 2 trials, except in the case of life-threatening conditions.(Food and Drug Administration 1977) The policy strictly excluded women who used contraception, who were single, or whose husbands had vasectomies.(Food and Administration 1993) In 1979, the Belmont Report further stipulated that pregnant women should be considered vulnerable research subjects and should be protected at all costs.(Biomedical and Research 1975) The 1979 FDA Labeling Rule established the first classification system for identifying the risks prescription drugs posed to pregnant women, fetuses, and breastfeeding infants.(Food and Administration 1979)

Age

The phrase "therapeutic orphan" was coined by Harry Shirkey, MD in 1963 to describe the lack of modern drug therapy targeted toward children.(Shirkey 1968) Most authors have attributed this state of affairs to the shortage of relevant drug research in children, as private sector sponsors deemed the introduction of therapies targeting children to have little potential for profit.(MacLeod 2010) In 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published a report on Research Involving Children discussing the fundamental ethical permissibility of pediatric research, particularly research not benefiting the child involved.(The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978) Prior to this report, philosophers and ethicists held opposing views: some repudiated any ethical justification for research with a healthy child,(Ramsey 1976) while others claimed that even children bear a certain obligation to benefit society, justifying a

presumption of their consent to experiments of minimal risk.(McCormick 1974) The Commission contended that children might be entered in research entailing more than minimal risk and promising no individual benefit when (1) the risk entailed represents "a minor increase over minimal risk," (2) the experience presented by the intervention is "reasonably commensurate with those inherent in the actual or expected medical, psychological or social situation" of the subject, and (3) the research is likely to yield generalizable knowledge about the subject's condition that is "of vital importance for the understanding and amelioration of the condition" from which that class of subjects suffers.(Jonsen 1978) These recommendations were later adopted by the Department of Health and Human Services in its regulation titled "Additional protections for children involved as subjects in research" in 1983.(Department of Health and Human Services 1983)

In addition to creating risk classifications for drugs taken by pregnant women and lactating mothers, the 1979 FDA Labeling Rule sought to improve the safety and efficacy of drugs intended for diverse ages by requiring labeling content under "Pediatric Use" and "Geriatric Use."(Food and Administration 1979) Notably, the rule did not outline specific requirements for risk information provided under the pediatric and geriatric sections as it did for data on pregnant women and lactating mothers.(Food and Administration 1979)

Diversity among Investigators

The NIH Office of Diversity and Health Disparities (ODHD) was established more than 20 years ago and serves to strengthen a more diverse and robust extramural research workforce, attracting and retaining talented individuals from all backgrounds, and supporting research aimed at the NIH mission of reducing health disparities. Among its numerous endeavors, it provides funding to recruit and support high school, undergraduate, and graduate/clinical students, post-doctorates, and eligible investigators to work on an existing NIH-funded project in a particular area of interest.(Health 2021) This opportunity is also available to investigators who are or become disabled and need additional support to accommodate their disability to continue to work on the research project.

Modern Policies

NIH

The NIH is responsible for providing direction to research programs with goals to improve the health of the nation and to that end, the NIH creates policies to improve the nation's wellbeing.(National Institutes of Health 2021) The NIH is the largest federal sponsor of clinical trials in the US, devoting about $3 billion per year to funding trials.(National Institutes of Health 2017) Its stewardship over clinical trial policies has a substantial impact on the rigor, transparency, and effectiveness of the clinical trial enterprise.(Hudson, Lauer et al. 2016)

The first significant work toward inclusive clinical trial policies at the NIH emerged in response to the 1985 report of the US Public Health Service Task Force on Women's Health Issues outlining how underrepresentation of women in clinical trials had led to suboptimal women's health care.(Women's health 1985) The task force recommended increased participation of women in clinical trials, including women of child-bearing potential. They also recommended that research should emphasize diseases that are more prevalent in women.(Liu and Dipietro Mager 2016) In response to this report, the NIH adopted the Inclusion of Women and Minorities in Clinical Research policy in 1986.(National Institutes of Health 1987) The major goal of this policy was to ensure that research and clinical trials were designed to provide information about sex and race/ethnicity differences. Response to this policy was slow; guidance for its implementation was not developed until 1989 when a Memorandum on Inclusion announced that that research solicitations should encourage the inclusion of women and minorities and stipulated that a rationale should be provided when women and minorities were excluded.(National Institutes of Health 1989)

In 1990, the General Accounting Office (GAO), later known as the Government Accountability Office, a legislative branch agency that provides auditing, evaluation, and investigative services for the US Congress, investigated the NIH implementation of the guidelines for the inclusion of women and minorities. In its report, the GAO revealed that the 1986 Inclusion of Women and Minorities in Clinical Research policy had been poorly communicated and inconsistently applied before the 1990 grant review cycle.(Nadel 1990) The GAO identified two major limitations of the policy. The policy only pertained to extramural research conducted by investigators who had been awarded NIH grants, but not intramural research overseen by scientists employed by the federal government. In addition, the policy provided little incentive for researchers to analyze study results by gender.(Nadel 1990) As criticism mounted in response to the GAO report, the Congressional Women's Caucus took legislative action by passing a package of bills known collectively as the

Women's Health Equity Act of 1990.(S.2961 - 101st Congress (1989-1990) 1990) Responding to this new legislation, the NIH founded the Office for Research on Women's Health in the same year.(National Institutes of Health 2001) The ORWH helped the research community understand the importance of inclusion of women in clinical trials by monitoring and promoting NIH-wide efforts to ensure the representation of women and by prioritizing diseases, disorders, and conditions that primarily affect women.(National Institutes of Health) The ORWH also supports initiatives to advance women in biomedical careers and ensures that women are included in clinical research funded by the NIH.(National Institutes of Health) Also in 1990, the Office of Minority Programs (OMP) was established in the NIH Office of the Director.(Public Law 1993)

The establishment of these offices and lessons learned from the original inclusion policy contributed to the development of the NIH Revitalization Act in 1993, which became an updated version of the original inclusion policy but also provided additional guidance on the inclusion and reporting and analysis of sex/gender and racial/ethnic differences in intervention effects for NIH-defined Phase 3 clinical trials.(Night 2010) The Act emphasized that the NIH should ensure that women and minorities be included in all clinical research, that Phase 3 clinical trials had sufficient numbers of participants to allow for analysis, that populations were not to be excluded from trials due to cost, and that the NIH must maintain outreach efforts to include women and minorities in clinical studies.(Liu and Dipietro Mager 2016) The law was designed to ensure that clinical research determines whether an intervention differently affects men, women, or members of a minority population.(Liu and Dipietro Mager 2016) Scientists at the time largely supported the Act and it sparked discussions around the importance of appropriate trial design and subsequent subgroup analyses. In implementation of the act, women and minorities were increasingly included in clinical trials.(Boissel, Gueyffier et al. 1995, Freedman, Simon et al. 1995) Currently, females make up 49% of subjects in NIH-funded clinical trials.(Blehar, Spong et al. 2013) Under the Act, the Office of Minority Programs also changed its name to the Office of Minority Health Research (OMHR). At this point, the OMHR did not have grant-funding authority.(Public Law 1993)

