Considering Modifications to Existing FDA Regulatory Incentives to Achieve Greater Racial and Ethnic Diversity in Pivotal Clinical Trials for Drug Approvals

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ABSTRACT

When clinical trials for new drug approvals fail to adequately represent racial and ethnic groups, there is a lost opportunity to collect data on people who will be prescribed these medications. In this Paper, we consider data published by the U.S. Food and Drug Administration reflecting the current state of diversity in pivotal clinical trials, which establish the safety and efficacy data to be considered for drug approval. We offer recommendations based on the information revealed in these data, which show a persistent under-representation of diverse populations in pivotal trials despite decades of guidance and proposed actions intended to achieve greater diversity.

I. INTRODUCTION

In November 2020, the U.S. Food and Drug Administration (FDA) issued the final guidance, "Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs," providing recommendations on how clinical trial sponsors can approach enrollment of underrepresented patient populations.[1] This effort builds on more than a decade of initiatives to increase racial and ethnic diversity in clinical trials at both FDA and the National Institutes of Health (NIH). However, despite guidance to and investment in clinical trial sponsors and researchers, the FDA data shows that most pivotal clinical trials for new drug approvals do not enroll participants that reflect the racial and ethnic diversity of the U.S. population. There are several reasons for a lack of racial diversity in pivotal clinical trials for drug approval, including historical distrust of the medical community, limited participation and engagement of diverse healthcare professionals as investigators, typically used

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[1] *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ENHANCING THE DIVERSITY OF CLINICAL TRIAL POPULATIONS—ELIGIBILITY CRITERIA, ENROLLMENT PRACTICES, AND TRIAL DESIGNS (Nov. 2020) [hereinafter FDA, ENHANCING THE DIVERSITY OF CLINICAL TRIAL POPULATIONS].

inclusion and exclusion criteria in trials, concerns about adherence to clinical trial procedures, and sponsor focus on rapid enrollment and expected treatment effect size.[2]

While FDA has discussed and assessed clinical trial diversity at length, many of its stated goals are centered around further dialogue and communication with sponsors, patients, and other community-level stakeholders. The agency has recommended changing criteria for including participants in studies that have the effect of disproportionately excluding people who are not white. With the legacy of racism in the United States and its effect on health and the expectation of health outcomes from a treatment, diverse trials are costlier and more time-consuming for sponsors. The issue goes beyond recruitment and trust; it also includes managing co-morbid conditions and changing trial sizes due to the expected efficacy of treatment. These are changes that can have a meaningful effect on the cost and duration of a trial. As a result, guidance to make certain changes may not be a sufficient incentive. We believe the additional step of establishing regulatory incentives (as opposed to any regulatory mandates) is a feasible option for the agency.

Specifically, we suggest that FDA consider extending regulatory incentives that currently offer sponsors access to certain expedited programs or to extended data protection.[3] Certain types of expedited programs could also be an available option where sponsors are establishing and executing plans, in good faith, to recruit and retain racial and ethnic minorities in their clinical trials. We argue that, if sponsors are provided regulatory incentives, there may be a more marked change in sponsor behavior to ensure more substantial recruitment and retention of racial and ethnic minorities. This can also be of benefit to racial minorities and the healthcare system: providing opportunities for increased access to patient care, expediting the development of an investigational product candidate, and generating data on a more representative patient population to better anticipate how the drug will work in practice.

II. CHALLENGES TO RACIAL AND ETHNIC DIVERSITY IN CLINICAL TRIALS FOR DRUG APPROVALS

While the term "pivotal" is not specifically defined in regulation, it is generally understood that pivotal clinical trials collect substantial data and evidence to support a determination by FDA of whether a drug warrants approval.[4] In this section, we summarize the existing evidence related to how the current pivotal clinical trial protocols and practices may limit participation by some races and ethnicities.

A pivotal clinical trial is generally large in scale relative to earlier stage trials to generate substantial evidence to support the indication and identify potential safety issues prior to marketing approval. Typically, there are two or more trials, so the results

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[2] In this Paper, we focus on diversity as it reflects race and ethnicity but acknowledge that achieving age and gender diversity are also a focus of clinical trial diversity efforts in the public and private sector. We use the terms Black, Latinx, Native American, and Asian unless the research uses a different term (e.g., Hispanic in the census rather than Latinx).

[3] *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 1 (May 2014) [hereinafter FDA EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS].

[4] *See* Joel Lexchin, Janice Graham, Matthew Herder, Tom Jefferson & Trudo Lemmens, *Regulators, Pivotal Clinical Trials, and Drug Regulation in the Age of COVID-19*, 51 INT'L J. HEALTH SERV. 5 (2021).

are confirmed. The trials are conducted in a highly controlled environment. There can be hundreds or thousands of trial sites at hospitals and clinics with their investigators overseeing the protocol, and trials may require that subjects make frequent visits to a study site. Additionally, participants may be selected for their ability to adhere to a protocol, which requires them to be able to communicate and follow a set of directions.[5] Certain conditions, including uncontrolled hypertension, history of poor mental health, or being in an advanced state of cancer rather than newly diagnosed, are frequently criteria for exclusion.[6]

None of these criteria appear to have a racial bias; however, with centuries of racism and social and economic disenfranchisement in the United States, certain clinical trial design criteria have the indirect effect of discriminating against and excluding lower income people, as well as Black, Latinx, Asian, and Native Americans. Criteria that often exclude an individual from participation include having conditions such as history of heart or metabolic disease that is not well controlled, chronic pain, pregnancy, advanced or young age, use of non-prescribed or illegal drugs, and mental health issues.[7] Many of these conditions are more prevalent or a more serious risk in certain non-white groups.[8] Furthermore, by excluding people with conditions that tend to be more prevalent in certain racial and ethnic minority groups from the drug evaluation and testing process, the data collected in that pivotal clinical trial does not represent the full health profile of a population that may ultimately take the drug.

People who fall into the "lower income" category, where certain minority and ethnic groups are over-represented relative to the U.S. population, are far less likely to be enrolled and participate in clinical trials.[9] Transportation and flexibility on timing to align with work schedules are both recognized as barriers to trial participation.[10] Consider that whites, who have not had the same barriers to education and capital as non-whites in the United States, are more likely to have higher education, work in high income jobs, and have flexible work schedules.[11] Whites are also more likely to use

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[5] *See* Galen Joseph & Daniel Dohan, *Diversity of Participants in Clinical Trials in an Academic Medical Center: The Role of the "Good Study Patient?"* 115 CANCER 608 (2009).

[6] David B. Fogel, *Factors Associated with Clinical Trials that Fail and Opportunities for Improving the Likelihood of Success: A Review*, 11 CONTEMP. CLINICAL TRIALS COMM. 156 (2018).

