FDORA: IMPLICATIONS FOR TODAY'S CLINICAL RESEARCHERS AND INDUSTRY

D.R.I.V.E. INITIATIVE

FEBRUARY 23, 2024

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FDORA

- In December 2022, Congress passed the Food and Drug Omnibus Reform Act (FDORA)
  - Section 3601 of FDORA requires that sponsors submit a Diversity Action Plan for a Phase III study or other pivotal study. The Diversity Action Plan should include
    - The sponsor's goals for enrollment in the clinical study,
    - sponsor's rationale for such goals,
    - An explanation of how the sponsor intends to meet such goals
  - The Diversity Action Plan should be disaggregated by age, sex, race, and ethnicity characteristics of clinically relevant study populations . May include characteristics such as geographic location and socioeconomic status
  - Requires that FDA issue or update guidance on diversity action plans and conduct public workshops to enhance clinical study diversity

Food and Drug Omnibus Reform Act of 2022 (FDORA) included as part of the Consolidated Appropriations Act (dec 2022) (P.L. 117-328)

Current State of Affairs

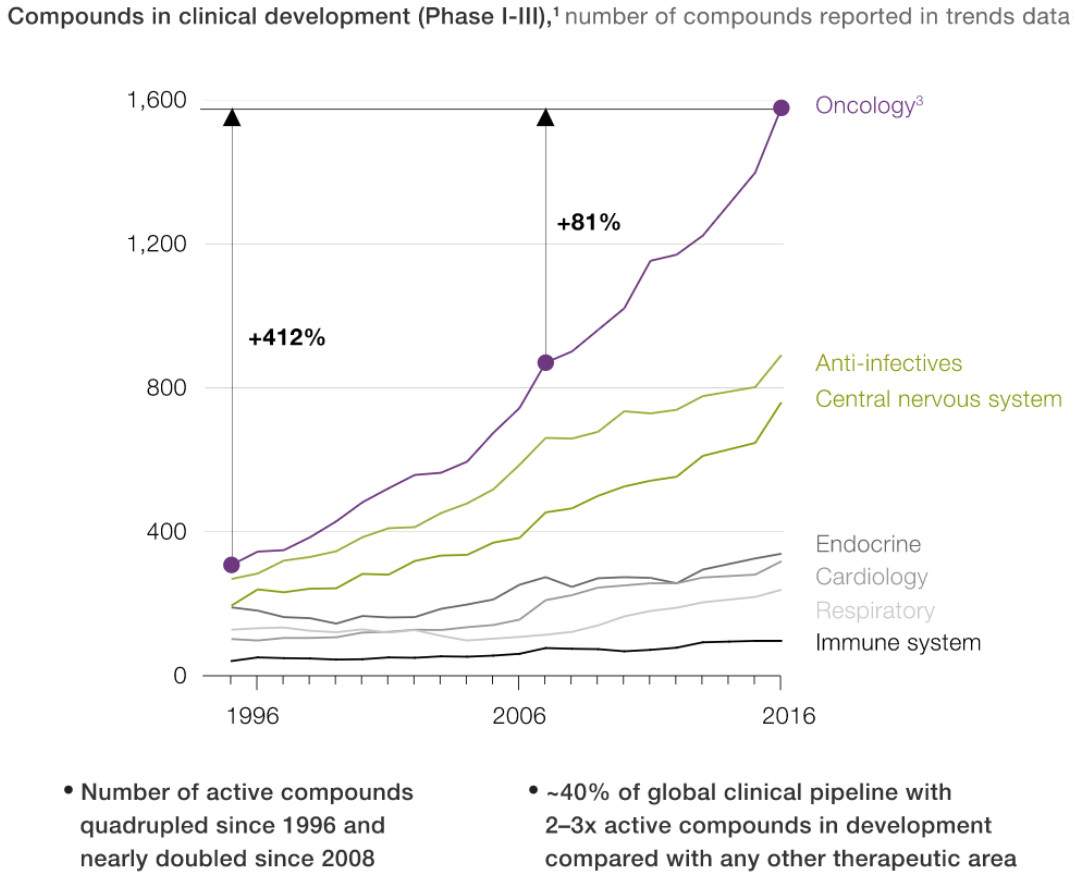
In 2023, the FDA approved…

14 New molecular entities (NMEs) for Oncology

51 Supplemental approvals for additional oncology indications or patient populations

15 505(b)2 applications

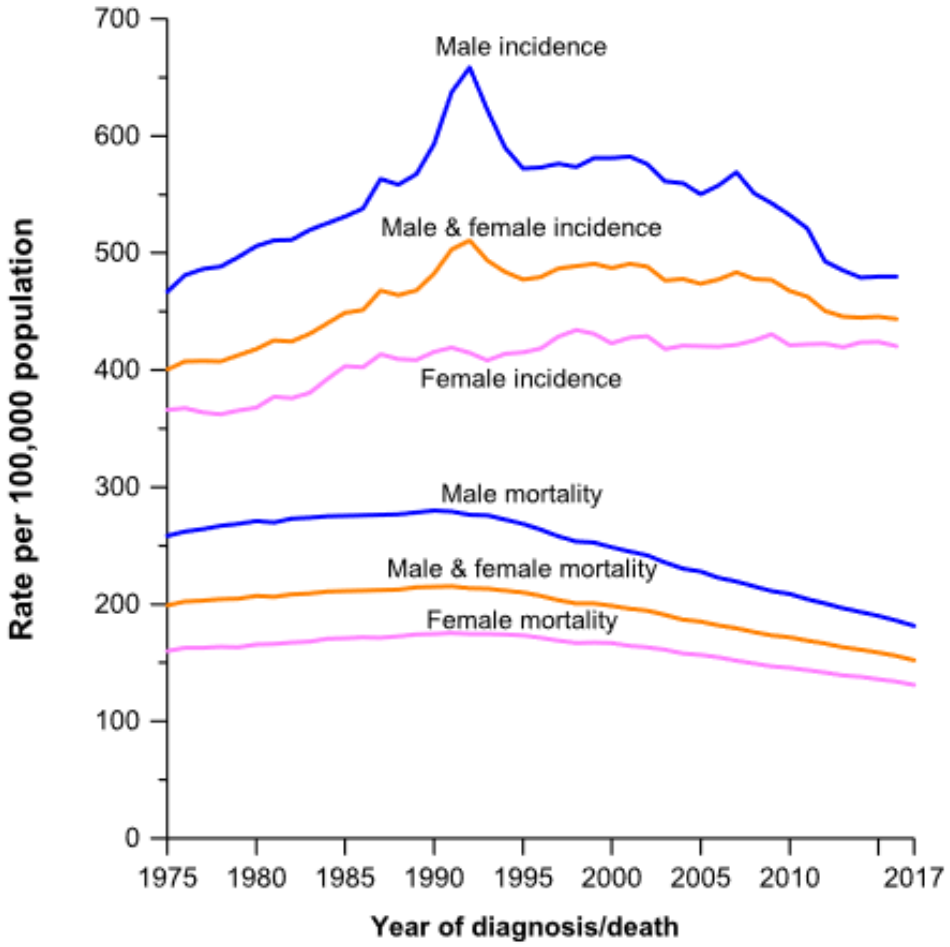
1 Biosimilar



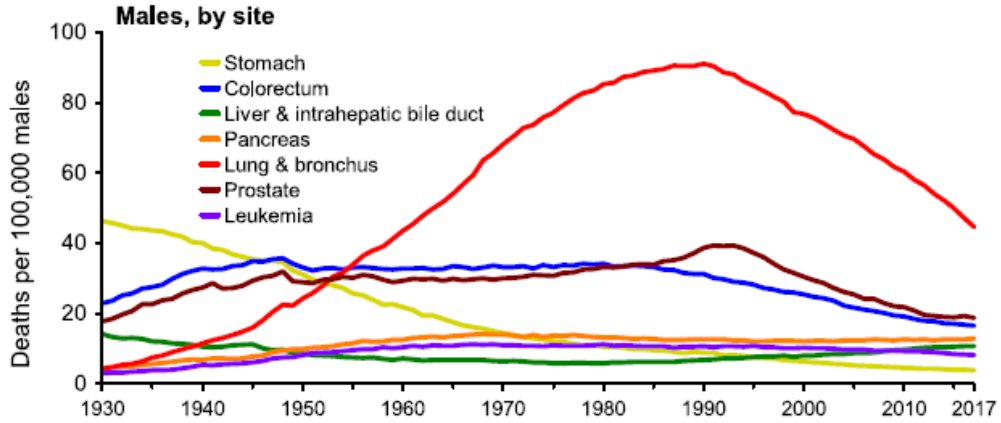
Accessed at https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/pursuing-breakthroughs-in-cancer-drug-development on 2/4/2020