Key gaps remained regarding inclusivity of NIH-funded trials. A study comparing the ethnic distribution of patients enrolled in trials funded by the National Cancer Institute in 2000 through 2002 with those enrolled in 1996 through 1998 found that the proportion of minority trial participants did not change significantly and that the proportion of participants who were black had declined. After adjusting for age, cancer type, and sex, patients enrolled in 2000 through 2002

were 24% less likely to be black.(Murthy, Krumholz et al. 2004) Ten years into the NIH Revitalization Act's implementation, another GAO report found that although women were taking part in clinical studies in greater numbers than men and more funding was available for studying diseases that disproportionately affected women, only a small fraction of publications based on NIH-funded research reported findings stratified by sex.(Helmuth 2000) Twenty years post-NIH Revitalization Act, another study concluded that minorities remained disproportionally underrepresented in cancer clinical trial enrollments in 2014. In addition to persistent barriers for minority participation in cancer clinical trials, the study reported a dearth of cancer clinical trials that focus primarily on racial/ethnic minority populations, as well as a lack of usable trial data about racial/ethnic minority populations.(Chen Jr, Lara et al. 2014)

In 1998, the NIH Guide for Grants and Contracts published guidelines for including children in research supported by the NIH, unless there were scientific or ethical reasons not to include them.(National Institutes of Health 1998) The goal of the policy was to obtain appropriate data on treatment outcomes in children. This policy applied to all initial applications/proposals and intramural projects submitted to NIH and it provoked discussions among investigators and ethicists surrounding the ethical dilemma of balancing improving access and recruitment of children in clinical trials with the need to protect this vulnerable population.(Glantz 1998, Kopelman 2000, Tauer 2002) The impact of this guideline seemed to lag behind those targeting women and minorities' enrollment. A survey was conducted in 2008 to access NIH Scientific Review Group (SRG) members' experiences and attitudes regarding the NIH inclusion guidelines for women/minorities and children, released in 1994 and 1998 respectively. While about half of the SRG members surveyed agreed that the inclusion guidelines resulted in an increase in the number of women and minorities enrolled in clinical research, less than one-third responded that the guidelines expanded the inclusion of children.(Taylor 2008)

In 2000, with the passage of the Minority Health and Health Disparities Research and Education Act, the office became the National Center on Minority Health and Health Disparities (NCMHD).(Public Law 2000) The Act gave NCMHD the authority to fund grants and called for the development of a comprehensive NIH strategic research plan and budget for health disparities research. The center was again re-designated as the National Institute on Minority Health and Health Disparities (NIMHD) in 2010 with the passage of the Patient Protection and Affordable Care Act.(National Institutes of Health 2010) The office gained authority to plan, review, coordinate, and

evaluate the minority health and health disparities research and activities conducted and supported by the NIH Institutes and Centers.(Kneipp, Schwartz et al. 2018)

In 2001, the NIH policy and guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research from 1986 were updated.(National Institutes of Health 2001) The original purpose of the 1986 policy was to ensure the inclusion of women and minority groups in NIH-funded clinical research and that these research findings should be generalizable to a broad population.(Mastroianni, Faden et al. 1994) However, the policy lacked a clear definition of clinical research and did not require specific analyses by racial groups to be included when reporting population data.(Nours 2021) Thus, the updates provided guidance on clarifying the definitions of racial and ethnic categories and reporting analyses of sex and racial minorities in clinical trials.(Nours 2021) These updates included the Office of Management and Budget (OMB) Directive's racial and ethnic categories that are to be used to monitor population data for clinical trials. Though the Directive claimed that "the categories in this classification are social political constructs and should not be interpreted as being scientific or anthropological in nature," scholars argued that standards reflected an important step in moving beyond a simplistic concept of race and its impact on health and provided state and federal public health agencies with an important opportunity to collect, tabulate, and analyze data on program participation and community health that more accurately reflected the racial and ethnic nuances of contemporary American society.(Friedman, Cohen et al. 2000, Hattam 2005) According to a 2015 GAO report, however, the reporting of the racial/ethnic composition of study participants did not improve since 2004.(Government Accountability Office 2015)

In 2009, the NIH commissioned the Institute of Medicine to conduct a study on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. The resulting report, "The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding," concluded that major knowledge gaps exist in the health needs of LGBT people and urged NIH to support additional research.(Institute of Medicine of the National Academies 2011) The NIH LGBT Research Coordinating Committee was established to develop and coordinate NIH's LGBT research and training, expand knowledge of LGBT health, and improve methods to reach these populations through specific trial networks such as the Adolescent Medicine Trials Network for HIV/AIDS Interventions, HIV Prevention Trials Network, HIV Vaccine Trials Network, and Microbicide Trials Network.(National Institutes of Health 2015)

To support transgender inclusion, the trial networks adopted a 2-step method in data collection forms, separating birth sex and gender identity into 2 variables.(Sausa, Sevelius et al. 2009) In addition, the trial networks updated protocol design with language for transgender inclusion, implemented staff training for cultural sensitivity, consulted with transgender individuals, and conducted new research on transgender individuals.(Siskind, Andrasik et al. 2016)

In his 2015 State of the Union address, President Obama announced the Precision Medicine Initiative. In response to this initiative, the NIH created an ethnically diverse research cohort amounting to 1 million or more Americans who had agreed to have their clinical data tracked for research purposes.(Collins and Varmus 2015) This effort was accompanied by workshops hosted by the NIH that examined the reproducibility and transparency of clinical research and aimed to maximize cohort diversity, inclusion, and attention to health disparities.(National Institutes of Health 2015, National Institutes of Health 2015),(ACD Precision Medicine Initiative Working Group Public Workshop 2015) To further catalyze diversity in research, analysts suggested that NIH should be empowered to set and enforce recruitment of diverse research populations by race and ethnicity as the default and require scientific justification for limited or selected study population enrollment,(Oh, Galanter et al. 2015) similar to what had been created for sex balance.(Clayton and Collins 2014)

The NIH revisited its policies on age in response to the passage of Section 2038(H) of the 21st Century Cures Act in 2016. This Act instructed the NIH to hold a workshop accounting for differences across the lifespan, publish guidelines addressing consideration of age in clinical research, and ensure that researchers conducting applicable Phase 3 clinical trials report results of analyses by sex/gender at ClinicalTrials.gov.(Nours 2021) As a result of these efforts, the Inclusion Across the Lifespan (IAL) policy was created. This policy required that NIH-funded studies include individuals of all ages (including older adults and children) in clinical trials unless age-based exclusions are scientifically or ethically justified. The policy outlined when certain age groups may be excluded and noted that grantees are required to annually report on the age at enrollment of their participants along with sex/gender, race, and ethnicity.(National Institutes of Health 2017, National Institutes of Health 2017, Nanna, Chen et al. 2020, National Institutes of Health 2020)

The Inclusion Across the Lifespan Policy is still in its nascent stages, and more data are needed to assess its impact (the policy went into effect in January 2019).(Nanna, Chen et al. 2020) Further policy work may also be warranted, as solely extending the age of eligibility for clinical trials is insufficient to make a study truly representative of the general population as social factors such as socioeconomic status may influence access to trials by marginalized groups.(Lauer 2020)

An "Inclusion Across the Lifespan" workshop held in 2017 resulted in several publications related to people with disabilities,(Lockett 2017) including a *JAMA* article reporting that a present-day review of 338 Phase 3 and 4 NIH-funded actively recruiting studies in ClinicalTrials.gov found that most of the trials did not mention individuals with disabilities in either the inclusion or exclusion criteria (more than 90% did not mention physical disabilities and more than 80% did not mention intellectual disabilities).(Spong and Bianchi 2018) Explicit exclusion was mentioned in 12.4% of the studies for those with intellectual or developmental disabilities (including criteria based on IQ, defined intellectual disability, or cognitive impairment).(Spong and Bianchi 2018) Explicit exclusion was mentioned in 1.8% of studies for those with physical disabilities (including inability to ambulate, extreme immobility, and paraplegia).(Spong and Bianchi 2018) Further, there are non-explicit barriers to trial participation for people with disabilities, as those with cognitive impairment may be limited by lack of ability to comply with the study protocol or procedures and individuals with physical disabilities can face limited access to study facilities or face challenges with physiological measurements.