[7] *See* Céline Buffel du Vaure, Agnès Dechartres, Constance Battin, Philippe Ravaud & Isabelle Boutron, *Exclusion of Patients with Concomitant Chronic Conditions in Ongoing Randomised Controlled Trials Targeting 10 Common Chronic Conditions and Registered at ClinicalTrials.gov: A Systematic Review of Registration Details*, 6 BRIT. MED. J. OPEN E012265 (2016).

[8] *See* SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION (SAMHSA), HHS PUBLICATION NO. SMA-15-4906, RACIAL/ETHNIC DIFFERENCES IN MENTAL HEALTH SERVICE USE AMONG ADULTS (2015); Ctrs. for Disease Control and Prevention (CDC), *Underlying Cause of Death 1999–2020*, CDC WONDER (last reviewed June 13, 2022), https://wonder.cdc.gov/wonder/help/ucd.html.

[9] *See* Isabelle Yates, Jennifer Byrne, Susan Donahue, Linda McCarty & Allison Mathews, *Representation in Clinical Trials: A Review on Reaching Underrepresented Populations in Research*, 34 CLINICAL RESEARCHER 27 (2020).

[10] OFFICE OF RESEARCH ON WOMEN'S HEALTH, NATIONAL INSTITUTES OF HEALTH (NIH), REVIEW OF THE LITERATURE: PRIMARY BARRIERS AND FACILITATORS TO PARTICIPATION IN CLINICAL RESEARCH (Oct. 15, 2015), https://orwh.od.nih.gov/sites/orwh/files/docs/orwh_outreach_toolkit_litreview.pdf.

[11] *See* Neil Bhutta, Andrew C. Chang, Lisa J. Dettling & Joanne W. Hsu, *Disparities in Wealth by Race and Ethnicity in the 2019 Survey of Consumer Finances*, FED. RSRV. SYS: FEDS NOTES (Sept. 28, 2020), https://www.federalreserve.gov/econres/notes/feds-notes/disparities-in-wealth-by-race-and-ethnicity-in-the-2019-survey-of-consumer-finances-20200928.htm; Rose A. Woods, *Job Flexibilities and Work*

non-public transportation relative to Blacks.[12] People living in rural areas typically use less healthcare overall, which would result in less exposure to healthcare providers who are the single biggest conduit to clinical trial enrollment.[13]

Centuries of unequal access to capital and education and discriminatory behavior in the U.S. have fostered both mistrust and physical barriers to the healthcare system, which have contributed to sizeable and costly hurdles to greater diversity in clinical trials.[14] The costs of enrolling non-whites in clinical trials have been estimated to be as much as five times higher than whites.[15] The additional time that may be needed to engage with a participant who has distrust in the medical system, or with one who requires a translator, transportation support, or other material support, are all additional trial costs. Furthermore, healthcare provider outreach and internal referral are demonstrated to be among the most cost-effective strategies for recruitment. As a result, people who lack consistent access to a recruiting physician—who are more often non-white—may be more costly to reach and enroll.[16]

III. RECENT FDA VIEWPOINTS, DISCUSSION, AND GUIDANCE ON CLINICAL TRIAL DIVERSITY

Through research, internal agency initiatives, and discussions with various stakeholders, FDA has consistently found that racial and ethnic minorities are underrepresented in clinical trials. Further in this Paper, we share FDA's data that demonstrates the continued under-representation of certain races and ethnicities even in studies where the prevalence of the condition is high in those groups. In this section, we describe initiatives and guidance undertaken by the agency in the last twenty years with the intent to achieve more appropriate levels of diversity in pivotal clinical trials.

A. Dialogues on Diversifying Clinical Trials

In collaboration with the Society for Women's Health Research, FDA's Office of Women's Health hosted "Dialogues on Diversifying Clinical Trials" in September

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Schedules in 2017–18, BLS: Spotlight on Statistics, U.S. BUREAU OF LABOR STATISTICS (Apr. 2020), https://www.bls.gov/spotlight/2020/job-flexibilities-and-work-schedules/home.htm.

[12] Janice C. Probst, Sarah B Laditka, Jong-Yi Wang & Andrew O. Johnson, *Effects of Residence and Race on Burden of Travel for Care: Cross Sectional Analysis of the 2001 U.S. National Household Travel Survey*, 7 BMC HEALTH SERV. RES. 40 (2007).

[13] Julia T. Caldwell, Chandra L. Ford, Steven P. Wallace, May C. Wang & Lois M. Takahashi, *Intersection of Living in a Rural Versus Urban Area and Race/Ethnicity in Explaining Access to Health Care in the United States*, 106 AM. J. PUB. HEALTH 1463 (2016).

[14] Luther T. Clark, Laurence Watkins, Ileana L. Piña, Mary Elmer, Ola Akinboboye, Millicent Gorham, Brenda Jamerson, Cassandra McCullough, Christine Pierre, Adam B. Polis, Gary Puckrein & Jeanne M. Regnante, *Increasing Diversity in Clinical Trials: Overcoming Critical Barriers*, 44 CURRENT PROBS. CARDIOLOGY 148 (2019).

[15] Miriam A. Marquez, Joan M. Muhs, Ann Tosomeen, B. Lawrence Riggs & L. Joseph Melton, *Costs and Strategies in Minority Recruitment for Osteoporosis Research*, 18 J. BONE MIN. RES. 3 (2003).

[16] *See* Sravya Kakumanu, Braden J. Manns, Sophia Tran, Terry Saunders-Smith, Brenda R. Hemmelgarn, Marcello Tonelli, Ross Tsuyuki, Noah Ivers, Danielle Southern, Jeff Bakal & David J. T. Campbell, *Cost Analysis and Efficacy of Recruitment Strategies Used in a Large Pragmatic Community-Based Clinical Trial Targeting Low-Income Seniors: A Comparative Descriptive Analysis*, 20 TRIALS 577 (2019); Alexander Dew, Seema Khan, Christie Babinski, Nancy Michel, Marie Heffernan, Stefanie Stephan, Neil Jordan, Borko Jovanovic, Paula Carney & Raymond Bergan, *Recruitment Strategy Cost and Impact on Minority Accrual to a Breast Cancer Prevention Trial*, 10 CLINICAL TRIALS 292 (2013).