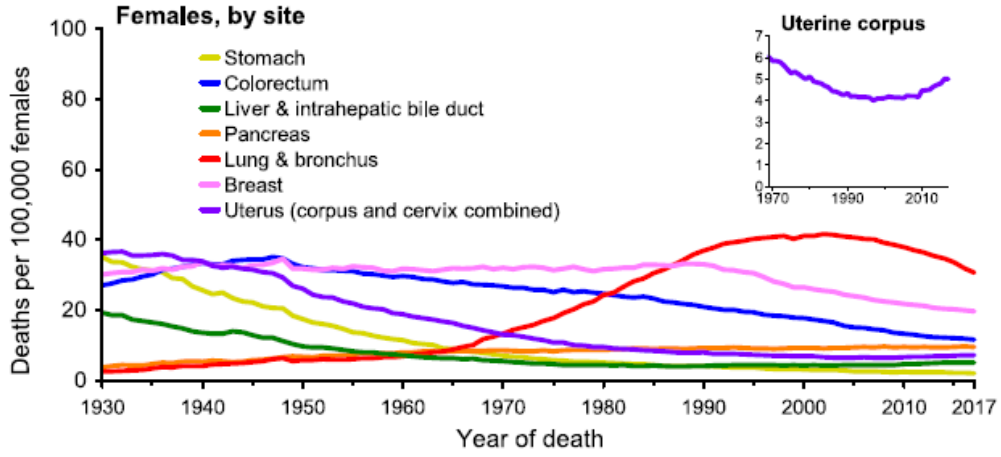
Improvements in Outcomes

Cancer Incidence and Mortality



Site-Specific Mortality





Siegel et al. Ca Caner Clin 2020; 70

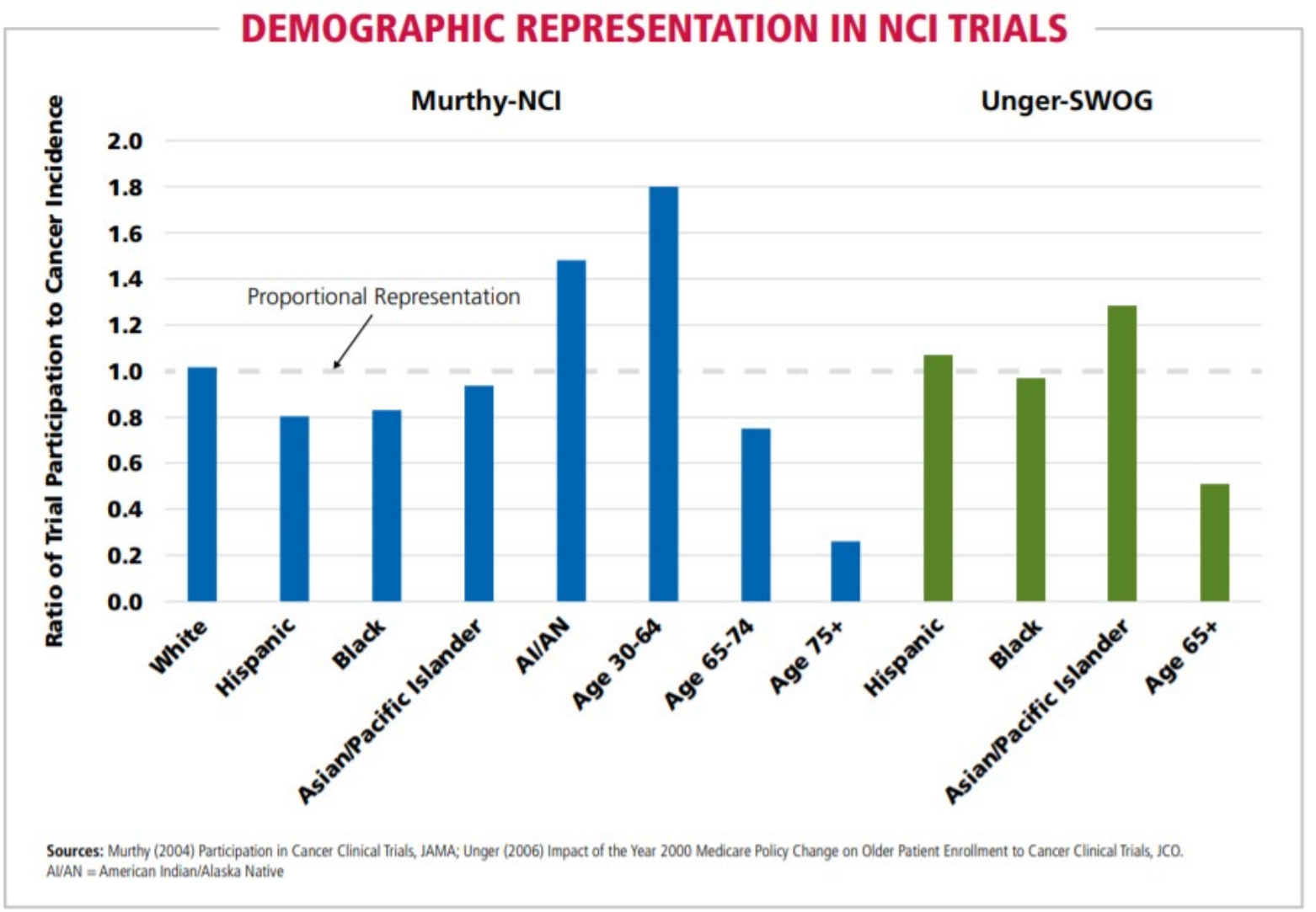
Outcomes by Race and Ethnicity

Cancer Incidence and Mortality by Race and Ethnicity

	ALL RACES COMBINED	NON-HISPANIC WHITE	NON-HISPANIC BLACK	ASIAN/PACIFIC ISLANDER	AMERICAN INDIAN/ ALASKA NATIVE[a]	HISPANIC
Incidence, 2012-2016						
All sites	448.4	464.6	460.4	288.4	380.7	346.4
Male	489.4	501.2	540.0	292.3	399.2	372.9
Female	421.1	440.7	407.2	289.5	370.9	333.4
Mortality, 2013-2017						
All sites	158.2	162.9	186.4	98.1	144.0	111.8
Male	189.3	193.8	233.2	116.4	172.6	135.6
Female	135.5	139.9	157.5	85.0	122.9	95.1

Siegel et al. Ca Caner Clin 2020; 70

Clinical Trial Representation



Accessed at www.fightcancer.org/policy-resources/clinical-trial-barriers on 2/5/2020