The Sex as a Biological Variable (SABV) Policy, which was passed in January 2016, plays an important role in consideration of preclinical research and the design of clinical trials. It established the expectation that gender be considered not only when volunteers sign up for a study but that investigators balance the proportion of males and females in preclinical investigations from the earliest stages of study design.(Arnegard, Whitten et al. 2020) The policy requires researchers to take sex into account when creating research questions, designing experiments, analyzing data, and reporting results.(Nours 2021) In the 5 years since the NIH enacted SABV, progress has been made.(Clayton 2021) A survey of NIH study section members revealed growing favorability toward the policy, despite some unsupportive perspectives. The number of grant applications that appropriately consider SABV also has increased.(Woitowich and Woodruff 2019)

Regarding diversity among investigators, the NIH Advisory Committee to the Director Working Group on Diversity was formed in 2013 in response to the Working Group on Diversity in the

Biomedical Research Workforce (WGDBRW) recommendations. The working group includes a subgroup on individuals with disabilities that focuses on systematically identifying data, strategies, and experiences of individuals with disabilities in the scientific workforce to address the multiple barriers they face. In 2017, the working group established a second subgroup, the Diversity Program Consortium, which supports numerous initiatives designed to build infrastructure leading to diversity, research mentorship for diverse scientists, and awards and resource support.(Health 2013)

Despite these efforts, the 2021 "Women, Minorities, and Persons with Disabilities in Science and Engineering" report published by the National Center for Science and Engineering Statistics at the National Science Foundation found that even though the share of science and engineering degrees awarded to underrepresented minorities increased over the past decade, several disparities remained. Scientists and engineers with disabilities have an unemployment rate much greater than their peers, and even greater than that of the US general labor force.(Rivers 2017) Female scientists and engineers have lower median salaries than do their male counterparts in most broad occupational groups.(Rivers 2017) Underrepresented minorities also hold a small (8.9%) share of academic positions, which is considerably lower than their share of the population.(Rivers 2017)

Enforcement and Accountability

To ensure the success of NIH inclusion policies, internal monitoring systems include offices, working groups, and committees established across the NIH. An example of a committee used to monitor the progress of NIH policies on the inclusion of women, minorities, and individuals across the lifespan in clinical research is the Inclusion Governance Committee (IGC), which is responsible for monitoring NIH extramural grants and ensuring diversity reporting.(Nours 2021) The NIH also seeks information and advice from the public and hosts workshops that provide researchers with evidence-based approaches in meeting these policies.(National Institutes of Health 2020) For example, the Inclusion Across the Lifespan-II Workshop provided researchers information regarding the inclusion of pediatric and older populations in clinical studies in meeting the IAL policy.(National Institutes of Health 2020)

Accountability to inclusion policies occurs differently for intramural and extramural clinical research.(Nours 2021) Intramurally, monitoring for adherence toward these policies occurs primarily at the scientific or chief director level. Extramurally, researchers applying for NIH grants must justify their study populations as part of the process to be considered for funding.(Nours

2021) Extramural researchers must also work with NIH staff to resolve any issues concerning lack of inclusion of certain populations prior to grant approval.(Nours 2021) Progress reports on a study's development are monitored by NIH program officers to ensure that all principal investigators meet an acceptable threshold for the number of participants and inclusion criteria in the study's population.(Nours 2021) Phase 3 clinical trials are required to report results of sex/gender and race/ethnicity data into ClinicalTrials.gov so that this information can be monitored.(Nours 2021)

NIH also requires that funded researchers submit a Research Performance Progress Report (RPPR) annually that asks grantees about their current accomplishments for the project, upcoming plans, and significant changes regarding human or animal subjects.(National Institutes of Health 2018) This information is entered into eRA Commons and is used for accessing and sharing information over the life of a study.(National Institutes of Health 2016) These progress reports must be NIH-approved for continued funding.(Nours 2021) NIH then externally reports their inclusion data in a format that is disaggregated by Research, Condition, and Disease Categorization (RCDC) categories.(Nours 2021) This RCDC data can be found on the NIH Research Portfolio Online Reporting Tools (RePORT) website.(Nours 2021)

Throughout the history of NIH policies, adaptation has been critical, as some policies have not been sufficient to encourage scientists to broaden their study inclusion criteria.(Nours 2021) Although current policies are encouraging, women and marginalized populations are still underrepresented in clinical trials of some diseases such as cardiovascular disease, hepatitis, digestive diseases, HIV/AIDS, Alzheimer's disease, and chronic kidney disease. Improper analyses and disaggregated data in publications exist due to the lack of inclusion in clinical research, impeding the generalizability of scientific findings to the broader population.(Nours 2021) Therefore, further adaptation is needed to adequately diversify clinical trial participation. Investigator bias must also be addressed. In a 2018 study to evaluate compliance with inclusion and assessment of women and minorities in RCTs, it was found that both male and female researchers perform equally poorly during analysis and reporting of women in clinical studies, and both male and female participants show the same amount of gender bias in decision making.(Geller, Koch et al. 2018)

Much work also remains to achieve compliance with existing policies. Organizations such as the ORWH, which monitor compliance, are crucial. The ORWH has created resources such as the

Inclusion Outreach Toolkit to help principal investigators fulfill their responsibility to conduct inclusive research.(Nours 2021) (Mistretta and Mistretta 2016) Furthermore, the NIH created three free e-learning courses as well as a high-level quarterly publication called the Women's Health Focus to raise awareness of the health of women and marginalized populations.(Nours 2021) Strengthening ORWH and other institutional accountability mechanisms could likely help to improve achieving inclusivity objectives.

FDA

The FDA has been working for decades to ensure that people of different ages, races, ethnic groups, and genders are included in clinical trials. The official stance of the FDA is that clinical trial participants should be representative of the patients who will ultimately use the medical products that the FDA evaluates because people of different ages, ethnicities or races can react differently to medical products for a variety of reasons.(Food and Drug Administration 2020) The agency has primarily promoted diversity by publishing guidelines that inform sponsors and drug manufactures of the FDA's current thinking and regulatory interpretations.(Food and Drug Administration 2021)

In 1985, the FDA introduced "Content and Format of a New Drug Application (21 CFR 314.50 (d)(5)(v))," its first guidance on analyzing specific subgroups such as pediatric, geriatric, and renal failure patients to evaluate whether dosing modifications were necessary in these populations.(Food and Drug Administration 1985) The inclusion of renal failure patients could be considered early progress with regard to individuals with disabilities. This regulation did not include gender and race as subgroups.