2011.[17] The focus of this discussion was to address the lacking representation of women and minorities in clinical trials. In the resulting white paper from this discussion, there were a number of proposals and suggestions put forth to increase engagement in clinical trials, including, for example, increasing the number of women and minority physician investigators, community engagement, education, and building trust through communication.[18] At that time, it was acknowledged that regulatory action is an option, although the white paper stated that "this could create more problems than it solves," and that "[i]deally, industry as a whole will catch on to the value of diverse trial enrollment without the need for new regulatory guidelines."[19]

B. Section 907 of the Food and Drug Administration Safety and Innovation Act

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law and, among other things, required FDA to produce a report regarding the "inclusion of demographic subgroups in clinical trials and data analysis in applications for drugs, biologics, and devices."[20] The aim of this report was to provide an analysis "addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity, is included in applications submitted to the Food and Drug Administration, and shall provide such publication to Congress."[21] FDA subsequently released its report in August 2013 and related action plan in August 2014. In its key findings in the August 2013 report, FDA found that "[w]hites represented a high percentage of clinical trial study participants for biologic, drug, and medical device applications," while "other racial subgroups were underrepresented."[22]

Subsequently, the August 2014 "FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data" set forth three priorities to ensure that clinical trial data are reflective of the eventual population of patients receiving access to medical products.[23] The priorities identified were quality, participation and transparency relative to data collection, barriers to access and to participation in clinical trials, and assurance of demographic subgroup data availability and transparency.[24] Identifying and working toward fulfilling the specific goals established within these priorities, FDA stated that "[b]y improving data quality, encouraging greater participation in clinical trials, and making demographic subgroup data more

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[17] *See generally* Meghan Coakley, Emmanuel Olutayo Fadiran, L. Jo Parrish, Rachel A. Griffith, Eleanor Weiss & Christine Carter, *Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities in Clinical Trials*, 21 J. WOMEN'S HEALTH 713 (2012).

[18] *Id.* at 716.

[19] *Id.*

[20] Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993, § 907 (July 9, 2012).

[21] *Id.*

[22] U.S. FOOD & DRUG ADMIN., FDA REPORT: COLLECTION, ANALYSIS, AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA FOR FDA-APPROVED MEDICAL PRODUCTS 5 (Aug. 2013), https://www.fda.gov/media/86561/download.

[23] *See generally* U.S. FOOD & DRUG ADMIN., FDA REPORT: FDA ACTION PLAN TO ENHANCE THE COLLECTION AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA (Aug. 2014), https://www.fda.gov/media/89307/download [hereinafter FDA ACTION PLAN].

[24] *Id.* at 2.

available and transparent, we can help to ensure that researchers, health professionals and consumers will have easy access to meaningful clinical information about medical products that will help them make informed decisions."[25] In part, as a result of this Action Plan, the agency has set forth certain guidance for sponsors in collecting demographic subgroup data.[26] Additionally, FDA argued in the Action Plan that enhancing communication efforts, particularly with community-based stakeholders, including advocacy groups, could positively impact engagement of diverse subpopulations in clinical trials.[27] More recently, Janet Woodcock echoed this sentiment, noting the agency's continued support for community engagement in increasing clinical trial diversity and stating, "[w]e have to move clinical research out into the community, and we have to support that if we're going to be successful in any way in enrolling populations who reflect this country."[28]

C. Section 610 of the Food and Drug Administration Reauthorization Act of 2017 and FDA Guidance on Enhancing the Diversity of Clinical Trial Populations

Signed into law on August 18, 2017, the Food and Drug Administration Reauthorization Act of 2017 (FDARA) amended the Federal Food, Drug, and Cosmetic Act (FDCA) to extend and revise user fees for medical products and required certain reports and plans.[29] Under Section 610 of FDARA, FDA was required to convene a public meeting on clinical trial eligibility criteria, which resulted in the workshop "Evaluating Inclusion and Exclusion Criteria in Clinical Trials" on April 16, 2018, convening various stakeholders across the healthcare system involved in the clinical trial ecosystem.[30] The focus of this workshop was not specific to the disparities in clinical trial enrollment and data collection pertaining to racial and ethnic minorities, although certain factors relevant to these populations in the United States were addressed relative to low clinical trial participation, for example, geographic location of clinical trial sites, potential financial burdens, ability to travel to clinical trial sites, and mistrust of clinical trials due to historical events.[31] Proposed solutions set forth in the workshop included transparency and communication regarding the criteria for clinical trial participation, closer scrutiny by sponsors in setting inclusion and exclusion criteria (i.e., avoiding the same inclusion and exclusion criteria across clinical trials and assessing the extent to which flexibility is permissible without

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[25] *Id.* at 17.

[26] *See, e.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA ADMINISTRATION STAFF: COLLECTION OF RACE AND ETHNICITY DATA IN CLINICAL TRIALS (Oct. 26, 2016) [hereinafter COLLECTION OF RACE AND ETHNICITY DATA IN CLINICAL TRIALS]; U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: INTEGRATED SUMMARY OF EFFECTIVENESS (Oct. 2015).

[27] FDA ACTION PLAN, *supra* note 23, at 13.

[28] Sue Sutter, *Clinical Trial Diversity Requires Community-Based Research Infrastructure, U.S. FDA's Woodcock Says*, PINK SHEET, Mar. 29, 2021.

[29] FDA Reauthorization Act of 2017, Pub. L. No 115-52, 131 Stat. 1005 (Aug. 18, 2017).

[30] *Id.* at §610(a)(1); *see generally* U.S. FOOD & DRUG ADMIN., PUBLIC WORKSHOP REPORT: EVALUATING INCLUSION AND EXCLUSION CRITERIA IN CLINICAL TRIALS (Apr. 16, 2018) [hereinafter FDA WORKSHOP REPORT].

[31] FDA WORKSHOP REPORT, *supra* note 30, at 6–7.

impacting the data overall), utilizing different types of clinical trial designs, and assessing utility of expanded access programs.[32]

The workshop further resulted in the FDA guidance, "Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs," which largely expands on the strategies outlined in the workshop report.[33] This guidance focuses on solutions for expanding inclusion and exclusion criteria for both demographic and non-demographic (i.e., patients with certain medical conditions that may be traditionally excluded from clinical trials) populations. Relative to racial and ethnic minorities, "FDA recommends that for drugs and biologics, sponsors include a plan for inclusion of clinically relevant populations no later than the end of the Phase 2 meeting" consistent with the guidance in "Collection of Race and Ethnicity Data in Clinical Trials."[34] Planning for inclusion of data for racial and ethnic minorities can lead to additional information to explain "[d]ifferences in response to medical products (e.g., pharmacokinetics, efficacy, or safety) [that] have already been observed in racially and ethnically distinct subgroups of the U.S. population," which "may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors."[35] Additionally, the guidance provides recommendations for increasing enrollment of diverse populations in clinical trials, including easing the burden of clinical trial participation, mapping out enrollment and retention strategies to ensure inclusivity (continuing with the recommendation to involve community-based strategies, public outreach, and engagement), and relying on opportunities for expanded access programs where patients may not meet the eligibility criteria for clinical trials.[36]

D. Next Steps for FDA and Industry

The biopharmaceutical industry and FDA have made commitments to improve diversity in clinical development. Biopharmaceutical companies have made public commitments to and investments in increasing diversity in clinical development and the biopharmaceutical industry trade association recently revised its clinical trial code of conduct to address diversity.[37]

Each of these efforts discussed by FDA over the past decade in public meetings, action plans, white papers, and guidance documents requires a collective, good faith effort from industry, academic medical centers and other research institutions or clinics, and other relevant stakeholders to push clinical trial diversity forward. Recently, there have been many public efforts from industry to further initiatives committing to increasing clinical trial diversity.[38] Although there is movement in the

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[32] *Id.* at 8–10.

