Promoting Clinical Research Diversity: DRIVEing BEYOND The Indianapolis Black Paper

Ruemu Ejedafeta Birhiray, MD

Program Chair

CEO, Indy Hematology Education, Inc.,

Partner, Hematology Oncology of Indiana, American Oncology Network, PA, Indianapolis, IN

Clinical Professor of Medicine,

Marian University College of Medicine, Indianapolis, IN

HEMATOLOGY ONCOLOGY of INDIANA
A DIVISION OF AMERICAN ONCOLOGY PARTNERS, P.A.

MARIAN UNIVERSITY Indianapolis College of Osteopathic Medicine

IHE

CONFLICTS OF INTEREST

Speakers Bureau
Consultant,
Advisory Board

SPEAKERS BUREAU

JANSSEN BIOTECH, INC.
AMGEN INC
ASTELLIS.
PUMA BIOTECHNOLOGY, INC.
LILLY USA, LLC
INCYTE CORPORATION
PHARMACYCLICS LLC, AN ABBVIE COMPANY
GENZYME CORPORATION
DOVA/SOBI PHARMACEUTICALS
EXELIXIS INC.
E.R. SQUIBB & SONS, L.L.C.
ASTRAZENECA PHARMACEUTICALS LP
SANOFI
DIACHI SANCHO
MORPHOSYS
REGENERON
GLAXO ONCOLOGY
SEAGEN
CTI
BLUE MEDICINES
STEMLINE
TAIHO
COHERUS
SERVIER
BEIGENE

ADVISORY BOARD/CONSULTANT

ADVISORY BOARD AND CONSULTING
ARRAY BIOPHARMA INC.
LILLY ONCOLOGY
JANSSEN SCIENTIFIC AFFAIRS, LLC
EPIZYME
TG THERAPEUTICS
REGENERON
JANSSEN
ABBVIE
TAKEDA
SANOFI
IPSEN
GENENTECH
TAIHO
ABBVIE
EXECELIS
COHERUS