An early breakthrough for gender inclusion came following the work of the first HHS task force on women's health, which produced a 1985 report on Women's Health Issues encouraging reexamination of extant policies excluding women of childbearing potential from clinical trial participation. The FDA responded with the 1987 publication of a guidance for industry, "Guideline for the Format and Context of the Nonclinical Pharmacology/Toxicology Section of an Application," which set an expectation that both sexes of animals should be used to provide valuable information in pre-clinical drug safety studies.(Food and Drug Administration 1987) In the following year, the FDA released a "Guidance for the Format and Content of the Clinical and Statistical Section of an Application" in which it recommended analyzing data from clinical pharmacology studies for safety and efficacy by sex, race, and age.(Food and Drug Administration 1988) In addition, the FDA issued

a 1989 guidance aimed at drugs used in the elderly that included "Guidelines for the Format and Content of the Clinical and Statistical Sections of an Application."(Food and Drug Administration 1989) This guideline recommended the analysis of safety and efficacy data to determine the influence of demographic factors such as age and sex in Phase 2 or Phase 3 trials (the final two stages of clinical testing prior to drug approval).

Although the 1988 and 1989 guidance documents aimed to promote evaluation of drug effectiveness based on gender, a landmark GAO Report in 1992 concluded that women were nonetheless being underrepresented in clinical trials and trial data were often not analyzed for differences in therapeutic response by sex.(Government Accountability Office 1992) This report was prompted by a request from Congress based on studies in the medical literature that women tended to metabolize antihypertensive and cardiovascular drugs at a slower rate than men,(Tamargo, Rosano et al. 2017) and that drug interactions with female hormones and use of oral contraceptives could have caused different responses putting women at risk if the FDA approved drugs on the basis of clinical trials in which women were underrepresented.(Government Accountability Office 1992) The GAO report found that for more than 60% of drug trials, the representation of women in the trial population was less than the proportion of women in the population with the corresponding disease. The GAO concluded that the FDA had not issued adequate guidance for drug manufacturers to determine the extent and sufficiency of female representation in Phase 1 and 2 trials. For example, the FDA did not define the term 'representative' and drug manufacturers were uncertain of FDA expectations around that term.

While the 1992 GAO report did not evaluate the 'appropriateness' of the FDA policy of excluding women of child-bearing potential, in 1993 the FDA withdrew its restriction on the participation of women in early clinical trials.(Government Accountability Office 1992) This retraction was believed to have been prompted by analyses of published clinical trials that showed that trials of aspirin or anti-anginal drugs had few or no women in them, which made it uncertain how they worked in women.(Food and Drug Administration 1989, Government Accountability Office 1992) In addition, there had been concerns that the 1977 policy may have led to a general lack of participation of women in drug development studies.(DiPietro and Liu 2016) Concerns about the efficacy of drugs in women also arose at a time when the FDA and the scientific community were focusing the need for individualized treatment and there had been a lack of specific studies of pharmacokinetics in women even when gender-related differences may be expected or important, such as differences

due to menopause or the menstrual cycle, or oral contraceptive use, or differences based on body fat percentage, weight, or muscle mass.(Food and Drug Administration 1993) In addition, the 1977 policy had prevented the gathering of early information on drug response in women that could be used in the design of Phase 2 and 3 trials and may have delayed discovery of gender-based variation in drug effects.(Food and Drug Administration 1993) Earlier participation of women in clinical trials could have led to making appropriate gender-based adjustments in larger studies, such as doses based on weight rather than fixed doses. Still, the FDA did not require that women be included in trials.(Wood 2021) The agency merely stated that it would expect careful, gender-based characterization of drug effects, such as quantifying differences in dose-response and maximum size of effects. The FDA also recommended pharmacokinetic and pharmacodynamic screening in women as a tool to detect differences and analyses of safety and efficacy by sex.

In 1994, the FDA Office of Women's Health was established to guide the agency around policies on the inclusion of women in clinical trials.(Part 1994) Within the same year, an Institute of Medicine report, "Women and Health Research," called attention to the forms of historical gender bias in the design and implementation of trials.(Mastroianni, Faden et al. 1994) Spurred by these concerns, Congress released a 1997 Regulation "FDMA Section 115: Clinical Investigations (b) Women and Minorities Regulation" that required the FDA and NIH to review and develop guidance on the inclusion of women and minorities in clinical trials.(S.830 - 105th Congress 1997) To comply with this regulation, the FDA issued the Demographic rule in 1998, revising the New Drug Applications (NDA) content to require safety and efficacy data to be presented by gender, age, and racial subgroups and dosage modifications be identified for specific subgroups.(Food and Drug Administration 1998) This rule gave the FDA the authority to refuse any NDA that did not analyze safety and efficacy data appropriately. It also required data on participation in investigational new drug (IND) applications to be presented by sex, age, and race so that any potential deficiencies in the NDA submission could be identified. In addition, a 1999 FDA Guidance recommended the use of population pharmacokinetics to help identify differences in drug safety and efficacy among population subgroups.(Food and Drug Administration 1999) In 2000, Congress passed a law titled "Amendment to the Clinical Hold Regulations for Products Intended for Life-Threatening Diseases (21 CFR 312.42)" that permitted the FDA to place clinical holds on IND studies if men or women were excluded due to reproductive potential from clinical trials on a serious or life-threatening illness.(Congress 2000)

Although these policies aimed to increase the inclusion of women and minorities in trials, there were important shortcomings. The 1998 Demographic regulation had the force of law but lacked specificity relative to previous guidance, as it did not include criteria to determine the number of women to be included.(Government Accountability Office 2001) The guidance issued in 2000 also did not require the inclusion of any particular number of men or women.(Government Accountability Office 2001) A 2001 GAO report that examined these policies found that around one-third of NDAs and 39% of IND documents failed to meet the requirements of the 1998 FDA regulation. Although the FDA had the authority to suspend research if women were excluded for their reproductive potential, it had never done so. In addition, the report found that women were only 22% of the participants in the small-scale safety trials in which dosage levels were set. There also was no management system to track the inclusion of women in trials or to monitor compliance with existing regulations. The FDA had no criteria to determine whether reviews of NDAs adequately addressed sex differences and FDA medical officers had not been required to discuss sex differences in their own reviews of NDAs. Thus, the FDA lacked tools to enforce its own regulations and ensure that its reviewers consistently documented sex differences in NDAs.(Government Accountability Office 2001)

To address some of these limitations, between 2002 and 2005, the FDA issued multiple recommendations around the inclusion and safety of pregnant women in clinical trials. In 2002, an FDA regulation on 'Establishing Pregnancy Exposure Registries' provided guidance on monitoring the outcomes of pregnancies exposed to specific medical products with the goal of providing clinically relevant data to medical providers for treating patients who are pregnant or expectant.(Food and Drug Administration 2002) In a 2004 guidance, the FDA provided a basic framework for designing and conducting pharmacokinetic and pharmacodynamic studies in pregnant women, and provided instructions on how to assess the influence of pregnancy on pharmacokinetics and pharmacodynamics of medical products.(Food and Drug Administration 2004) A final draft guidance was released in 2018 entitled "Pregnant Women: Scientific and Ethical considerations for Inclusion in Clinical Trials" that supported an informed and balanced approach around gathering data on the use of medical products during pregnancy by encouraging judicious inclusion of pregnant women in trials and careful attention to fetal risk.(Food and Drug Administration 2018)