[33] *See generally*, FDA, ENHANCING THE DIVERSITY OF CLINICAL TRIAL POPULATIONS, *supra* note 1.

[34] *Id.* at 7; *see also* COLLECTION OF RACE AND ETHNICITY DATA IN CLINICAL TRIALS, *supra* note 26.

[35] COLLECTION OF RACE AND ETHNICITY DATA IN CLINICAL TRIALS, *supra* note 26, at 6–7.

[36] *Id.* at 9–11.

[37] *See* PHARMACEUTICAL RESEARCH & MANUFACTURERS OF AMERICA (PHRMA), THE BIOPHARMACEUTICAL INDUSTRY: IMPROVING DIVERSITY & INCLUSION IN THE WORKFORCE (Dec. 2020).

[38] *See, e.g.*, PHARMACEUTICAL RESEARCH & MANUFACTURERS OF AMERICA (PHRMA), PHRMA PRINCIPLES ON CONDUCT OF CLINICAL TRIALS COMMUNICATION OF CLINICAL TRIAL RESULTS. These Principles were updated in November 2020, and took effect in April 2021, reflecting the importance and

conversation, and to a lesser extent improved inclusivity in clinical trials, we believe that even under existing statutory authority there are additional steps that FDA can take to further enhance and more actively incentivize clinical trial diversity across the industry.

IV. Implications of Making Trials More Inclusive Consistent with FDA Guidance

In the twenty years of guidance we reviewed, key guidance recommendations include: collection of data on race and ethnicity, implementation of a plan to include a more representative population of race and ethnicity prior to the pivotal studies, reducing the burden of the trial on the participants, public outreach and clearer communication, and reconsidering inclusion and exclusion criteria. Here, we consider how more representative enrollment may change the size and expected outcomes in the trial.

Given the unequal prevalence of diseases in certain racial and ethnic groups, permitting enrolling participants with more co-morbid conditions would in general make pivotal trials more accessible to non-whites provided that other barriers can be addressed. Relaxing concurrent disease exclusions, however, may also increase the chance of a negative outcome during the trial, the participant withdrawing due to an illness other than the one being studied in the trial, or the condition may interact with the indication being studied in the clinical trial. This would have an impact on the data collected to submit the drug for approval.

When a negative outcome or death occurs in a clinical trial, it is reported as an adverse event, even if it is unlikely to be related to the drug being studied.[39] Participants may be removed from the trial for serious adverse events. If there are too many adverse events, the entire clinical development program is at risk, and the product's label, if approved, would likely carry the listing of adverse events in the prescribing information.[40] When a clinical trial is stopped, not only is the cost of the clinical trial lost to the sponsor, but it may also result in a new drug never being launched or launched at a delay, which can represent millions or even billions of dollars in lost revenue and people forced to go without treatment. However, collecting and knowing information about adverse events is important to protect health and safety when the drug is on the market.

The single biggest factor that increases clinical trial costs is the number of people needed to enroll.[41] This number is typically based on the anticipated effect of the treatment relative to the placebo or comparator therapy, and the proportion of people expected to complete the trial. Both adverse events and ability to complete the required protocol can result in a participant being removed from a trial. There are a number of

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focus by industry of enhancing diversity in clinical trials. The new section of the Principles is entitled "Commitment to Enhancing Diversity in Clinical Trial Participation." *See id.*

[39] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND INVESTIGATORS: SAFETY REPORTING REQUIREMENTS FOR INDS AND BA/BE STUDIES (Dec. 2012).

[40] *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ADVERSE REACTIONS SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—CONTENT AND FORMAT (Jan. 2006).

[41] *See* Thomas J. Moore, James Heyward, Gerard Anderson & G. Caleb Alexander, *Variation in the Estimated Costs of Pivotal Clinical Benefit Trials Supporting the U.S. Approval of New Therapeutic Agents, 2015–2017: A Cross-Sectional Study*, 10 BRIT. MED. J. OPEN (2020).

therapies for which the expected response rate or presence of adverse events in clinical trials has been seen to differ by race or ethnicity, including trials of therapies to address smoking cessation, colon cancer, and cardiovascular disease.[42] As discussed previously, less flexible work and barriers to transportation are more prevalent in certain racial and ethnic groups which may impact the participant's ability to complete the required visits associated with a trial.

A. Sample Size Calculation: An Example

Consider an example: a drug under investigation is expected to achieve a successful outcome in 35% of participants, and 25% of the participants receiving the placebo will achieve that outcome. Essentially, the drug is expected to be 1.4 times as effective as the placebo in achieving a response. Furthermore, assume 15% of people enrolled in the trial will drop out. Then the sponsor must enroll a total of 383 people to generate evidence in a study that will detect a difference of that size. Then assume that the sponsor enrolls a population where both the drug effect and the placebo effect are expected to be lower, 28% and 20%, respectively, such as would occur if the population had poorer health at trial initiation relative to the first group. In this example, the active drug is still 1.4 times the effect of the placebo. Assume in the second group 20% of people will drop out or be removed. Then the sponsor must enroll 554 people, or 45% more participants relative to the higher effect comparatively to detect a difference of that magnitude. The second trial is much larger and will take longer to enroll. Even if the drop-out rates were the same at 15%, the second trial would still require 36% more participants. But the relative rate improvement in health is the same between the drug and the placebo. While this is a simple example, it illustrates the impact of expected effect size and retention of enrolled participants on trial size with a simple statistical calculation, smaller effect sizes require a larger sample to detect a difference.[43]

Sample Size	**Higher Effect**	**Lower Effect**
N to Enroll	383	554
N to Complete	325/15% drop out	443/20% drop out
Prob (Active)	35.0%	28.0%
Prob (Placebo)	25.0%	20.0%

V. CURRENT RATES OF DIVERSITY IN PIVOTAL CLINICAL TRIALS

FDA's 2020 Drug Trials Snapshot describes the demographics of the pivotal clinical trial participants of the fifty-three drugs approved in 2020. The report shows

[42] *See* Hanna K. Sanoff, Daniel J. Sargent, Erin M. Green, Howard L. McLeod & Richard M. Goldberg, *Racial Differences in Advanced Colorectal Cancer Outcomes and Pharmacogenetics: A Subgroup Analysis of a Large Randomized Clinical Trial*, 27 J. CLINICAL ONCOLOGY 4109 (2009); Anuradha Ramamoorthy, Michael A. Pacanowski, Jonca Bull & Lei Zhang, *Racial/Ethnic Differences in Drug Disposition and Response: Review of Recently Approved Drugs*, 97 CLINICAL PHARMACOLOGY & THERAPEUTICS 263 (2015).