RESEARCH GRANT/INVESTIGATOR

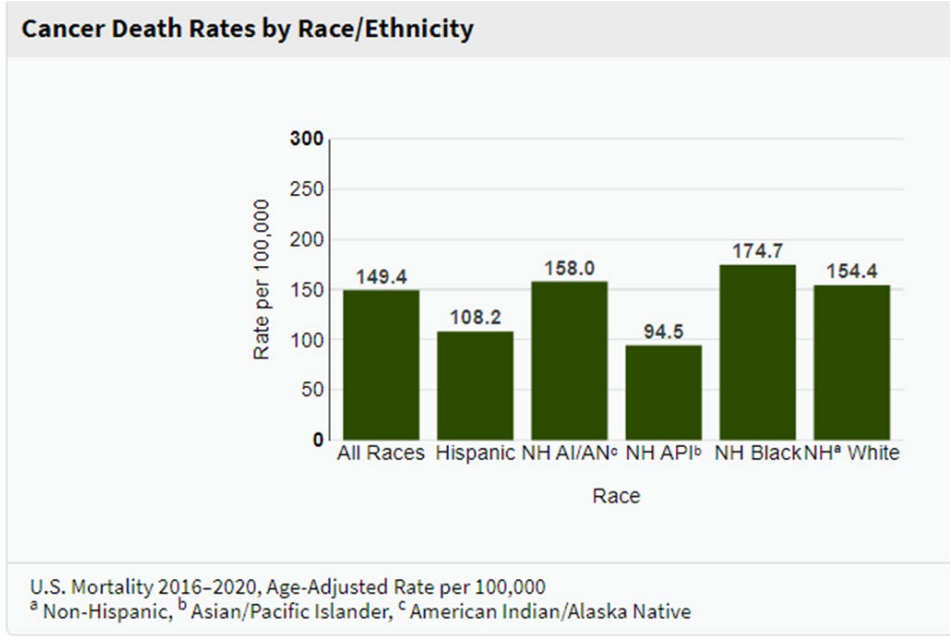
TAKEDA
REGENERON
GENDENTECH

Causes of Racial Disparities in Cancer Occurrence and Outcomes

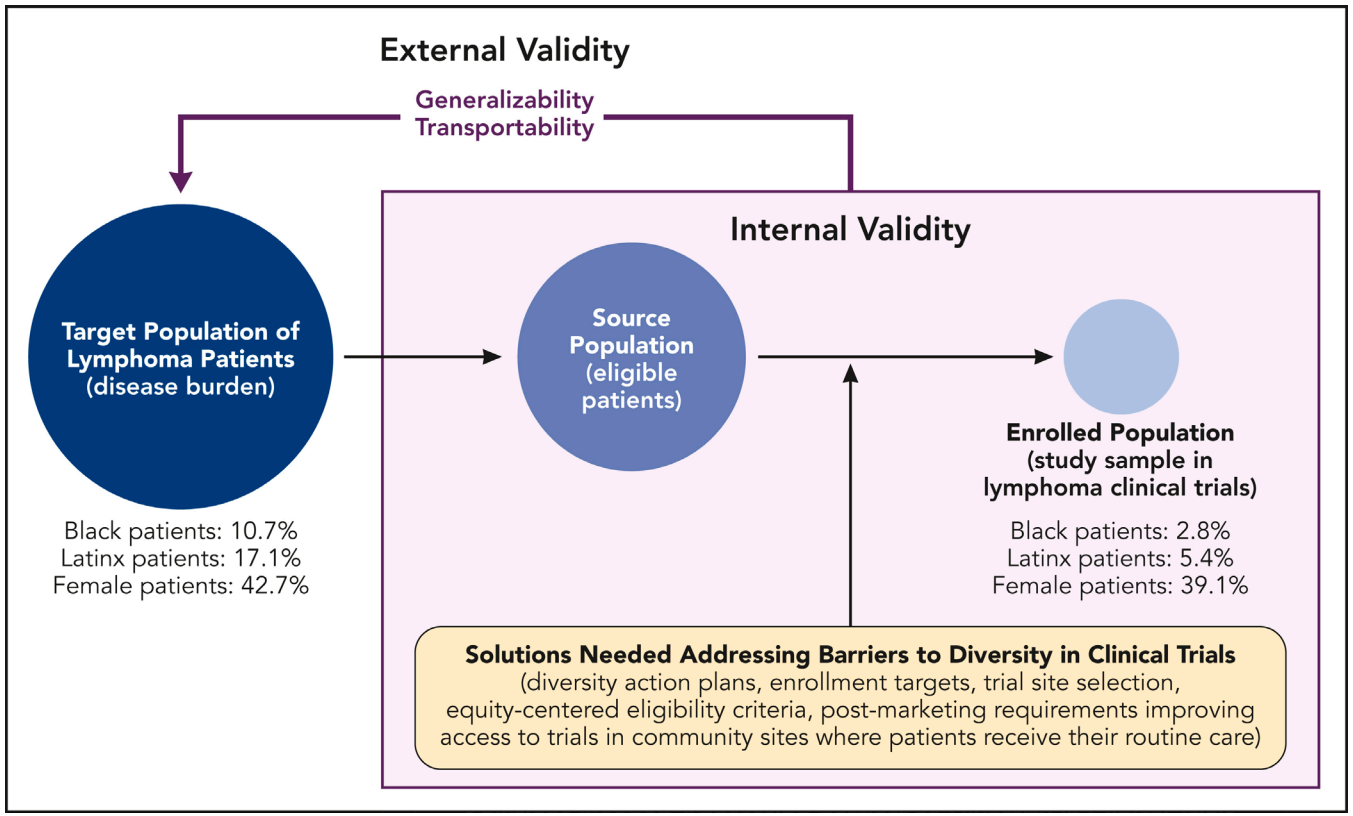
- Interplay between structural, socioeconomic, socio-environmental, behavioral and biological factors
- Longstanding inequalities in wealth results in differences in risk factor exposures and access to equitable cancer prevention, early detection, and treatment
- Disproportionate wealth stems from hundreds of years of structural racism, including segregationist and discriminatory policies in criminal justice, housing, education, and employment, altered balance of prosperity, security, and other social determinants of health

✓ Social determinants of health are defined by the WHO as the conditions in which individuals are born, grow, live, work, and age

✓ Structural racism refers to the totality of ways in which societies foster racial discrimination through mutually reinforcing systems of housing, education, employment, earnings, benefits, credit, media, **health care**, and criminal justice



External Validity of Lymphoma Clinical trials



Generalizability and Transportability of Clinical Results

- **Generalizability** refer to concerns with making inference on the average treatment effect from a possibly biased sample of the target population back to the full target population.
- **Transportability** refers to making inference on the treatment effect for a target population when the study sample and target population do not overlap (partially or entirely)

Peter M Rothwel et al:

"In making treatment decisions, doctors and patients must take into account relevant randomised controlled trials and systematic reviews. Relevance depends on external validity (or generalisability)--ie, whether the results can be reasonably applied to a definable group of patients in a particular clinical setting in routine practice. There is concern among clinicians that external validity is often poor, particularly for some pharmaceutical industry trials, a perception that has led to underuse of treatments that are effective"

Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet. 2005 Jan 1-7;365(9453):82-93.