A push for diversity spurred Congress to pass Section 907 of the FDA Safety and Innovation Act of 2012 (FDASIA) that directed the FDA to investigate how well demographic subgroups were included in clinical trials and whether subgroup-specific safety and efficacy data were available.(Food and Drug Administration 2012) This law also required the FDA to provide Congress with an action plan that addressed improving the completeness and quality of data analyses on demographic subgroups. To fulfill these directives, the FDA drafted a report, "Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products," to address the extent to which demographic subgroups participated in clinical trials and whether the relevant subgroup analyses were performed in a manner consistent with FDA regulations.(Food and Drug Administration 2013) The FDA found variability across medical product types in the extent to which demographic data were analyzed. In some applications, subgroup analyses were limited by low sample size. Racial minorities were often underrepresented in trials. Communication of demographic information to the public also tended to vary for medical devices compared to drugs and biologics due to differences in the FDA regulatory frameworks. In 2014, the FDA released an "Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data" as necessitated by Section 907. This action plan outlined recommendations for the inclusion of demographic data in labelling and the public availability of these data. It also included new guidelines to encourage greater demographic subgroup inclusion in trials, plans to work with sponsors to improve information on demographic subgroups in NDAs and INDs, and intentions of strengthening FDA reviewer training by adding education around inclusion, analysis, and communication of clinical data.(Food and Drug Administration 2012) In another 2014 guidance, the FDA outlined their expectation around sex-specific patient enrollment, analysis of the data, and reporting of the study information with the intention of improving the quality and consistency of data. Through this guidance, the FDA encouraged sponsors to investigate reasons for the lack of enrollment of women and suggested measures to correct this imbalance. For example, if women's participation dropped substantially after the initial trial screening, then the study criteria may have to be examined to reduce the unintentional exclusion of women. The guidance also provided recommendations to improve enrollment such as targeting investigation sites where women could be more easily recruited, considering alternative communication strategies for recruitment, and maintaining open enrollment for women until a target proportion has been achieved.(Food and Drug Administration 2014)

Although several FDA regulations in the 1990s addressed the inclusion of women in trials, fewer regulations specifically targeted the inclusion of racial and ethnic minority groups. When the Office of Women's Health sought to raise the issue of terminology around race in the 1990s, the FDA initially exempted itself from Office of Management and Budget (OMB) definitions of race.(Wood 2021) The Office of Women's Health raised the issue again in 2004 when it drafted the first guidance around inclusivity on race that adopted the OMB definition of race and ethnicity for reporting trial populations. This draft was not finalized until 2016.(Wood 2021) The Office of Minority Health was only established in 2010 as part of the Affordable Care Act to advise the FDA on reducing health disparities among racial and ethnic subgroups.(DiPietro and Liu 2016) In 2016, the FDA released the guidance entitled "Collection of Race and Ethnicity Data in Clinical Trials: Guidance for Industry and Food and Drug Administration Staff" to provide instructions on the use of standardized terminology for demographic information (age, sex, gender, race, and ethnicity) based on OMB directives, to ensure that subgroup data was collected consistently.(Food and Drug Administration 2016) This was a very limited guidance that only discussed the terms used to describe 'non-white' populations but did not explicitly encourage inclusion of these populations in trials. A guidance for medical devices was released in 2017, "Evaluation and Reporting of Age-, Race-, and Ethnicity- Specific Data in Medical Device Clinical Studies," in which the FDA provided recommendations for the evaluation and reporting of demographic-specific data in clinical studies.(Food and Drug Administration 2017) The guidance covered why diverse representation was important and identified potential barriers to enrollment, as well as provided recommendations to overcome those barriers. Around this time, the FDA also began to require the use of 'Drug Snapshots' that provided information about the populations that participated in FDA-supported clinical trials, and highlighted whether there were any differences in benefits and/or side effects by sex, race, ethnicity, and age.(Food and Drug Administration) Although the use of snapshots has marked progress in ensuring that demographic information is transparent and made available to the public, it has had limitations. The snapshots only cover 2015 onward, and only provide information from Phase 3 studies or products that already have been approved.(Wood 2021) A final guidance was issued in 2020 titled "Guidance for Industry: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs," specifically addressing the need to enhance diversity of clinical trial populations by modifying eligibility criteria, enrollment practices, and trial designs.(Food and Drug Administration 2020) The guidance advises that drug sponsors have a "plan for inclusion of clinically relevant populations no later than the end of the Phase 2 meeting." Through this guidance, the FDA satisfied a mandate under section

601 (a)(3) of the FDA Reauthorization Act of 2017 (FDARA) to broaden and develop eligibility criteria with no unnecessary exclusions for clinical trials, improve trial recruitment so that trial participants reflect the population that will use the drug, and apply these recommendations to clinical trials.(Food and Drug Administration 2020)

This guidance also aimed at promoting enrollment of individuals with disabilities in clinical trials. For individuals such as older adults, disabled, or cognitively impaired individuals who need caregiver help or transportation, a requirement to make frequent visits to trial sites can be problematic and hinder participation. To make participation in clinical trials less burdensome, the FDA has proposed measures such as reducing the frequency of visits, considering whether visits could be replaced by telephone or virtual means, making participants aware of reimbursements for travel and lodging expenses for trial participation, and using mobile medical professionals to visit and evaluate participants or collect blood samples.(Stephenson 2020)

While historically, the FDA has often used sex and gender synonymously, this guidance noted that the FDA recognizes that for some clinical trial participants, gender and sex may not be concordant. Still, it stated that discussion of this topic falls outside the scope of the guidance. Sexual minorities remain largely overlooked by FDA policies.(Food and Drug Administration 2020)

Enforcement and Accountability

Thus far, the FDA has undertaken various measures to improve diversity in clinical trials primarily via guidance documents and the use of drug snapshots. Despite these efforts, certain demographic groups have remained underrepresented in many trials. The measures taken by the FDA have limitations that must be addressed so that populations participating in trials reflect the diversity of the population at large that will be using the drugs/medical products. One such limitation is the lack of enforcement of FDA guidance. Notably, most guidance documents contain the following disclaimer: *"FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required."*

The FDA encourages inclusivity but lacks the power to enforce recommendations made in published guidance documents. Although the FDA can make recommendations, they have limited capacity to enforce them. This dynamic may have developed in part because the FDA does not fund investigational drug trials, but rather assesses them, giving the agency less bargaining power compared with the NIH, which can provide funding. However, this is not an insurmountable barrier, especially since the 2000 law gave the FDA the power to put a clinical trial on hold if men or women were being excluded due to reproductive potential. Although the FDA does not appear to have ever put a trial on hold for this reason, such regulations can be leveraged to ensure that sponsors do everything in their power to improve enrollment practices and increase ease of enrollment so that clinical trials can be more inclusive. For example, the FDA could ensure that to show that a drug is sufficiently safe and effective, the trial population must reflect the diversity of the target population for which the drug is indicated. In addition, the FDA can also mandate that demographic information be made public across all stages of the trials. Ensuring adequate representation in clinical trials can be better woven into the approval process so that sponsors try to fulfill their obligations in this area. More broadly, it would be useful to advance policies of accountability rather than recommendations. Currently, the FDA has no clear authority for requiring sponsors to ensure that trials are inclusive. Such authority can only be bestowed through a congressional statute.