[43] Sample size for proportion calculated to detect the difference with 80% power and 5% significance.

that 75% of trial participants were white, 8% Black, 11% Hispanic, and 6% Asian.[44] In 2019, considering the forty-eight drugs approved by FDA, of the pivotal clinical trial participants, 72% were white, 9% Black, 18% Hispanic, and 9% Asian.[45] Blacks are 13% of the U.S. population, Hispanics are 19%, and Asians are 6%.[46]

Race/Ethnicity	**Proportion of U.S. Population**	**Representation in 2020 Pivotal Trials for Approved Drugs—proportion in population**	**Representation in 2019 Pivotal Trials for Approved Drugs—proportion in population**
Black	13%	8% (-5%)	9% (-4%)
Hispanic	19%	11% (-8%)	18% (-1%)
Asian	6%	6% (0%)	9% (+3%)

In 2020, only six drugs approved, and in 2019 only two approved, had enrolled Blacks and Hispanics in a proportion equal to the U.S. population. Asians were enrolled proportionally to their representation in the population in a far greater number of trials than Blacks or Latinx.

Cancer mortality is higher in Blacks and Hispanics relative to whites, but their representation in oncology clinical trials is often lower relative to their representative proportion of the population with cancer diagnoses.[47] Representation in clinical trials for approved cancer drugs in 2020 averaged 5% for Blacks and, in trials for particular medicines, ranged from a maximum of 16% Blacks enrolled in any of the trials for one approved drug to 0% Blacks enrolled in any trials for two approved oncology drugs. Most trials for approved oncology drugs had low single digit representation from Blacks. For Hispanics, the average was 6% enrollment in oncology clinical trials; the highest rate was 11% with many trials also enrolling low single digit percentages for enrolled Hispanics in approved oncology drugs. The leading causes of death in the United States in 2018 for Blacks, Hispanics, and Native Americans was heart disease, cerebrovascular disease, and cancer.[48] Death rates from heart disease in Blacks are higher relative to whites and other race and ethnic groups.[49] However, according to the FDA 2020 drug trials snapshot, of the one drug approved for a condition related to heart disease in 2020, only 3% of the trial population was Black.

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44 U.S. FOOD & DRUG ADMIN., 2020 DRUG TRIALS SNAPSHOT SUMMARY REPORT (Feb. 2021).

45 U.S. FOOD & DRUG ADMIN., 2019 DRUG TRIALS SNAPSHOT SUMMARY REPORT (Jan. 2020).

46 U.S. Census Bureau, U.S. Census 2019.

47 *See* Cassandra Grenade, Mitch A. Phelps & Miguel A. Villalona-Calero, *Race and Ethnicity in Cancer Therapy: What Have We Learned?*, 95 CLINICAL PHARMACOLOGY & THERAPEUTICS 4 (Jan. 13, 2014).

48 MELONIE HERON, CTRS. FOR DISEASE CONTROL & PREVENTION, DEATHS: LEADING CAUSES FOR 2018, 70 NAT'L VITAL STATISTICS REPORT 4 (May 17, 2021).

49 *Number of Heart Disease Deaths per 100,000 Population by Race/Ethnicity*, KAISER FAMILY FOUND., https://www.kff.org/other/state-indicator/number-of-heart-disease-deaths-per-100000-population-by-raceethnicity-2/.

VI. THE CASE FOR REGULATORY INCENTIVES FOR RACIAL DIVERSITY IN INDUSTRY-SPONSORED CLINICAL TRIALS—EXPEDITED PROGRAMS AND BEYOND

In prior sections, we considered how following the guidance to achieve more appropriate representation of races and ethnicities in clinical trials may affect trial size and subsequently cost and trial duration. Increasing trial cost and duration can reduce the return on the sponsor's investment in the study in two ways. First, the clinical trial costs more, so even if the drug were successful, the cost net of investment in its development is reduced. Second, patents for drugs are awarded early in clinical development, typically far before the pivotal trial. If the pivotal trials take longer, there is less time for the sponsor to receive a return on their investment during the time period before a generic may enter the market and compete at a low price leveraging the originator's trial data. Therefore, in this section, we consider the potential of offering certain regulatory incentives similar to incentives that are now extended to sponsors developing medical products to address certain serious conditions where previously the return on the investment in clinical development was less certain or when there was not a sufficient market to stimulate investment in clinical development for certain disease indications.

There are existing regulatory incentives for sponsors, such as Priority Review Vouchers (PRVs) for sponsors of rare pediatric diseases or tropical disease product applications, expedited programs for sponsors developing products to treat serious conditions, and extended data exclusivity for undertaking studies in pediatric populations.[50] For instance, 21 C.F.R. Part 312, Subpart E "establish[es] procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists."[51] These procedures are further discussed in the FDA guidance entitled "Expedited Programs for Serious Conditions—Drugs and Biologics," establishing four expedited programs for serious conditions: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review.[52]

In addition to these currently available programs, FDA should consider whether it is feasible to extend access to certain expedited programs and other regulatory incentives, to sponsors engaging in and implementing data driven, good faith efforts and initiatives to include a significant number (as defined below) of racial and ethnic minorities in clinical trials. We propose the availability of the following regulatory incentives for sponsors relative to inclusion of racial and ethnic minorities in clinical trials: Fast Track Designation, Priority Review, PRV, and Pediatric Exclusivity.

There is no indication that FDA has previously planned to *require* a certain number of racial and ethnic minorities in clinical trials or specific studies of subpopulations in consideration of sponsors receiving access to expedited programs or in order for sponsors to receive approval of regulatory applications for investigation or marketing of product candidates. In establishing the final rule for New Drug Application (NDA)

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50 *See* 21 U.S.C. § 360ff; 21 C.F.R. Part 312, Subpart E.

51 *See* 21 C.F.R. § 312.80. For the corresponding subpart under the Biologics License Application (BLA) regulations, see 21 C.F.R. Part 601, Subpart E.

52 *See* FDA EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS, *supra* note 3.

format and content requirements for demographic subpopulations and Investigational New Drug (IND) applications for tabulating demographic data in IND annual reports, FDA is forthright by stating in the preamble to the Final Rule that: "This rule does not address the requirements for the conduct of clinical studies and does not require sponsors to conduct additional studies or collect additional data. It also does not require the inclusion of a particular number of individuals from specific subgroups in any study or overall. The rule refers only to the presentation of data already collected."[53] Further, in the preamble to the Final Rule, FDA addresses concerns from some commenters about the requirements to tabulate and report on subpopulation data given that such "data in these reports already have little power" with FDA, acknowledging this and underscoring its requirement for sponsors to only provide a tabulation of such data in the IND annual report.[54]

As discussed earlier, FDA and sponsors are aware of the importance of increasing the representation of racial and ethnic minorities. Beyond encouraging such representation, we believe the currently elevated discussion of clinical trial diversity within the agency and among industry sponsors and other stakeholders provides a ripe opportunity for lawmakers and regulators to consider an approach, not dissimilar to that of expedited programs for serious conditions, that would incentivize sponsors with the goal of increasing clinical trial diversity and providing greater access to racial and ethnic minorities to clinical trials (and to a larger extent, improved access to the healthcare system).