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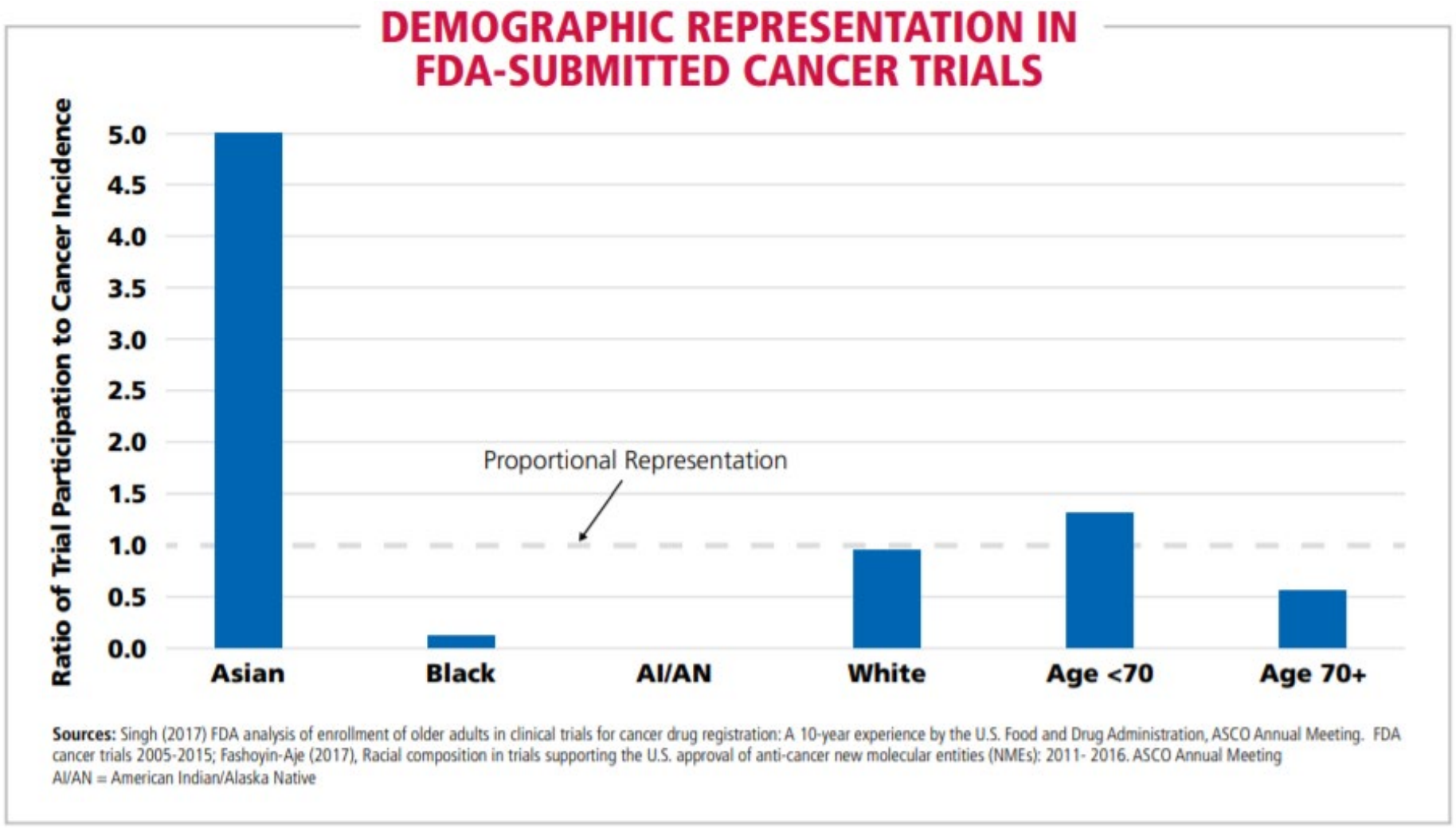

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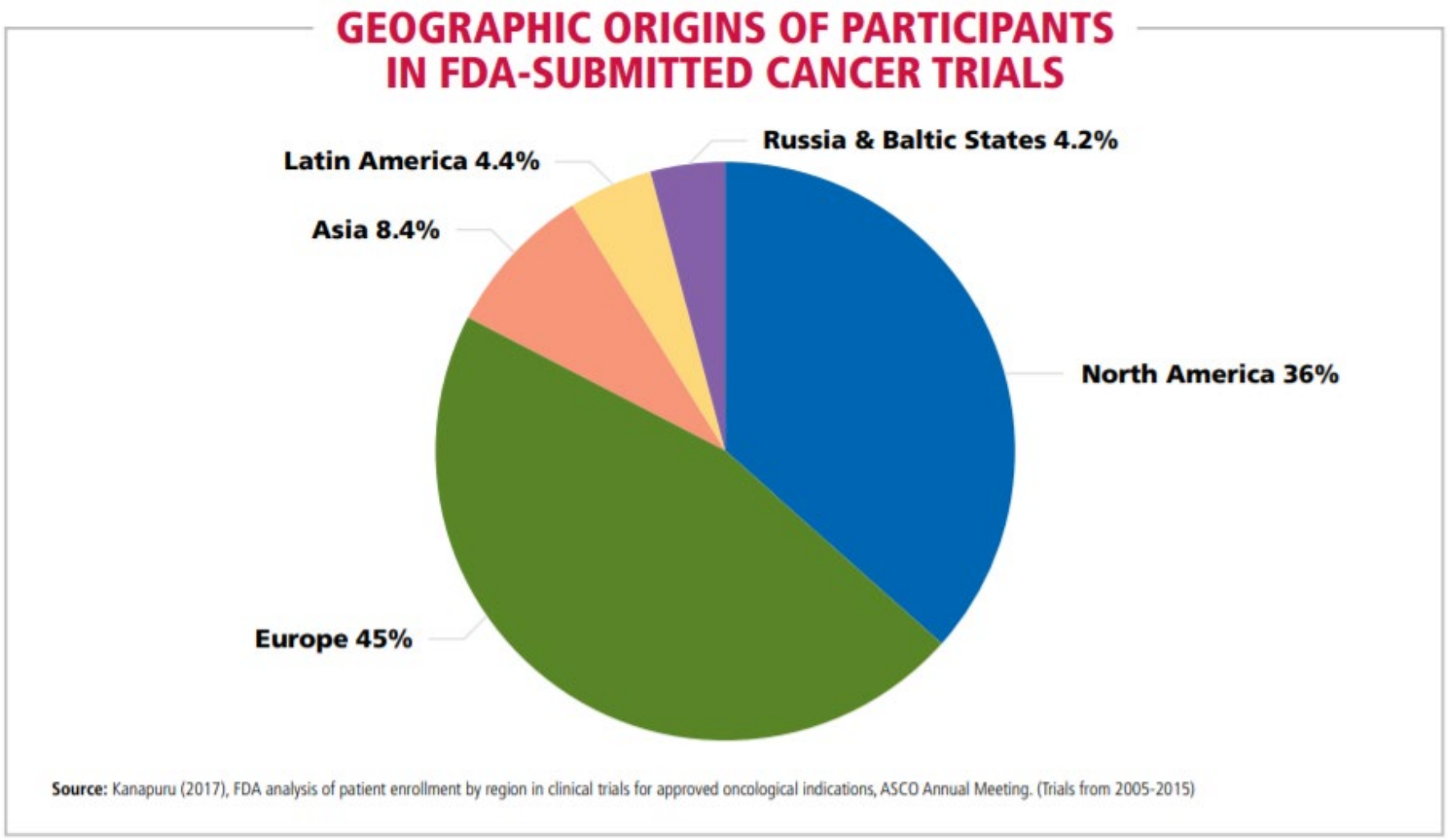