FDA progress has also been slow and tends to be reactive to Congressional prodding. Developing a guidance is a long and resource-intensive process, and often there has been a lack of bandwidth to produce guidelines to improve inclusivity in trials.(Wood 2021) Such guidelines have been created in response to laws from Congress but in the absence of such legal directives there has been limited planning to promote diversity. Changes have tended to arise not from leadership within the agency but from congressional action.(Wood 2021) The lack of internal initiative and leadership to independently create policies around inclusion has hampered progress toward diversity. In addition, too often if gender or race/ethnicity differences are not proven (e.g. difference in symptoms of a heart attack in women), then they have been treated as though absent.(Wood 2021) A more cautious approach could help to increase concern around the lack of diversity in clinical trials. Finally, the lack of standardization of submission of NDAs and INDs has been problematic. Since every sponsor tends to design trials differently and can label trial characteristics differently in the database,(Wood 2021) there has been no clear standard of submission. Thus, analyzing data and obtaining intersectional data from the FDA has been challenging. Setting guidelines for submission across trials of medical products and drugs could help standardize data collection

which could further aid in analysis. Although the FDA has made major progress in ensuring more inclusivity within clinical trials, it must continue to try to enforce its recommendations to ensure that trial populations reflect the diversity of populations at large.

CDC and Other Institutions

The Centers for Disease Control and Prevention (CDC) sponsor a wide range of public health initiatives – including providing funding for local and state public health agencies. The research mission of the CDC is to support public health studies and it often sponsors retrospective examinations of public health issues. Funding clinical trials makes up a small portion of the CDC's research budget, but the agency still regulates recruitment of diverse demographics.

CDC policies promoting inclusion of diverse populations in research have been largely catalyzed by federal laws. The 1993 NIH Revitalization Act did not govern the CDC, but the legislation spurred the CDC to create its own policies on inclusion of women and diverse races and ethnicities in research participation.(Geller, Koch et al. 2011) In 1995, the CDC issued the "Policy on the Inclusion of Women and Racial and Ethnic Minorities in Externally Awarded Research," applying to extramural research activities.(Centers for Disease Control and Prevention 1995) In 1996, the CDC released "Inclusion of Women and Racial and Ethnic Minorities in Research," which applied to intramural research.(Centers for Disease Control and Prevention 1996) The ordinances stated that women and members of racial and ethnic minority groups should be adequately represented in all CDC research involving human subjects, in the absence of a compelling reason for exclusion. They further stipulated that women of childbearing potential should not be routinely excluded from research without proper cause. The policies provided guidance on how these goals for inclusion could be met by investigators. For example, if all diverse groups could not be included in a single study, multiple studies could be conducted. The policies also stated that it was not necessary to provide the statistical power to test hypotheses in all groups separately, but that if differences between groups are plausible, this should be tested in the study design. Further, study proposals should include discussion of the inclusion or exclusion of minority groups.(Centers for Disease Control and Prevention 1995) (Centers for Disease Control and Prevention 1996)

The CDC policy on inclusion of women and ethnic and racial minorities was closely followed by the more general policy in 1997, "CDC Procedures for Protection of Human Research Participants."(Centers for Disease Control and Prevention 1997) This new policy restated an

abridged version of the 1996 ordinance, placing it into context of protections of other policies for the protection of human subjects.

The CDC revised the 1996 "Inclusion of Women and Racial and Ethnic Minorities in Research" policy in 2010. This policy united the past separate policies on extramural and intramural research into a single policy. The revised policy strengthened the call for representation in clinical research by stating that direct efforts should be made to actively recruit and enroll women and minorities in all funded research.(Centers for Disease Control and Prevention 2010)

Protections for children in clinical research were codified in the 1997 "CDC Procedures for Protection of Human Research Participants." The 1997 guidelines deferred to local and state laws on medical consent for minors to determine whether it is appropriate for a minor to participate in a research study. However, the policy also stated that the minimum requirements for consent in a local jurisdiction do not necessarily authorize a minor's involvement in a research study. The policy gives latitude to the study's institutional review board (IRB) to determine the ethical parameters for a minor's involvement in research. The IRB should weigh risks to the children in the study with the benefits the research may provide to children as a group. The ordinance also stresses the importance that research pose a "minimal risk" to children, as adjudicated by the IRB. It outlines minimal risk research activities that are usually acceptable for children, such as urinalysis, venipuncture, electroencephalography, and allergy scratch tests.(Centers for Disease Control and Prevention 1997)

The CDC issued an explicit policy on children in research in 2006 (updated in 2011) entitled "Inclusion of Persons Under the Age of 21 in Research." According to this policy, research proposals must include a rationale to include or exclude persons under 21 in intramural or extramural research – similar to the provisions in the "Inclusion of Women and Racial and Ethnic Minorities in Research" policy.(Centers for Disease Control and Prevention 2011)

While there has been a plethora of academic attention to the CDC's public health research and initiatives, there has been less research on the clinical trial policies of the CDC. The CDC devotes a smaller proportion of its funding to clinical trials, but further attention to this issue may be useful.

In addition to the CDC, other federal agencies that sponsor or regulate clinical trials include the Department of Defense, the Agency for Healthcare Research and Quality (AHRQ), and the Centers for Medicare & Medicaid Services (CMS).(2017) The role that CMS plays in funding diverse clinical trials is especially important. While costs of routine care to participants in trials are usually covered by Medicare, there are many costs borne by the participants, decreasing participation especially among financially disadvantaged patients.(2009) For participants receiving Medicaid benefits, there were historically no federal mandates for clinical trial coverage, making it prohibitively expensive for many Medicaid beneficiaries to participate in clinical trials.(Winkfield, Phillips et al. 2018)

This changed in 2000, when President Clinton issued an executive memorandum directing the Secretary of HHS to cover the routine patient care costs associated with clinical trials, as well as costs due to any medical complications.(Secretary) The Health Care Financing Administration (the predecessor to CMS) responded to the executive order with a policy specifying that Medicare would cover "routine" costs that accompany clinical trial participation, including diagnostic tests, hospital charges, and provider fees, but excluding reimbursement for "items and services provided solely to satisfy data collection."(Services) The exception is thought to have created major barriers that prevented community providers from participating in clinical trial enrollment, which in turn disproportionately affected racial and ethnic minorities. CMS updated its clinical trial policy in July 2007 with clarifications and some additional coverage items. However, the policy still excludes items and services for data collection.(Services)

In 2014, CMS released an updated guidance that allows CMS to determine coverage of an item or service only in the context of a clinical study.(Services) In its coverage with evidence development for transcatheter mitral valve repair, for example, CMS explicitly noted, "study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial."(Services) Such requirements by CMS have the potential to change the landscape of clinical trial representation as millions of Americans served by Medicare who have been traditionally underrepresented in clinical trials could now be recognized and actively recruited. Additionally, the $2.3 trillion omnibus spending and relief package passed by Congress in 2020 guaranteed, for the first time, routine costs for clinical trials for Medicaid recipients by 2022,

expanding access for many low-income participants.(Takvorian, Guerra et al. 2021) Still, transportation, time away from work, and other ancillary costs remain barriers that will need to be addressed for participants despite their coverage status. Finally, while the updated version of this policy mandated that peer review of study protocols should assess "the adequacy of plans to include both genders, minorities, children, and special populations as appropriate for the scientific goals of the research," it left out sexual and gender minorities.(Services)