It is evident from prior FDA statements that the agency (at least currently) has no particular interest in requiring sponsors or applicants to include specific numbers of demographic subgroups in clinical trials in support of regulatory approval. In the resulting white paper from the September 2011 meeting "Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities in Clinical Trials," the following conclusion was reached with respect to the role of regulatory agencies on clinical trial design standards and diversity: "One critical aspect in regulation is the need for components that facilitate, rather than hinder, medical research. The unnecessary burden placed on trial sponsors can be felt both logistically and financially; stringent inclusion requirements make diverse patient enrollment more difficult, which then requires greater spending on recruitment efforts."[55] This sentiment is consistent throughout the November 2020 guidance document, in addition to recent statements by Acting Commissioner Woodcock on community-based, collaborative initiatives to encourage and promote clinical trial diversity.[56] Regulatory incentives, as opposed to mandates, could provide sponsors with the opportunity to approach clinical trial diversity with greater flexibility and creativity.

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[53] Investigational New Drug Applications and New Drug Applications, 63 Fed. Reg. 6854, 6854–55 (Feb. 11, 1998); *see also* 21 C.F.R. §§ 312.33(a)(2), 314.50(d)(5).

[54] *Id.* at 6857 (stating in response to commenter concerns about analysis of subpopulation data in an IND annual report that "[t]he agency is aware that many clinical trials do not contain enough patients from various subgroups to perform statistically rigorous comparisons of outcomes between subgroups. As a result, this rule does not require analysis of subgroup data in IND annual reports").

[55] SOC'Y FOR WOMEN'S HEALTH RSCH. & OFF. OF WOMEN'S HEALTH, U.S. FOOD & DRUG ADMIN., DIALOGUES ON DIVERSIFYING CLINICAL TRIALS: SUCCESSFUL STRATEGIES FOR ENGAGING WOMEN AND MINORITIES IN CLINICAL TRIALS (Sept. 22–23, 2011).

[56] *See* FDA, ENHANCING THE DIVERSITY OF CLINICAL TRIAL POPULATIONS, *supra* note 1; Sutter, *supra* note 28.

A. Potential Expansion, by Regulation, of the Qualifying Criteria for Fast Track and Priority Review

Unlike in 21 C.F.R. Part 312, Subpart E (with respect to drugs intended to treat life-threatening and severely debilitating illnesses), there is no clearly stated intention to expedite development of medical products that include significant enrollment of racial and ethnic minorities in clinical trials, regardless of the disease indication of such products. The IND regulations only mention race once in 21 C.F.R. § 312.33(a)(2) outlining the requirements for data tabulation in IND annual reports.[57] Similarly, in the NDA regulations, race is referenced in relation to both clinical data and safety information data tabulations under 21 C.F.R. § 314.50(d)(5).

FDA draws its statutory authority for Fast Track and Priority Review from 21 U.S.C. § 356(b) and the Prescription Drug User Fee Act (PDUFA), respectively, which it has used as the basis for implementing regulations on expedited programs and related guidance. Establishing any regulatory intention to develop or expand expedited programs to be applicable to sponsors reaching the "significant" threshold would be subject to notice and comment rulemaking. Feasibly, such a new rule would fit into the current framework regarding data tabulation and collection under the IND annual reports and NDA clinical data rules. This can open up ripe discussion in the comments with the expectation that feedback would be received from a variety of stakeholders, potentially suggesting even more expansive ideas than offered here on how expedited programs could be made available to sponsors relative to achieving clinical trial diversity.

FDA could propose to expand the criteria by regulation for both expedited programs (and other regulatory incentives discussed later) to include investigational drug products where clinical trials are conducted that enroll and retain a significant number of racial and ethnic minorities. The time period for enrollment and retention could be established in the relevant clinical protocol. In this scenario, a proposed definition of a significant number of racial and ethnic minorities included in a clinical trial, for purposes of sponsors potentially qualifying for the application of an expedited program (or other regulatory incentive as may be determined by FDA), could be defined as:

> the number of racial and ethnic minorities commensurate to their respective representation in the greater population based on the demographic numbers from the latest U.S. Census (2020), as well as other relevant, available epidemiological data identifying the number of racial and ethnic minorities impacted by the disease indication being studied in the clinical trial, and other applicable standards as may be determined by the agency and its experience and understanding of subpopulation data analyses.

In a notice and comment rulemaking procedure, providing this definition of "significant" would be important so that the agency can gain additional understanding

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[57] *See* 21 C.F.R. § 312.33(a)(2) ("The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.").

as to whether it may be considered prohibitive or if there are other potential barriers to meeting this threshold.

In assessing which available expedited programs might be expanded to be applicable for sponsors achieving certain parameters for clinical trial diversity, we believe they are Fast Track Designation and Priority Review. To qualify for Fast Track Designation, as set forth in the "Expedited Programs for Serious Conditions" guidance, a sponsor must show that the drug in development is "intended to treat a serious condition and nonclinical or clinical data demonstrate the potential to address unmet medical need" or the drug "has been designated as a qualified infectious disease product."[58] Sponsors are required to submit a request for Fast Track with the IND application or with the pre-NDA or pre-Biologics License Applications (BLA) meeting.[59] The benefits for Fast Track, if granted, include increased meetings with the FDA review team throughout the clinical development phase, potential for Priority Review, and rolling review of the marketing application.[60] There are a few instances where a sponsor may qualify for Priority Review, including: having "an application [] for a drug that treats a serious condition, and if approved, would provide a significant improvement in safety or effectiveness; or any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A; or an application for a drug that has been designated as a qualified infectious disease product; or any application . . . for a drug submitted with a priority review voucher."[61] Requests for Priority Review are submitted with an NDA or BLA and, if granted, give the sponsor an abbreviated review clock of six months instead of the ten-month standard review for marketing applications.[62]

For Fast Track Designation, this significant number can be identified and discussed with FDA in either the IND or pre-NDA/BLA meeting (where more data would be collected). In an IND submission, sponsors can provide detailed information by way of project plans for enrollment and retention of racial and ethnic minorities that would lead to reaching the significant threshold. In a pre-NDA or pre-BLA meeting, sponsors would present a summary of demographic data that would demonstrate significant enrollment and retention of racial and ethnic minorities, as well as prepare descriptions and explanations to FDA (if such plans were not presented in the IND) as to how the sponsor was able to achieve significant enrollment and retention. For Priority Review, data providing evidence that a sponsor was able to meet the significant threshold should be available in the NDA or BLA submission in support of this request.