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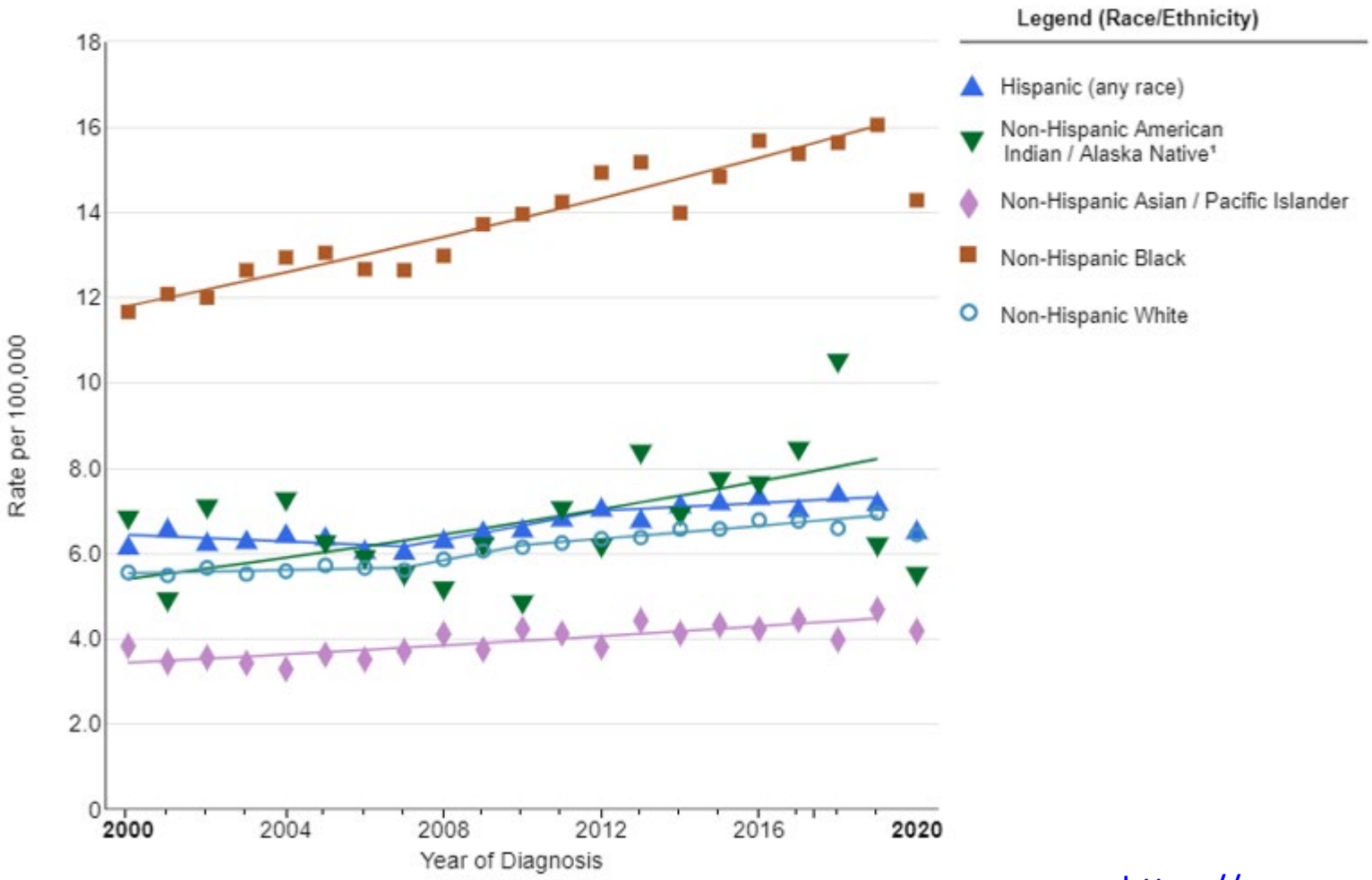
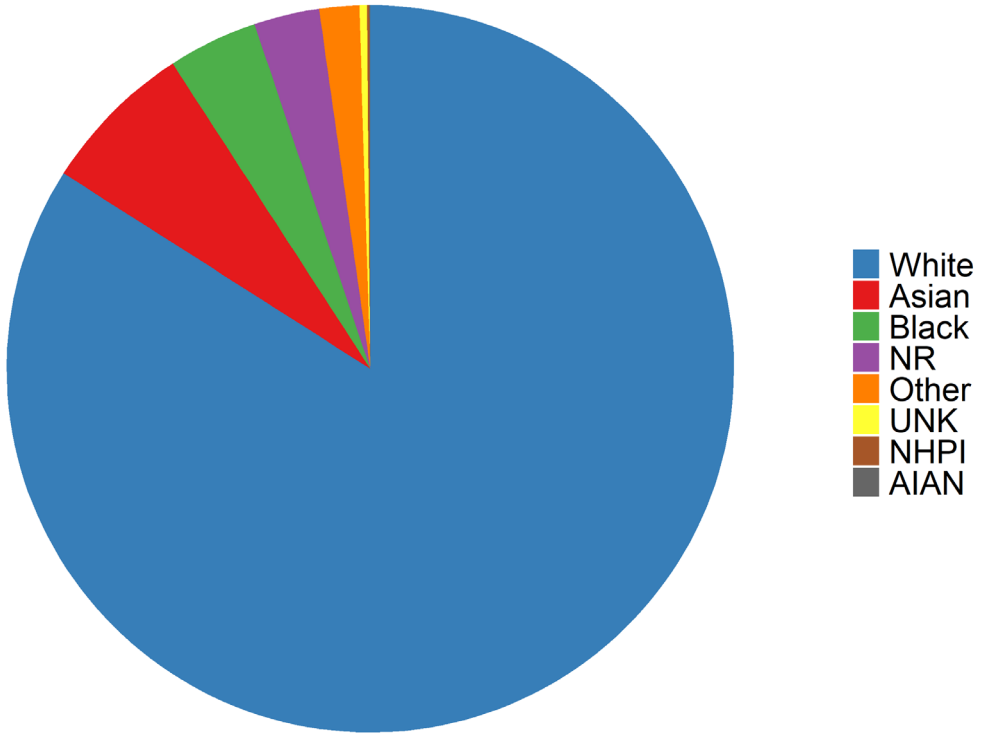
Multiple Myeloma Epidemiology



https://seer.cancer.gov/statistics-network/explorer, accessed 11/15/23

FDA Analysis of multiple myeloma trials

- **Applications between 2006-2019**
- **Pooled data from 19 trials with N=10157 Patients**
- **420 (4%) patients were of Hispanic ethnicity**



Race	N=10157
White or Caucasian	8535 (84%)
Asian	693 (7%)
Black Or African American	405 (4%)
Not Reported (NR)	295 (3%)
Unknown (UNK)	330 (3%)
Other	180 (2%)
Native Hawaiian Or Other Pacific Islander (NHPI)	10 (<1%)
American Indian Or Alaska Native (AIAN)	4 (<1%)

FDA Analysis of trial screen failures in myeloma

- **Applications between 2006-2019**
- **Pooled data from 16 trials with screen failure data**

Categories

Organ Function: Not meeting eligibility criteria for organ function; renal, hepatic, cardiac, or pulmonary function

Disease related: Not meeting eligibility criteria for measurable disease, plasma cell leukemia, meningeal involvement, amyloidosis etc.

Treatment Related: Requirement for receipt of specific lines of therapy or refractory to specific treatments etc.

Hematology labs: Not meeting eligibility based on protocol specified hemoglobin (Hb.), platelet count, absolute neutrophil count (ANC) lab criteria.