AHRQ is an agency within HHS that has a mission to improve the safety and quality of America's health care system. The Healthcare Research and Quality Act of 1999 (Public Law 106-129) established an Office of Priority Populations within AHRQ.(Public Law 1999) Subsequently, AHRQ has required that all AHRQ-supported research includes priority populations unless a compelling justification is provided against inclusion. Priority populations initially included women, children, racial and ethnic minorities, populations with special healthcare needs (chronic illness, disabilities, and end of life care needs), the elderly, low-income, inner-city, and rural populations.(Agency for Healthcare Research and Quality 2021)

In 2021, President Biden signed Executive Order 13985, titled "Advancing Racial Equity and Support for Underserved Communities Through the Federal Government" and defined underserved communities as individuals who have been denied "consistent and systematic fair, just, and impartial treatment." Specifically, it identified "Black, Latino, and Indigenous and Native American persons; Asian Americans and Pacific Islanders and other persons of color; members of religious minorities; lesbian, gay, bisexual, transgender, and queer (LGBTQ+) persons; persons with disabilities; persons who live in rural areas; and persons otherwise adversely affected by persistent poverty or inequality" as underserved communities.(2021) Subsequently, the AHRQ updated its Policy on the Inclusion of Priority Populations in Research (NOT-HS-21-015) to expand its definition of priority populations to match those groups identified in Executive Order 13985.(Agency for Healthcare Research and Quality 2021)

The Patient-Centered Outcomes Research Institute (PCORI) is a US-based non-profit institute created through the 2010 Patient Protection and Affordable Care Act (ACA). Its funding comes from the Patient-Centered Outcomes Research Trust Fund (PCORTF) authorized by Congress in 2010 under the ACA, and reauthorized again in 2020 under the Further Consolidated Appropriations Act.(Public Law 2020) With PCORTF funding, PCORI launched PCORnet, a national patient-centered

clinical research network in 2014.(Fleurence, Curtis et al. 2014) PCORnet published "Diversity and Inclusion in PCORnet: Need and Recommendations" to set guiding principles for diversity and inclusion in PCORnet. The guidance called for inclusion and prioritizing underrepresented groups impacted by the outcomes of research, including "people of color, rural/inner city populations, pregnant and lactating women, gender and sexual minorities, individuals with disabilities, and other audiences commonly underrepresented in clinical research."(Patient-Centered Outcomes Research Institute) PCORI has also undertaken numerous measures recently to expand its work toward diversity, equity, and inclusion. The agency created an internal steering committee that is developing a comprehensive action plan to enhance diversity, equity, and inclusion. PCORI is also developing a data collection strategic framework with attention to diversity and inclusion.

The Common Rule

Many federal agencies are subject to the Common Rule (45 CFR 46), most recently revised in 2018.(Department of Health and Human Services 2017) The Common Rule is the blanket federal policy for the protection of human subjects that IRBs are expected to follow. The Common Rule requires that selection of research subjects is equitable, but it does not further specify inclusive recruitment of diverse subpopulations. Rather, the rule states that IRBs should be particularly cognizant of the special problems of research with subjects vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons and that additional safeguards should be included in studies to protect the rights and welfare of these subjects. The rule requires that IRBs should be composed of diverse individuals and if an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, the IRB should consider including one or more members knowledgeable about and experienced in working with these categories of subjects. The Common Rule also specifies particular ethical regulations for children and pregnant women. One notable change in the 2018 revision was the removal of pregnant women from the "vulnerable" category of research subjects. This was in response to criticism that women were being unfairly excluded from research studies, to the detriment of designing treatments for women.(National Institutes of Health 2019) The revision aimed to increase the participation of women in research studies and to improve the recommendations for prescribing interventions for pregnant women.(Hurley 2017)

Enforcement and Accountability

US government agency policies on inclusion are enforced through different means. For example, CMS has an expectation that all supported clinical studies demonstrate adherence to inclusivity requirements, and that the agency would not anticipate approving a study that does not meet the requirements.(Services) The AHRQ peer review regulation requires that reviewers of grant and contract applications include their assessment of the proposed inclusion plan for priority populations in evaluating the overall scientific and technical merits of applications. Similarly, the CDC requires that grant reviewers abide by CDC policies on inclusion and diversity. Beyond grant review, accountability to inclusion policies also comes from a research applicant's IRB and oversight from HHS's Office for Human Research Protections (OHRP). The Common Rule grants latitude to IRBs to review research projects under the Common Rule's requirement that subject recruitment is equitable.(2017) However, the extent to which this is actually accomplished by IRBs in practice can depend upon the individual IRB's commitment to and interpretation of this objective. While OHRP does not directly oversee compliance of individual research studies, it does issue Written Assurances of Compliance to research institutions, such as universities and academic medical centers, which allow investigators to perform research within the institutions.(Participants. 2004) If an institution is noncompliant with the Common Rule, OHRP can revoke its assurance.

Discussion

Work toward inclusive clinical trials and clinical research on numerous fronts over the past several decades has led to meaningful progress, exemplified by the fact that roughly half or more of participants in NIH-funded clinical trials are now women.(Arnegard, Whitten et al. 2020) Still, policy gaps remain and lessons can be drawn from this history.

Substantial progress has been made regarding including women in research, although further attention is needed, particularly for pregnant women. Evidence-based medicine would benefit from more inclusive and informative trials regarding race and ethnicity, age, sexual minorities, and people with disabilities. Recruitment of these subpopulations has likely been more challenging than recruitment by binary sex, given that roughly half of the population is female, while other subpopulations are less numerous and therefore may be more difficult to enroll in trials. Potential risks of experimental therapies may pose possible enrollment challenges for children, the elderly, people with disabilities, and other vulnerable populations. True expansion of inclusion in clinical

trials calls for careful considerations and individual accommodations that eliminate invisible economic barriers. Additional time or human resources also need to be allocated to recruitment of children and people with dementia or intellectual disabilities to assist with informed consent processes.(Feldman, Bosett et al. 2014) Some physical disabilities also warrant particular considerations and adaptations of the pharmaceutical agent of interest, such as the development of alternative delivery routes including gastrostomy tubes or rectal suppositories.(Feldman, Bosett et al. 2014) Federal agencies funding clinical research should allocate additional financial resources to assist with including diverse populations, and the FDA should establish policies requiring drug and device sponsors to allocate sufficient resources toward trial inclusivity. Further efforts should also be made to increase the diversity of the scientific workforce and leadership.

Sexual minorities and people with disabilities have been largely neglected populations in clinical trial diversity policies. More policy attention should be given across agencies to bolster inclusivity of these groups and better incorporate them into existing policies aimed at trial diversity. Similarly, policies should better address economic and geographic barriers to trial participation. Filling these gaps is likely to require effort and demands appropriate allocation of resources.

While some policies have begun to recognize the complexity and difficulty of measuring and interpreting health outcomes by race and ethnicity, further attention should be given to the nuanced interplay between racism and health outcomes and the multifaceted and varied social influences on health by racial and ethnic background. Additionally, agencies should evaluate how they delineate and interpret associations with racial and ethnic groups, including mixed race individuals. Further geographic and ethnic specifications may also prove informative.

Historically, some policy strategies seem to have been effective. Federal legislation from Congress has been the most powerful stimulus of institutional change by empowering agencies to create new policies, measures, and monitoring of research inclusivity. Legislative action has also influenced institutional action. For example, although the 1993 NIH Revitalization Act did not apply to the CDC, the agency nevertheless created policies on inclusion of women and racial and ethnic minorities following its passage by Congress.