We do not propose any modification or expansion of the actual features of either Fast Track Designation or Priority Review (that is, the benefits gained for qualifying applicants). Rather, we propose that it would be a logical extension within the bounds of FDA's current statutory authority in support of sponsors enrolling and retaining significant numbers of racial and ethnic minorities in clinical trials of a drug product. This designation would expand expedited programs regardless of whether the product under development is intended to treat a serious condition and address an unmet medical need provided it met a diversity of enrollment criteria.

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58 FDA EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS, *supra* note 3, at 7.

59 *Id.* at 8.

60 *Id.* at 9–10.

61 *Id.* at 7.

62 *Id.* at 8.

B. Priority Review Vouchers

FDA currently has the authority to issue PRVs to encourage development of drug products treating rare pediatric diseases and tropical diseases, as established in FDASIA and the Food and Drug Administration Amendments Act of 2007 (FDAAA), respectively.[63] PRVs are issued at the time of approval of a drug product, which the applicant can redeem for Priority Review of a future product. The applicant may also opt to sell the PRV to another company.[64]

PRVs are another incentive that could encourage sponsors to increase the inclusion and significant representation of racial and ethnic minorities in clinical trials. Given that FDA's authority to issue PRVs is established through statutes, however, this approach is likely more difficult to achieve than setting forth additional regulatory incentives in expedited programs through notice and comment rulemaking. Congressional gridlock is a notable barrier, especially where specific legislation dealing with (in part) addressing inequities along the lines of race and ethnicity is likely to be met with some resistance and controversy.

Such proposed legislation, like the PRV statutes set forth under FDASIA and FDAAA, could be paired with, for example, other legislation such as PDUFA Reauthorization. In the commitment letter for PDUFA VII, for example, FDA has identified the use of digital health as a way to support drug development including the ability of digital health to "enable the conduct of decentralized clinical trials (DCTs)," which is a mechanism whereby greater inclusion of racial and ethnic minorities in clinical trials could be achieved.[65] Under such legislation, it would be important to define significant numbers of racial and ethnic minorities, link eligibility for PRVs (whether receiving and using a PRV in relation to an application) to clinical data, and ensure there is a general reference to disease incidence in the relevant patient populations in assessment of whether to issue a PRV.

Guidance from FDA, if such legislation is enacted, could cover specific illnesses where PRVs may be prioritized where sponsors achieve significant enrollment and retention of racial and ethnic minorities in a clinical trial. For example, FDA could identify certain centralized nervous system disease indications (e.g., smoking cessation, depression, and other mental health disorders), cardiovascular diseases, or dermatological disorders. Finally, this type of PRV could serve as a compelling economic incentive for applicants in consideration of further programs for clinical trial diversity initiatives in drug development programs.

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[63] *See* 21 U.S.C. §§ 360ff, 360n; Food and Drug Administration Amendments Act of 2007, Pub. L. 110-85, 121 Stat. 823 (2007).

[64] There is an active marketplace for purchasing PRVs, where applicants that have received PRVs from FDA may sell to other companies in exchange for millions of dollars. The market value of PRVs has ebbed and flowed over the past several years, but sales prices between $67 million and up to $350 million illustrate the value to many companies seeking to expedite their drug development programs. *See* Michael Mezher, Zachary Brennan & Alexander Gaffney, *Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers*, REGULATORY FOCUS (Feb. 25, 2020), https://www.raps.org/regulatory-focus/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fdas-priority-review-vouchers.

[65] U.S. FOOD & DRUG ADMIN., PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2023 THROUGH 2027, https://www.fda.gov/media/151712/download.

C. Pediatric Exclusivity for Inclusion of Racial and Ethnic Minorities in Clinical Trials

Pediatric exclusivity was established in the Food and Drug Administration Modernization Act of 1997 (FDAMA) in order to encourage more collection of information about how drugs work in children and subsequently include pediatric use in the product labeling.[66] Through a Written Request, FDA has the authority to ask a trial sponsor to study the drug in children, or a clinical trial sponsor can make a proposal to FDA asking for it to issue a Written Request to authorize a pediatric study.[67] The clinical trial sponsor, however, is not required to conduct a pediatric study if FDA issues a Written Request. If a sponsor undertakes the study meeting FDA's parameters outlined in the Written Request, it is granted an additional six months of protection on their clinical trial data.[68]

Pediatric exclusivity, or rather clinical trial diversity exclusivity, in this context would not be relegated specifically to pediatric studies but could be used to encourage sponsors to undertake clinical trials in racial and ethnic minority populations where FDA or the sponsor identify a specific need to collect additional data. A Written Request from FDA for additional clinical trials could, for instance, be specifically applicable to diseases where incidence or mortality is greater in certain racial or ethnic subgroups. Unlike pediatric studies, the data collected in expanded clinical trials including larger populations of racial and ethnic minorities would not necessarily result in a labeling change (although the six-month exclusivity would apply) but would offer healthcare providers, insurers, and other stakeholders greater insight into how a drug works.

Similar to issuance of PRVs by FDA, clinical trial diversity exclusivity as an incentive for achieving racial and ethnic diversity in clinical trials would require legislative activity with parameters identified at a high level for sponsors seeking to qualify for this benefit. The primary goal of this incentive would be to stimulate evidence generation in a postmarket environment. This contrasts with providing expanded regulatory incentives in expedited programs designed to encourage greater diversity in clinical trials before a drug is approved.

D. Recent Legislative Developments

On February 3, 2022, Members of the House of Representatives Anna G. Eshoo (D-CA), Chairwoman of the Energy and Commerce Health Subcommittee, Brian Fitzpatrick (R-PA), and Robin Kelly (D-IL) introduced the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act, which aims to increase diverse participation in clinical trials.[69] At a high level, the DEPICT Act, in part, sets forth

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[66] *See* 21 U.S.C. § 355a.

[67] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: QUALIFYING FOR PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 4 (Sept. 1999) [hereinafter FDA, QUALIFYING FOR PEDIATRIC EXCLUSIVITY]; *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A)*, U.S. FOOD & DRUG ADMIN. (Mar. 1, 2022), https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently.

[68] FDA, QUALIFYING FOR PEDIATRIC EXCLUSIVITY, *supra* note 67, at 13.

[69] Diverse and Equitable Participation in Clinical Trials Act, H.R. ____, 117th Cong. § 1 (2022), https://eshoo.house.gov/sites/eshoo.house.gov/files/ESHOO_058_xml.pdf.

requirements for FDA to promulgate regulations that would require drug and device clinical trial sponsors to develop diversity plans for clinical trials and to exercise its authority to require post-approval or postmarketing surveillance studies in demographic subgroups that the agency may determine "did not meet the applicable targets of enrollment."[70] Additionally, the DEPICT Act would require FDA to deliver an annual progress report on diversity in clinical trials, convene a public meeting on the impact of the COVID-19 pandemic and the permitted flexibility, conduct community engagement activities with the goal of achieving greater representation of racial and ethnic minorities in clinical trials, and award grants to encourage greater participation in clinical trials by community health centers.[71]

The DEPICT Act expands beyond FDA's current authority, which does not explicitly require sponsors to enroll and retain racial and ethnic minorities in pivotal clinical trials. Additionally, the DEPICT Act places more prescriptive responsibility on FDA to ensure that diversity in clinical trials is at the forefront of the agency's mission, outside of more recent actions of the past several years.