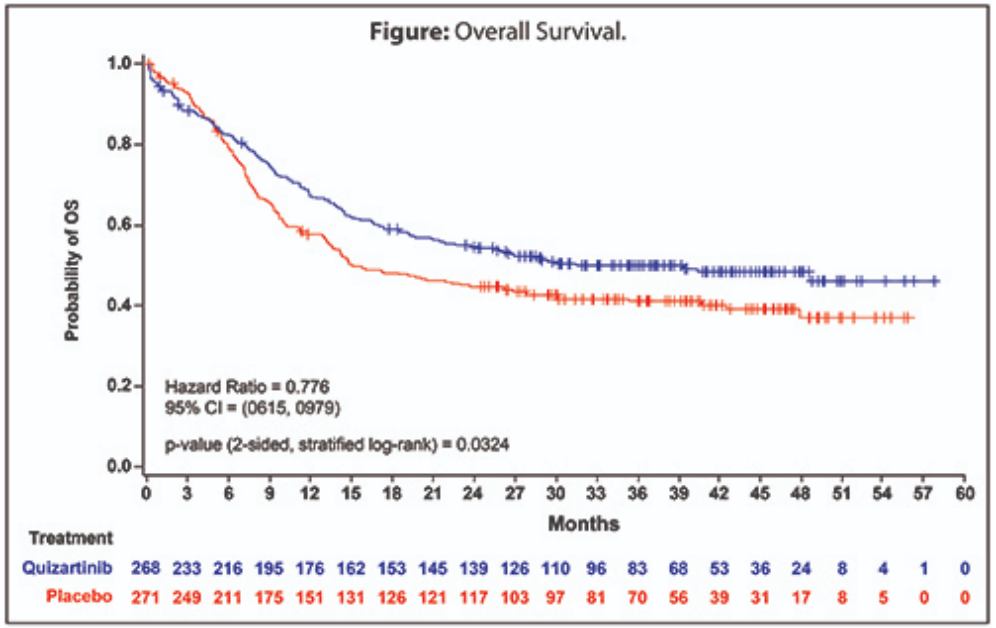
1. Calip GS, Royce TJ. External validity of lymphoma clinical trials. Blood. 2023 Aug 31;142(9):757-759.
2. Casey M, Odhiambo L, Aggarwal N, Shoukier M, Islam KM, Cortes J. Representation of the population in need for pivotal clinical trials in lymphomas. Blood. 2023 Aug 31;142(9):846-855.

20-Years of IMWG Guidelines in Myeloma: "Who is represented and what is the data?"

- Since 2003 the International Myeloma Working Group (IMWG) have published consensus guidelines
- What is the racial composition of supporting trials used by IMWG to publish their guidelines?
- 59 IMWG publications with 3956 references were reviewed. References (n=2047) were analyzed for their racial composition
- **RESULTS:**
- 8.8% (n=71/804) Clinical trials (n=804) with 189,244 patients reported race/ethnicity of studied patients.
- **2.6% (n=150,790) were black patients.**
- **1.7% of black patients are enrolled in the clinical trials (n=3156) and 1.6% in the observational studies.**
- **6.5% of the US trial patients are black patients (n= 2493/38,050) – but 20% of US Myeloma patients are Black**

Fahmawi, S et al. Under-Representation of Black Patients with Multiple Myeloma in Studies Supporting International Myeloma Working Group Guidelines. Blood 2022; 140 (Suppl 1): 13212–13213.

QUIZARTINIB PROLONGED SURVIVAL VS PLACEBO PLUS INTENSIVE INDUCTION AND CONSOLIDATION THERAPY FOLLOWED BY SINGLE-AGENT CONTINUATION IN PATIENTS AGED 18-75 YEARS WITH NEWLY DIAGNOSED FLT3-ITD+ AML



Characteristic (N= 539) Randomized patients	**Results**
Median Age	56 years (range 20-75 years)
Gender	46% male
Race	60% White
	29% Asian
	1% Black or African American
	10% Other Races

Torsades de pointes, cardiac arrest and ventricular fibrillation occurred in 0.2%, 0.6%, 0.1% respectively with 0.4% fatalities of patients treated in quizartinib AML clinical trials.

Cardiovascular disease rate is significantly higher in non-Hispanic Black participants compared with non-Hispanic White, even when adjusted for mean age- and sex[1].

What is the risk of cardiac events and sudden death in African Americans treated with quizartinib?