Legislative action and institutional policies have tended to derive from detailed and thorough reports and scientific analyses of the lack of diversity in clinical research, speaking to the value of

studying and reporting on matters of trial diversity. For example, the 1985 Report of the Public Health Service Task Force on Women's Health Issues led to the 1987 publication of a guidance for industry on women's inclusion by the FDA. Similarly, the GAO Report in 1992 helped spur the 1993 NIH Revitalization Act and the creation of the FDA Office of Women's Health in 1994. Scholarly studies describing limited clinical trial data on aspirin and anti-anginal drugs in women led to the 1993 FDA withdrawal of its restriction on the participation of women in early clinical trials. Federal legislation has also led to the collection of data that have informed further policy development. For example, when Section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 required that the FDA examine whether sub-group specific safety and efficacy data were available, the agency produced data that informed the 2014 "Action Plan to Enhance the Collection and Availability of Demographic subgroup data." Throughout the history of policymaking toward inclusive trials, scientific research and reports on limitations in trial diversity have been crucial in catalyzing federal laws and institutional policies, indicating the value of ongoing research and federal investigations into progress in trial diversity.

The policymaking process has also benefited from the creation of institutions such as the FDA Office of Women's Health and Office of Minority Health, and the NIH Office of Research on Women's Health and Office of Minority Health and Health Disparities (adding more on this above). The institutionalization of attention to diversity through these offices seems to have had a generative effect, as they have raised awareness and provided education, guidance, and information around inclusivity, or have played a role in policy compliance monitoring. There has also been a generative effect across offices; for example, the FDA Office of Women's Health drafted the first guidance around inclusivity on race in 2004. These offices have played an important role in supporting and advancing institutional work around research inclusivity and are likely useful centers for future policy implementation.

A review of the history of trial diversity and inclusion policies across agencies reveals certain patterns. Over time, many policies have had the same objectives of promoting trial inclusivity and trial participants that reflect the broader population demographics likely to be exposed to interventions under investigation. Yet, these objectives often seem elusive. Policies that contain broad goals without mechanisms of implementation have likely had an encouraging effect on research inclusivity. However, it seems that the most effective policies have involved specific action requirements paired with clear mechanisms of implementation and accountability, such as the NIH

requirement for reporting trial population diversity in ClinicalTrials.gov. The FDA guidance documents have not had means of implementation or enforcement, which may explain in part the seeming repetitive nature of guidance documents that seek to advance diversity and inclusion alongside the recurring problem of trial data that are not optimally comprehensive.

In the future, rather than proclaiming broad goals without clear mechanisms of implementation, policies should shift toward specific means of accomplishing trial diversification, as well as further building systems of monitoring accountability and compliance. Numerous mechanisms exist to measure trial diversity once research is completed but further attention is due to strengthen enforcement of existing policy objectives prior to and during trial enrollment. Normalizing and clarifying standards for diversity requirements could also be useful. For example, rather than simply providing guidance on inclusive objectives at the FDA, effort could be devoted toward establishing budgeting expectations for trial sponsors to devote resources toward recruitment of diverse research subjects. Similarly, additional NIH, CDC, and other agency funding streams could be created to support trial diversification.

It also would be helpful for the Common Rule (45 CFR 46) to be revised to better incorporate inclusivity. While the rule currently has language to protect vulnerable populations from exploitation, expanding discussion on equitable inclusion would be valuable, such as describing how ethical research should aim to recruit trial participants representative of the diversity of the ultimate population affected by the experimental therapy.

It is important for policies to move beyond simple inclusion to better address the complex meaning and use of collected data. Inclusivity should move toward requiring clinically informative and statistically rigorous data on subgroups to the extent possible. As availability of large datasets and the field of pharmacoepidemiology have expanded, it may be useful for federal agencies to broaden support and requirements for large epidemiological studies of interventions following the completion of experimental clinical trials. The FDA could require post-marketing drug surveillance studies of approved drugs to further examine any different outcomes to therapies by diverse patients at a population level. Similarly, the NIH and CDC could provide support for continued epidemiological surveillance of interventions studied in clinical trials receiving agency support.

The 2021 Executive Order 13985 requires that all federal agencies assess whether, and to what extent, their programs and policies perpetuate systemic barriers to opportunities and benefits for people of color and other underserved groups. It also requires analysis of whether new policies, regulations, or guidance documents may be necessary to advance equity in agency actions and programs.(2021) Given persistent inequalities in trial representation and the limitations of existing policies designed for inclusivity, it is incumbent upon federal agencies to modernize, strengthen, expand, and specify policies to improve meaningful trial inclusivity and to create mechanisms for better enforcement and accountability to existing policies.

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Appendix A

Search terms for Regulations.gov:

inclusion women clinical trial
inclusion race clinical trial
inclusion ethnicity clinical trial
inclusion diversity clinical trial
inclusion minorities clinical trial
inclusion age clinical trial
inclusion elderly clinical trial
inclusion children clinical trial
language accessibility clinical trial
Section 1557 clinical trial
inclusion disability clinical trial
Inclusion disabilities clinical trial
inclusion gender clinical trial
inclusion LGBT clinical trial
inclusion gender nonbinary clinical trial
inclusion transgender clinical trial
inclusion androgynous clinical trial
inclusion sexual minority clinical trial

Search terms for literature review on policy effectiveness (for each search term, agency names were added, e.g. NIH, FDA, and CDC):
representation women clinical trial
representation race clinical trial
representation ethnicity clinical trial
representation diversity clinical trial
representation minorities clinical trial
representation age clinical trial
representation elderly clinical trial
representation children clinical trial
language accessibility clinical trial
Section 1557 clinical trial
representation disability clinical trial
representation disabilities clinical trial
representation gender clinical trial
representation LGBT clinical trial
representation gender nonbinary clinical trial
representation transgender clinical trial
representation androgynous clinical trial
representation sexual minority clinical trial

Additional search terms for literature review on policy effectiveness (for each search term, agency names were added, e.g. NIH, FDA, and CDC):
regulation diversity clinical trial
regulation inclusion women clinical trial
regulation inclusion race clinical trial
regulation inclusion ethnicity clinical trial

regulation inclusion diversity clinical trial
regulation inclusion minorities clinical trial
regulation inclusion age clinical trial
regulation inclusion elderly clinical trial
regulation inclusion children clinical trial
regulation language accessibility clinical trial
Section 1557 clinical trial
regulation disability clinical trial
regulation disabilities clinical trial
regulation gender clinical trial
regulation LGBT clinical trial
regulation gender nonbinary clinical trial
regulation transgender clinical trial
regulation androgynous clinical trial
regulation sexual minority clinical trial

Final search terms for literature review on policy effectiveness (for each search term, agency names were added, e.g. NIH, FDA, and CDC):
history inclusion women clinical trial
history inclusion race clinical trial
history inclusion ethnicity clinical trial
history inclusion diversity clinical trial
history inclusion minorities clinical trial
history inclusion age clinical trial
history inclusion elderly clinical trial
history inclusion children clinical trial
history language accessibility clinical trial
history inclusion disability clinical trial
history inclusion disabilities clinical trial
history inclusion gender clinical trial
history inclusion LGBT clinical trial
history inclusion gender nonbinary clinical trial
history inclusion transgender clinical trial
history inclusion androgynous clinical trial
history inclusion sexual minority clinical trial