April 29, 2024

Re: Public Comment on Federal Docket # FDA–2016–D–3561
"Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products"

Submitted to: U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20990

To all in the Food and Drug Administration, including the Office of Minority Health and Health Equity, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research,

The USA Patient Network (USAPN) – a grassroots coalition of patients, caregivers, affected families, and community-based patient advocates from across the U.S., operating without industry or philanthropy funding or conflicts of interest, and united to ensure medical treatments are as safe, effective, and affordable as possible – **applauds this overdue focus on racial and ethnic diversity in clinical trials**. The USAPN also **urges several additions to the current draft guidance** for the Agency and its Industry partners, as part of our representation of hundreds of nationwide members and dozens of affiliate organizations through which members serve on FDA Advisory Boards, patient-centered outcomes research initiatives, and continuing medical education initiatives, with a cross-sectional focus on drugs, devices, and allocating appropriate resources and provisions to improve the quality of scientific study and FDA approval pathways to equitably place patients' well-being at the center of all regulatory decision making.

A Baseline, Not a Bargaining Chip

Clearly, the FDA is seeking to honor and right the wrongs of multiple, overlapping, prior histories of violence and dishonesty in clinical trials in the United States, as fueled by medical racism and ethnocentrism.[1] It will take decades of ongoing work to redress legacies of countless predominantly white institutions that extracted health, wealth, and life from Black, Indigenous, and immigrant populations in the name of medical science and experimentation, to help white scientists and industry leaders accrue status and profit.

In "II. Background" of the draft guidance, histories of harm stemming from lack of clinical trial diversity and ethical guidelines are mentioned **(**lines 104-113), and the USAPN urges an **additional note or footnote** in this section that emphasizes two core truths:

(1) **Building trust with underrepresented, minority racial and ethnic populations** in clinical trial diversity efforts **requires increased transparency and accountability** in trials.

(2) **Public trust in clinical trial diversity is built** when drugs and device studies **clarify specific goals** to **increase overall survival, reduce side effects** including injuries and toxicities, and/or **improve affordability** of effective, quality of life- and/or life-prolonging medical interventions.

[1] Nuriddin, Ayah, Graham Mooney, and Alexandre I.R. White. 2020. "Reckoning with Histories of Medical Racism and Violence in the USA." The Lancet, Perspectives: The Art of Medicine. 396 (10256): 949–51. doi.org/10.1016/S0140-6736(20)32032-8.

Relationships of trust are the basis of ensuring ethically diversified participation in clinical trials, and the draft guidance's focus on "*Swift development and approval of medical products" as a "highly desirable goal for the public, sponsors, and the FDA*" through "*increasing reliance on relatively small studies, intermediate endpoints, and innovative study designs to expedite development and approval of medical products*" (lines 115-118) is not only limited to "*rare diseases and for serious and life-threatening conditions*" as noted, but has bled into multiple fast track loopholes for a broad spectrum of drugs and devices, causing well documented recent controversies for patient safety, medical efficacy, and public crises of confidence in the FDA's approval pathways.

As just three examples among many, a demonstrated lack of benefit for overall survival, reduced side effects, or increased affordability over current standards of care in trials focused on surrogate endpoints or otherwise granted accelerated approval has resulted in numerous recently approved oncology drugs that do not improve length or quality of life,[2] dangerous brain swelling with the Alzheimer's drug Aduhelm,[3] and Makena's lack of efficacy in preventing preterm births.[4] Each of these common health concerns – as amplified by lack of transparency and accountability in FDA clinical trials in these and other cases – are already disproportionately fatal or injurious to Black, Brown, and other underrepresented, minority ethnic and racial populations in the U.S.,[5] and reflect the USAPN and many partner organizations' sense of urgency around ensuring clinical benefit and patient safety, especially for populations already experiencing health inequities.