Category	White N=1338	Black N=88	Hispanic N=70
Disease related	368 (28%)	16 (18%)	15 (21%)
Treatment related	167 (12%)	15 (17%)	7 (10%)
Hematology lab	132 (10%)	17 (19%)	2 (3%)
Organ function-renal	44 (3%)	4 (5%)	N/A

- **Black Patients had higher rates of ineligibility (24%) compared to White patients (17%)**
- **Hispanic patients had high rates of ineligibility (20%)**

Addressing the Disparity

U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

FINDING CURES TOGETHER℠

FDA-AACR Workshop to Examine Under-representation of African Americans in Multiple Myeloma Clinical Trials

February 13, 2020

Workshop Objectives:

- Discuss biology and genetics underlying racial and ethnic differences in multiple myeloma.
- Characterize racial and ethnic data available from multiple myeloma registrational trials and real-world data sources.
- Discuss implications of limited clinical data in racial and ethnic minorities with multiple myeloma.
- Explore approaches to increase our knowledge of the safety and efficacy of anti-myeloma therapeutics in racial and ethnic minorities.

Addressing the Disparity

- Recommendations from the Workshop
  - Require sponsors to set targets for representativeness and inclusion (e.g., for recruitment, accrual, and retention) during clinical study, including by planning for enhanced outreach to African Americans and other patient groups.
  - Require sponsors to set prospective plans for how to meet targets in the post-market setting if goals are not met in pre-market trials.
  - If plans include the use of supplemental real-world data, sponsors should prespecify what analyses will incorporate those data and recognize the lack of randomization to control for unknown confounders.
  - Conduct prespecified, exploratory analyses to identify differences among sub-populations defined by race and ethnicity when there is a safety signal or question about efficacy.

SCIENCE IN SOCIETY

Recommendations on Eliminating Racial Disparities in Multiple Myeloma Therapies: A Step toward Achieving Equity in Healthcare

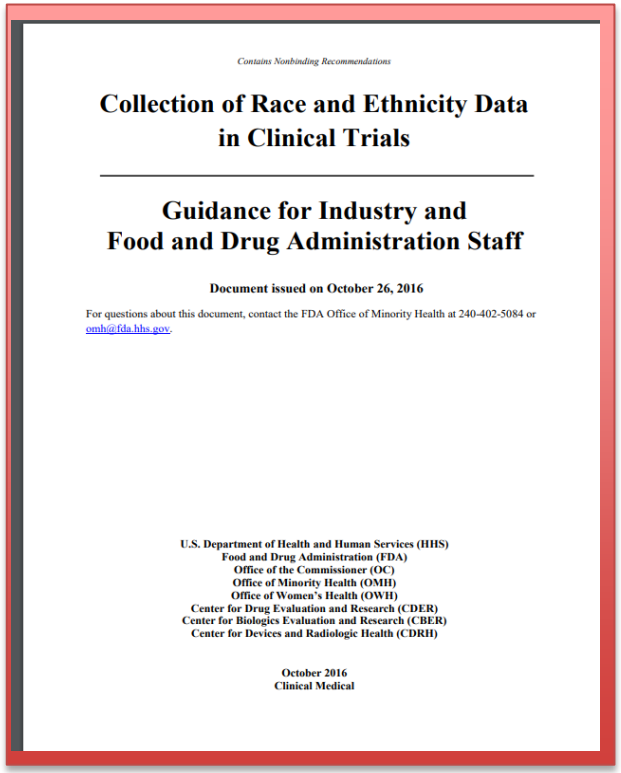
Nicole Gormley[1], Lola Fashoyin-Aje[1], Trevan Locke[2], Joseph M. Unger[3], Richard F. Little[4], Ajay Nooka[5], Khalid Mezzi[6], Mihaela Popa-McKiver[7], Rachel Kobos[8], Yelak Biru[9], Tiffany H. Williams[10], and Kenneth C. Anderson[11]

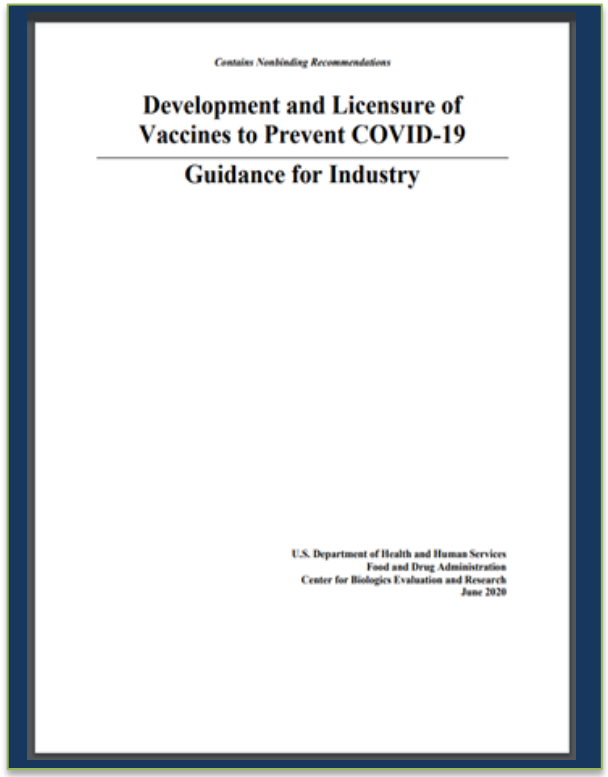
Summary: African Americans are at higher risk of multiple myeloma (MM) yet are underrepresented in clinical trials and reap fewer benefits from novel therapies of the disease. To improve representation of African Americans in MM clinical trials, researchers, healthcare providers, patients, industry partners, and regulators at an FDA–AACR workshop developed recommendations to all stakeholders. The outlined principles offer a road map to addressing disparities broadly in clinical trials.

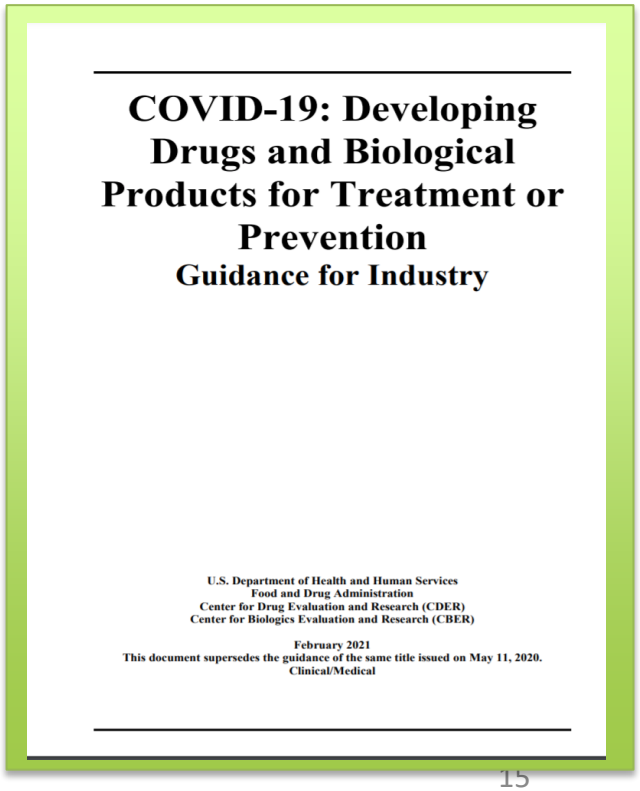
- Outlines recommendations for pre-approval clinical trials, post-approval clinical trials and real-world studies