In balancing the proposed sponsor mandates such as those in the DEPICT Act, regulatory incentives should be considered, for example, where FDA requires post-approval studies in underrepresented demographic subgroups. It is imperative that any such legislation provide incentive pathways for sponsors to fulfill these proposed mandates. The value proposition of regulatory incentives is such that sponsors would be permitted to proactively and frequently engage with FDA, whether during pre-approval or post-approval studies, to ensure they are not only meeting the necessary enrollment and retention requirements, but the requirements are supporting enhanced quality and representation through data collection in a clinical trial.

E. Potential Pros and Cons of Regulatory Incentives

We consider a range of regulatory incentives and how they could be modified to encourage greater diversity in clinical trial enrollment, among them: Fast Track Designation, Priority Review, PRVs, and Extended Data Exclusivity. While all could have the benefit of increasing representation in clinical trials, each would be costly to the U.S. taxpayer and have a different effect on where and how research is conducted.

Fast Track and Priority Review could create an incentive to enroll more diverse participants in clinical trials pre-drug approval. However, a sponsor does not know for certain if these incentives would be offered so there may be an unwillingness to make the investment without any such certainty. Furthermore, to the extent that diverse trials are bigger or take longer to recruit, these programs could delay the collection of data to achieve new drug approvals. But, if successful, the data would be more diverse when the drug is put into the market.

On the other hand, Extended Data Exclusivity is proposed for trials conducted after the drug is approved and the sponsor has certainty that the exclusivity will be granted even if the data does not show an effect in the identified population. If additional effort or time are needed to collect data on a more representative population, the sponsor could conduct that trial after the drug is on the market, possibly achieving efficiencies by focusing on certain populations. However, the data would not be as representative at launch if relying on the postmarket data exclusivity incentive.

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[70] *Id.* § 3, at 9.

[71] *Id.* §§ 4–7.

These types of incentives could skew investment to focus on therapeutic areas where there is a greater non-white population in the underlying condition. Additionally, it may simply pay for behavior that would have been occurring without the incentive as trials sponsors may be responding to public interest in greater diversity already. If, however, the incentive is meaningful, sponsors will be willing to pay more to trial sites to update their approach to recruitment to achieve more equitable representation. Furthermore, this may emphasize the focus of trial research on new and recent drug approvals where the incentives would be meaningful at the cost of trials where older drugs are studied.

There is a cost to offering incentives. When drugs are approved more quickly, there is more time for the branded medicine to be in the market without a generic competitor in a less competitive pricing environment. For example, in 2002 the U.S. Congressional Budget Office (CBO) estimated that the pediatric data exclusivity extension of six months would increase costs to the federal government by $320 million from 2002–2011.[72] The CBO estimated the cost of extending the pediatric rare disease PRVs would be around $12 million over five years,[73] and a program to offer PRVs for medical countermeasures would increase federal costs by $94 million over five years.[74] The CBO estimate is an understatement of the total costs because faster approval of new drugs or longer time in the market also imposes costs on non-governmental insurers and payors.

There are several potentially positive outcomes to FDA establishing regulatory incentives for clinical trial diversity, but some may opine that any regulatory involvement—whether providing an incentive or mandate—should be avoided. In our current political environment, FDA could receive pushback from those who believe that providing regulatory incentives to sponsors for achieving clinical trial diversity is regulatory overreach and unnecessary given the agency's already-stated values, for example, in the November 2020 guidance and the importance and focus on efforts by industry to increase clinical trial diversity.

FDA could face pushback given the tense discussions around race and diversity, equity, and inclusion at the local and national level including with respect to public education, government programs, and corporate initiatives. Finally, regulatory incentives for clinical trial diversity could trigger challenges under *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, for example, questioning whether deference should be granted to FDA's interpretation of the FDCA to include establishing a regulatory framework for what may be perceived as diversity initiatives with respect to medical product development.[75] Given the current makeup of the federal courts, *Chevron* deference may be on borrowed time. What this could mean for these, or similar proposed regulatory incentives, remains to be seen.

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[72] Congressional Budget Office (CBO), Pay-As-You-Go Estimate, S. 1789, Best Pharmaceuticals for Children Act as cleared by Congress on December 18, 2001, and signed into law by the President on January 4, 2002 (Jan. 14, 2002).

[73] CBO, Cost Estimate, S. 1878, Advancing Hope Act of 2016 as reported by the Senate Committee on Health, Education, Labor, and Pensions on April 5, 2016 (July 7, 2016).

[74] CBO, Cost Estimate, S. 2055, Medical Countermeasure Innovation Act of 2016 as reported by the Senate Committee on Health, Education, Labor, and Pensions on March 14, 2016 (Aug. 8, 2016).

[75] *See generally* Chevron U.S.A., Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837 (1984).

VII. CONCLUSION

As there is continued discussion on how to increase clinical trial diversity, regulatory incentives can serve as a catalyst for more innovation, collaboration, and to another extent, competition in the industry. Indeed, regulatory incentives are market incentives. Additionally, while regulatory incentives can impact clinical trial diversity, there are other potentially positive outcomes, especially racial and ethnic minorities participating in clinical trials having access to highly trained and experienced physicians in the healthcare system that may not be readily available to some depending on the geographic area in which they reside. This is not a long-term remedy, although opportunities for more constructive interactions with the healthcare system and healthcare professionals in a clinical trial setting could provide solutions to address disparate health outcomes beyond development of new drug products and therapies. Further, by establishing regulatory incentives for clinical trial diversity, beyond stated goals and policy or guidance documents, FDA has an opportunity to fulfill its mission in an inclusive manner by truly "advancing the public health."[76]

Overcoming the barriers to racial and ethnic minority participation in clinical development will be expensive, although there are existing regulatory incentives that FDA can leverage to encourage drug development and data collection for certain diseases and patient populations. These regulatory tools, including Fast Track Designation, Priority Review, PRVs, and Extended Data Exclusivity, should be considered as potentially viable incentives to sponsors for expanding clinical trial diversity. Because of the legacy of racism and disenfranchisement in the United States, there is significant variability in the health status and presence of disease in different races and ethnicities, even if there are not clearly defined biomarker or genetic differences. Differential living environment, access to capital, and access to healthcare means that the expectation of an outcome from a particular treatment is heterogenous across different groups in a way that affects pivotal trial size and costs. Even with advances in clinical trial approaches, such as digitally enabled trials and community-level outreach, without additional incentives to change current behavior, the environment will continue to work against diversity in clinical development.

[76] *What We Do*, U.S. FOOD & DRUG ADMIN. (Mar. 28, 2018), https://www.fda.gov/about-fda/what-we-do.