The USAPN additionally hopes to ensure that the FDA or its various advisory panels are **not pressured to incentivize clinical trial diversity by cutting regulatory corners** as suggested in recent years by scholars and industry advocates.[6] The simple, overdue fact of diverse trial enrollment, to include racial and ethnic diversity, must not be reason to enable:

- Eligibility for fast-track approval
- Underfund the FDA with reduced or waived fees for sponsors
- Extended patents for market exclusivity, or tax breaks to build market share

As the draft guidance is not yet binding for the FDA or industry, requirements for racial and ethnic diversity in clinical trials must remain an end in themselves, not a means to an end. Per "4. Specific plan of action to enroll and retain diverse participants" (line 226, page 9), the FDA must **ensure protection for vulnerable populations** such as **unhoused** or **incarcerated people**, where disproportionately high representation of racial and ethnic minorities reflects the effects of racism and ethnocentrism in the United States. Sponsors' efforts to enroll and retain diverse racial and ethnic populations

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[2] Rupp, Tracy, Zuckerman, Diana. 2017. "Quality of Life, Overall Survival, and Costs of Cancer Drugs Approved Based on Surrogate Endpoints." *JAMA Internal Medicine.* 177(2):276-277. <doi:10.1001/jamainternmed.2016.7761>

[3] Salloway S, Chalkias S, Barkhof F, et al. 2022. "Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients With Early Alzheimer Disease." JAMA Neurol. 79(1):13–21. <doi:10.1001/jamaneurol.2021.4161>

[4] Rubin R. (2020). Confirmatory Trial for Drug to Prevent Preterm Birth Finds No Benefit, So Why Is It Still Prescribed?. *JAMA*, *323*(13), 1229–1232. <https://doi.org/10.1001/jama.2020.1486>

[5] National Cancer Institute. 2024. "NCI: Health Disparities and Cancer." <www.cancer.gov/about-cancer/understanding/disparities>, National Institute on Aging. 2022. "Alzheimer's Disease and Related Dementias: Population Studies and Health Disparities." <www.nia.nih.gov/2021-2022-alzheimers-disease-related-dementias-scientific-advances/population-studies-health>, Brown J, Chang X, Matson A, et al. 2023. "Health disparities in preterm births. Front Public Health. 2023;11:1275776." <doi:10.3389/fpubh.2023.1275776>

[6] Hwang, Thomas J., Brawley, Otis W. 2022. "New Federal Incentives for Diversity in Clinical Trials." N Engl J Med. 387:1347-1349. <https://www.nejm.org/doi/full/10.1056/NEJMp2209043>

must also ensure vulnerable populations receive adequate support and information to give true informed consent and that any injuries sustained will be met with appropriate, reparative healthcare.

Specificity is Vital

In both clinical trial and observational study design, standardized language documenting participants' race and ethnicity can ensure more detailed data reflects the lived realities that affect health outcomes. The USAPN is **pleased that more than one racial/ethnic category choice is allowed** for demographic data collection. Additional, more precise information can be gained when ethnicities including "Middle Eastern or North African" are included as subsets for self-identified white people, in addition to "White - European" (as part of improving upon Statistical Policy Directive No. 15) . Given updates to SPD 15, the USAPN recommends that the FDA's draft guidance **consistently require** the most **detailed, precise racial and ethnic information in FDA questionnaires** to create meaningful, granular data, which in turn can clarify the difference between race and ethnicity and the effects of racism and ethnocentrism in clinical interactions and outcomes.[7]

To prevent further confusion, the FDA must also clarify in its draft guidance that "race" and "ethnicity" do not represent meaningful biological differences as categories on their own, but do reveal the effects of racism and ethnocentrism manifest in health outcome differences relevant to clinical trials. This is due to well-documented effects of **health weathering due to racism and ethnocentrism** — for example, resulting in higher rates of heart disease, hypertension, and cancer in Black men, women, and gender nonbinary people in the U.S.,[8] as well as **infrastructural barriers to healthcare access**[9] and **healthy environments**[10] for racial and ethnic minorities. Additionally, the ways in which white **clinicians may communicate differently about clinical trials** with racial and ethnic minorities, to include considerations of risks, benefits, and informed consent, can be affected by implicit racial and ethnic bias – meaning that it is not intentional but is measurable on the part of clinicians, necessitating institutional policy changes and resources to address persistently unequal healthcare provision.[11]

Among other directions already noted in the draft guidance, the USAPN hopes **next steps for promoting clinical trial diversity** at the FDA will include:

- Opportunities to report biological sex in addition to gender identity, to document outcomes for populations whose **gender may differ from sex assigned at birth**[12]

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[7] Metzl, Jonathan M, Hansen, Helena. 2014. "Structural competency: Theorizing a new medical engagement with stigma and inequality." *Social Science & Medicine* 103:126-133.