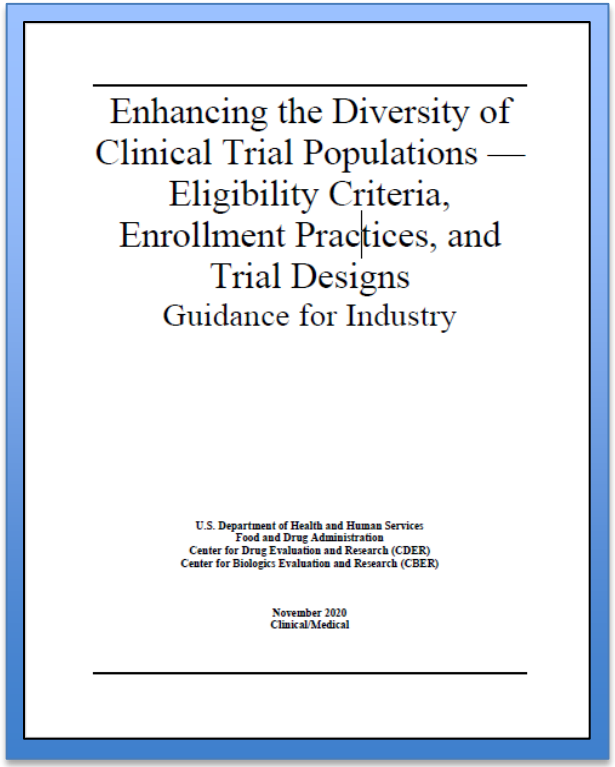
Gormley Blood Cancer Discovery 2021

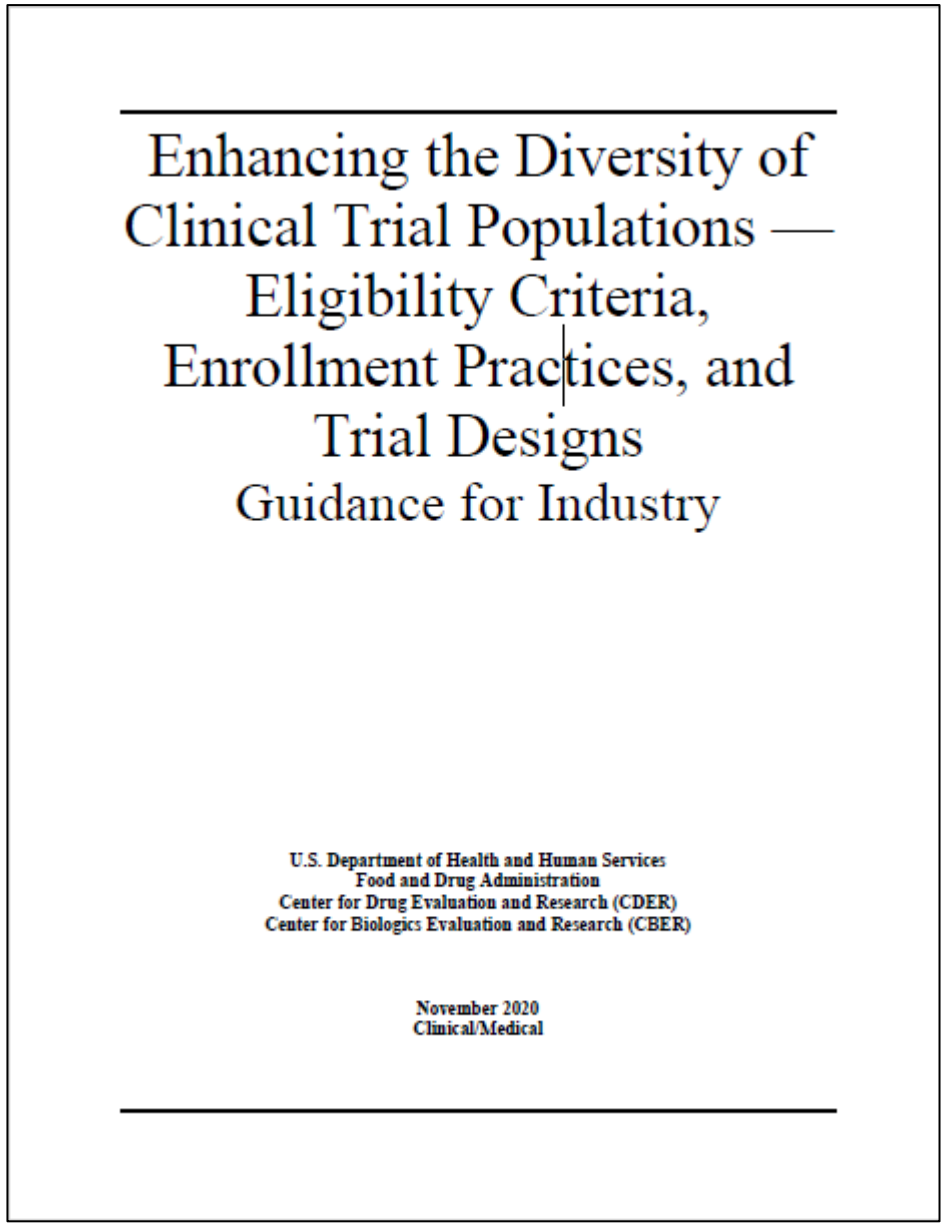
Guidance Related to Participants from Historically Underrepresented Racial/Ethnic Groups










Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2020
Clinical/Medical

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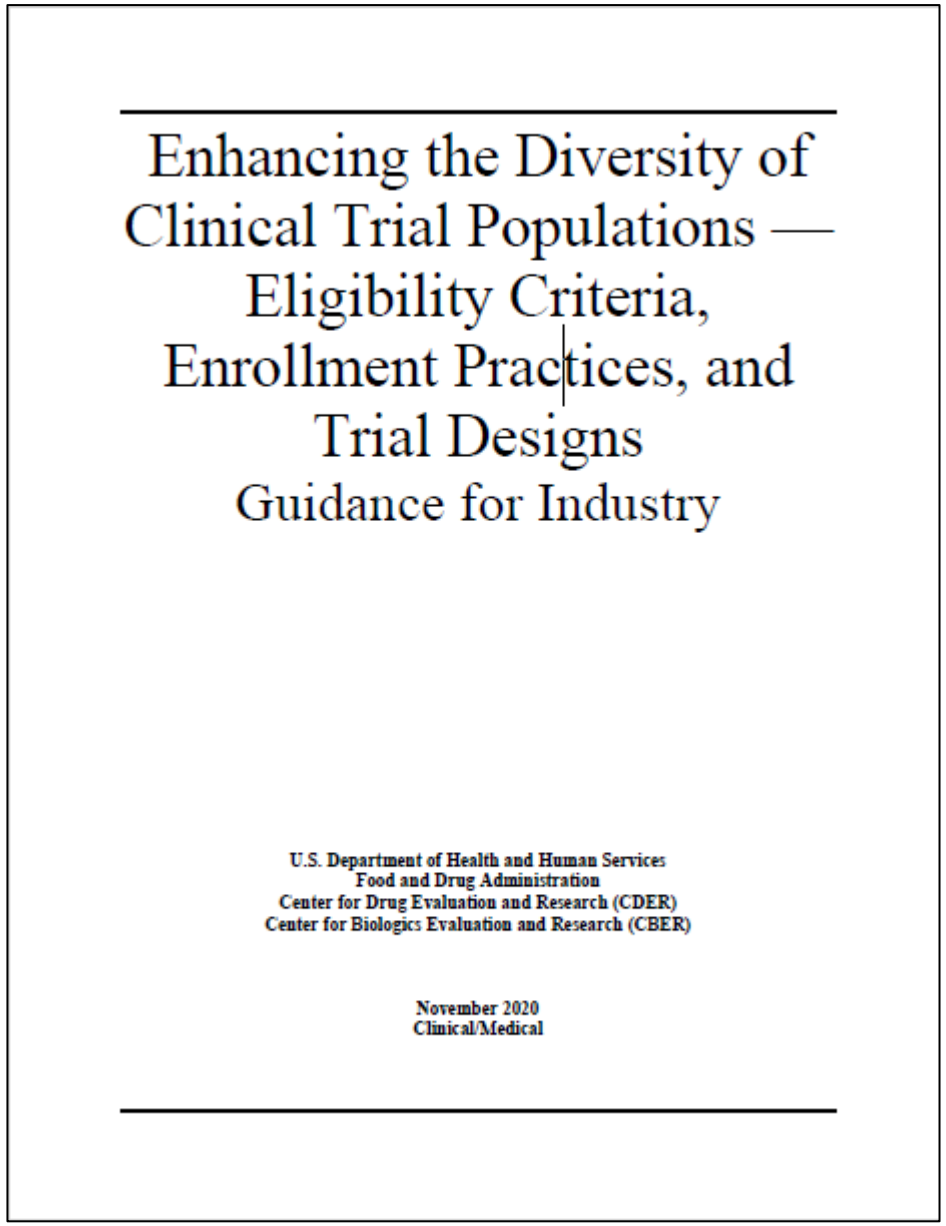
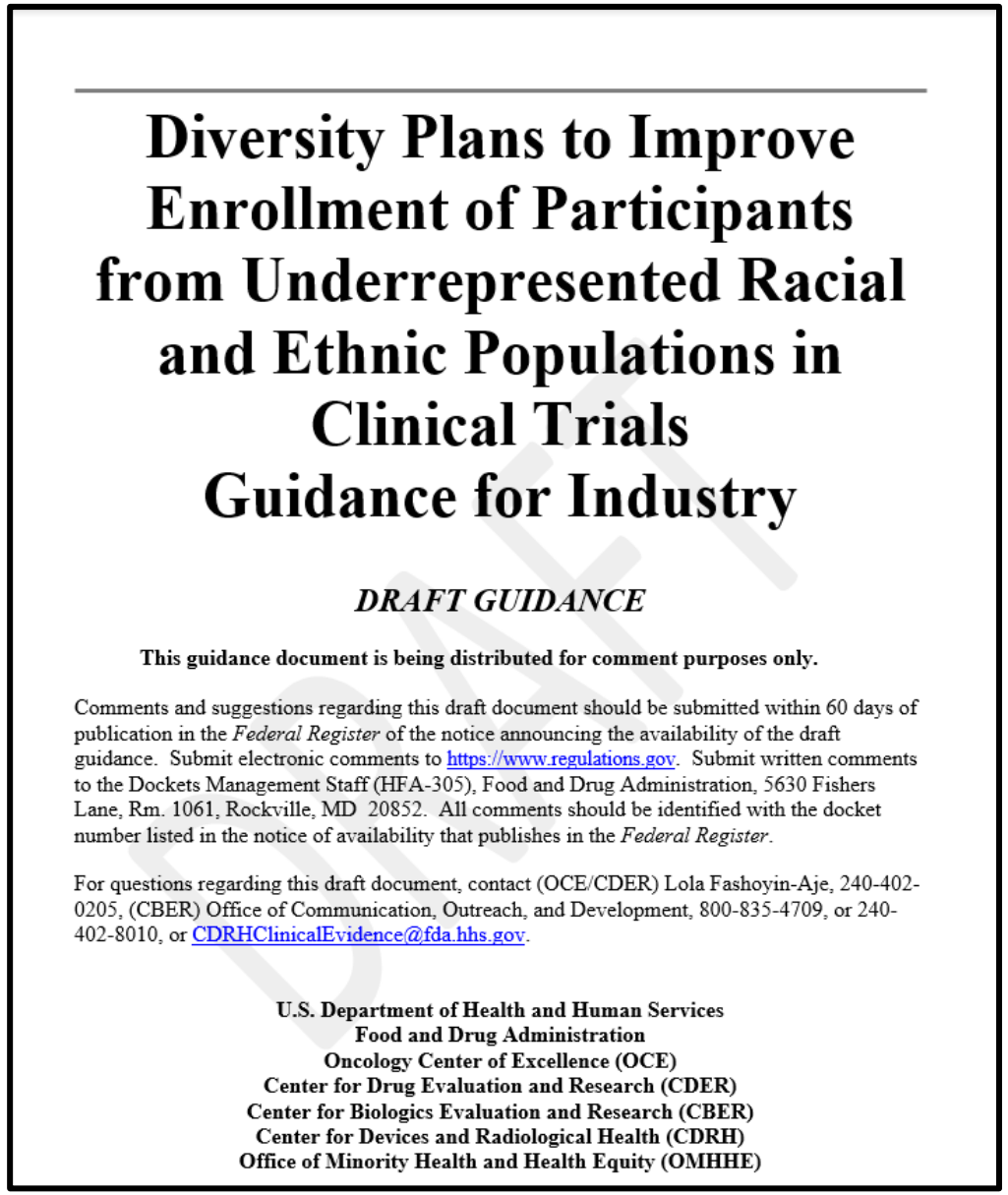


- **Summary:**
  - Broadening the eligibility criteria to allow the trial results to reflect the patient population likely to use the drug if approved
    - Eliminate unnecessary exclusion criteria
    - Expand eligibility criteria as a drug development progresses from earlier to later phases
    - Enroll participants who reflect the characteristics of the clinically relevant population
  - Early characterization of the drug metabolism and clearance can help limit exclusion of specific patient populations
  - Make trial participation less burdensome for participants
    - Consider visit frequency, financial costs, remote trial features, financial reimbursements.
  - Enrollment & retention practices to enhance inclusiveness
    - Community engagement, recruitment events, geographic location considerations and trial resources in multiple languages



Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OCE/CDER) Lola Fashoyin-Aje, 240-402-0205, (CBER) Office of Communication, Outreach, and Development, 800-835-4709, or 240-402-8010, or CDRHClinicalEvidence@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Minority Health and Health Equity (OMHHE)

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What are the implications of FDORA?

- What is required?
  - Sponsor must submit to the FDA a Diversity Action Plan for phase 3 or other pivotal clinical study

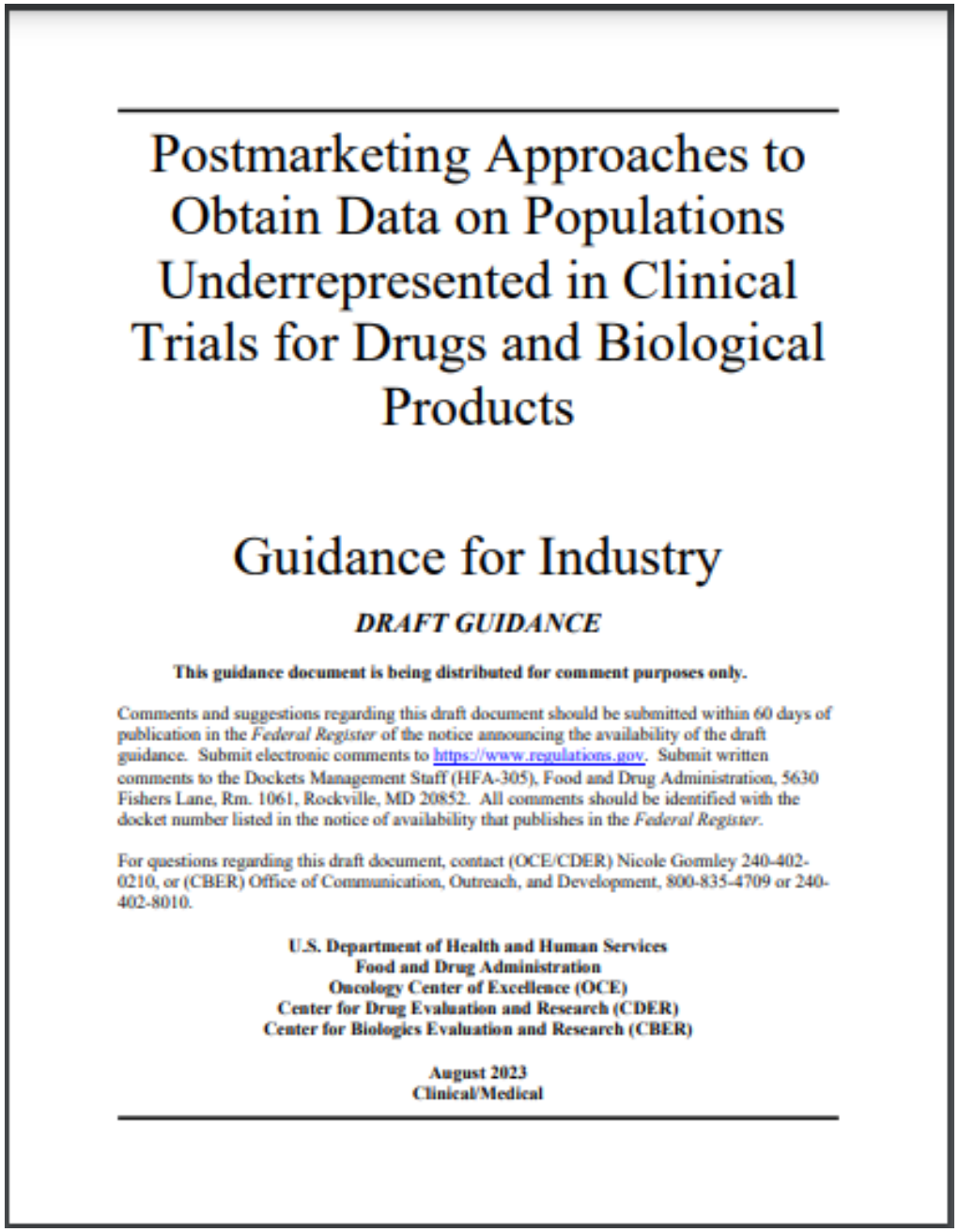
- What is recommended?
  - Sponsor develop a comprehensive strategy for diversity across a drug's development program, including early studies

Diversity Action Plan: Enrollment Goals

- Enrollment goals should be informed by the estimated prevalence or incidence of the disease in a U.S. patient population
  - This can be derived from literature, registry data or other epidemiologic data available
  - If there is data to suggest differential safety or efficacy, increased enrollment of a specific subpopulation may be needed

Diversity Action Plan: Operational Measures

- DAP should outline specific measures to address the enrollment and retention of patients in the study
  - Site location
  - Trial Accessibility
  - Community Engagement
  - Methods to reduce burden of trial participation
- The DAP should describe metrics for success



Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products

Guidance for Industry

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August 2023
Clinical/Medical

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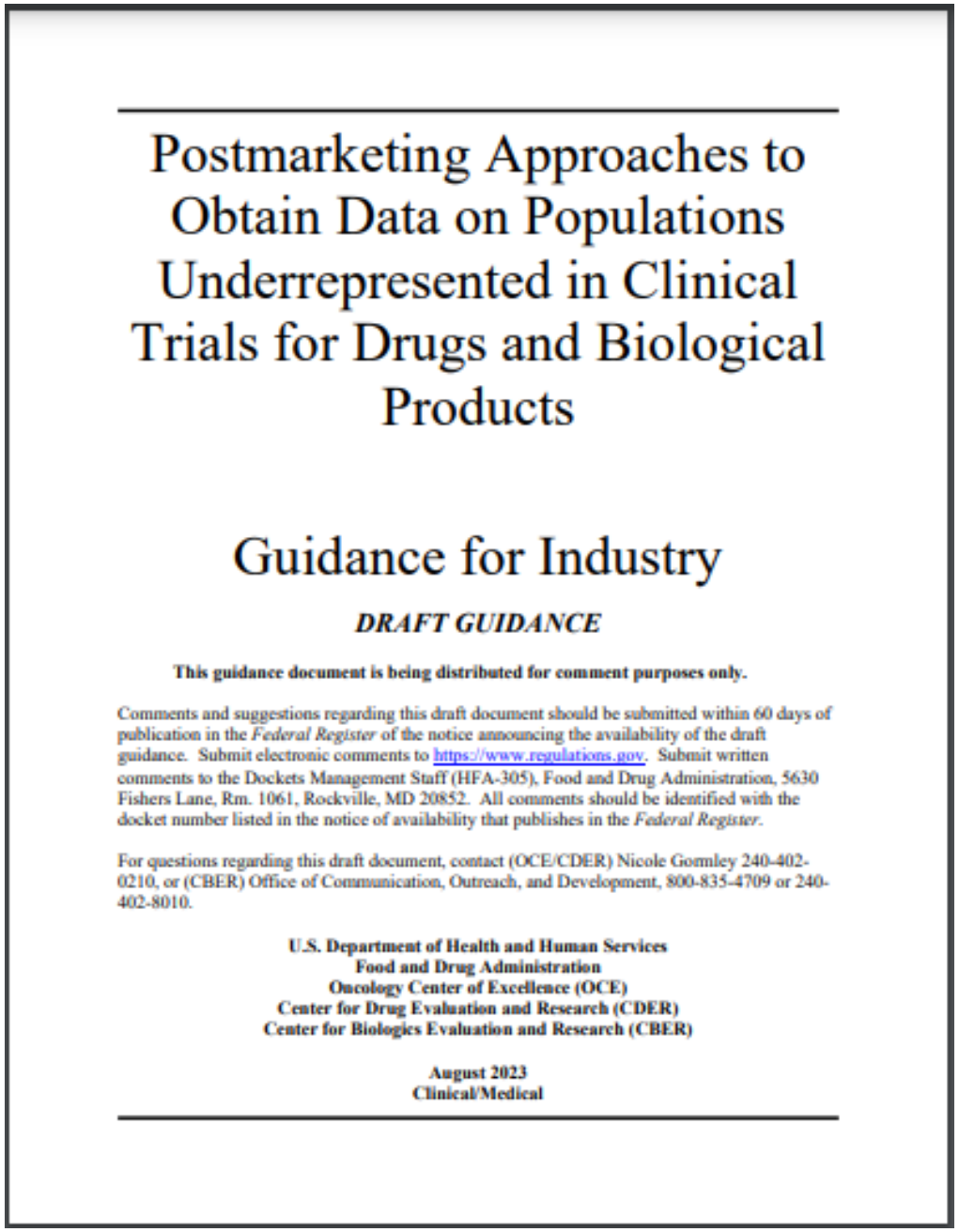

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August 2023
Clinical/Medical

- **Summary:**
  - FDA may require a sponsor to conduct a post-marketing study or clinical trial to assess a known or potential serious risk
    - For example, if there is a higher rate of a serious adverse event observed in a population defined by race, ethnicity, age, etc., FDA may require a study to evaluate the signal in that population.
  - FDA may enter into a written agreement with the applicant to conduct a post-marketing study
    - For example, if there is significant under-representation of a population that is likely to receive the product after approval, FDA may request additional studies to further characterize the benefit or safety in that subpopulation

In Conclusion…

- Under-representation of racial and ethnic minorities in oncology clinical trials used to support registration
- Ongoing efforts to address disparities in clinical trials
- Representation should be addressed throughout a drug's development
- Diversity plans should be used to plan for diverse enrollment in trials intended to support marketing submission
- Diversity plan enrollment goals should be based on the disease prevalence and should include specific measures to address representation
- FDA may require or request that additional information on diverse patient populations be obtained after approval

Acknowledgements

- Marc Theoret
- Kirsten Goldberg


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