[8] Goosby, Bridget J., and Chelsea Heidbrink. 2013. "Transgenerational Consequences of Racial Discrimination for African American Health." Sociology Compass 7 (8): 630–43. <doi.org/10.1111%2Fsoc4.12054>

[9] Moore, Alexis, Earp, Jo Anne L. 2008. "The Long Reach to Basic Healthcare Services" in *Patient Advocacy for Health Care Quality: Strategies for Achieving Patient-Centered Care*. Earp, Jo Anne L., French, Elizabeth A., Gilkey, Melissa B. Sudbury: Jones and Bartlett Publishers.

[10] Lerner, Steve. 2010. Sacrifice Zones: The Front Lines of Toxic Chemical Exposure in the United States. Cambridge: MIT Press.

[11] Matthew, Dayna Bowen. 2015. *Just Medicine: A Cure for Racial Inequity in American Health Care.* New York: New York University Press.

[12] Shepherd, R., Bretherton, I., Pang, K. et al. 2022. "Gender-affirming hormone therapy induces specific DNA methylation changes in blood." *Clin Epigenet* 14, 24. <https://doi.org/10.1186/s13148-022-01236-4>

- Emphasis on **trial inclusion of populations most likely to be prescribed a drug or device**, such as people **aged 65 and older** and new classes of blood thinners[13]
- Prioritizing **adverse event reporting as the norm** rather than an optional afterthought, including to better inform clinicians' future prescribing practices[14]

In particular, as the USAPN envisions a future in which **adverse event reporting** and **post-market studies** are a **basic requirement** for all drugs and devices approved by the FDA (refer to footnote 24, page 5, "*In the event that recruitment goals are not met despite best efforts, sponsors should discuss with FDA a plan to collect this data in the post-market setting."*). Standardized adverse event reporting with collection of race and ethnicity data would offer **corrective action** on prior approved drugs and devices whose **trials have lacked meaningful racial, ethnic, and other core forms of diversity,** including age, gender, disability, and reproductive status. Documenting adverse events and conducting appropriate, overdue post-market studies that clarify patients' racial, ethnic, and other forms of diversity can ensure future, actionable information on which populations can best benefit from drugs and devices already on the market, and where adjustments for patient-centeredness must be made.

Thank you for your time, respect, and action on behalf of public health,

Marie Alison Garlock

Marie Garlock, PhD
On behalf of USA Patient Network
usapatientnetwork.org

[13] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1994. "Guideline for Industry – Studies in Support of Special Populations: Geriatrics." ICH-E7.<www.fda.gov/media/71317/download#:~:text=Drugs%20should%20be%20studied%20in,later%20created%20by%20the%20 drug>

Lau SWJ, Huang Y, Hsieh J, et al. "Participation of Older Adults in Clinical Trials for New Drug Applications and Biologics License Applications From 2010 Through 2019." JAMA Network Open. 2022;5(10):e2236149.< doi:10.1001/jamanetworkopen.2022.36149>

Example, post-market studies on intracranial hemorrhage and non vitamin-K antagonist blood thinners in populations 65 and older: Ray WA, Chung CP, Stein CM, et al. 2021. "Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation." JAMA. 326(23):2395–2404. <https://jamanetwork.com/journals/jama/fullarticle/2787319>

[14] Kesselheim, Aaron S., Woloshin, Steven, Eddings, Wesley, Franklin, Jessica M., Ross, Kathryn M. Schwartz, Lisa M. 2016. "Physicians' Knowledge About FDA Approval Standards and Perceptions of the 'Breakthrough Therapy' Designation." *JAMA*. 315(14):1516-1518.