He J, et al, Trends in Cardiovascular Risk Factors in US Adults by Race and Ethnicity and Socioeconomic Status, 1999-2018. JAMA. 2021;326(13):1286–1298

NON -DIVERSE CLINICAL RESEARCH DATA IS UNSAFE AND UNETHICAL

DATA APPLICABILITY TO RACIALLY DIVERSE POPULATIONS

Clinical trials clinician interactions and disease assessments may result in higher quality care

Non inclusion of underrepresented groups in trials generates inapplicable clinical data to these patients, both for efficacy and safety. **DIVERSITY = SAFETY**

Access to clinical trials is a moral imperative, as the treatments being tested are at the forefront of clinical innovation and should be equally accessible

Trial underrepresentation in a world of big data engenders further:

Data absenteeism (ie, lack of data representation from underprivileged groups)

Data chauvinism (ie, faith in the size of data without considerations for quality and contexts)

DATA HALLUCINATION (ie, the assumption and use of non-existent data to generalize treatment recommendations, outcomes and results)

1. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. Lancet. 2004;363(9405):263-270.
2. Nipp RD, Hong K, Paskett ED. Overcoming barriers to clinical trial enrollment. Am Soc Clin Oncol Educ Book. 2019;39(39):105-114.
3. Unger JM, Cook E, Tai E, Bleyer A. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. Am Soc Clin Oncol Educ Book. 2016;35(36):185-198.
4. Lee EWJ, Viswanath K. Big data in context: addressing the twin perils of data absenteeism and chauvinism in the context of health disparities research. J Med Internet Res. 2020;22(1):e16377.
5. O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. Clin Cancer Res. 2009;15(15):4806-4814.
6. Hantel A, Luskin MR, Garcia JS, Stock W, DeAngelo DJ, Abel GA. Racial and ethnic enrollment disparities and demographic reporting requirements in acute leukemia clinical trials. Blood Adv. 2021 Nov 9;5(21):4352-4360. doi: 10.1182/bloodadvances.2021005148. PMID: 34473244; PMCID: PMC8579250.

The MYTH: Black Patient's Refuse to Participate in Clinical Trials

Representativeness of Black Patients in in NCI sponsored and Pharma-sponsored trials

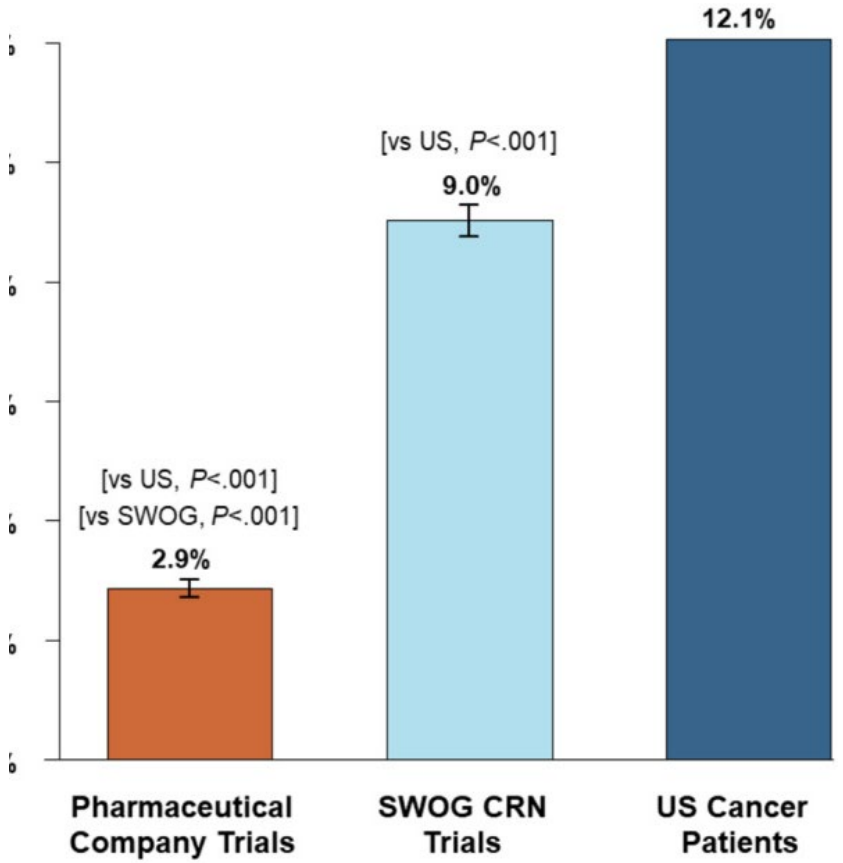
5 cancer types in between 2008-2018

358 trials: N=93,825

Pharmaceutical company-sponsored trials: 85; N=46,313

SWOG Cancer Research Network trials: N=47,512

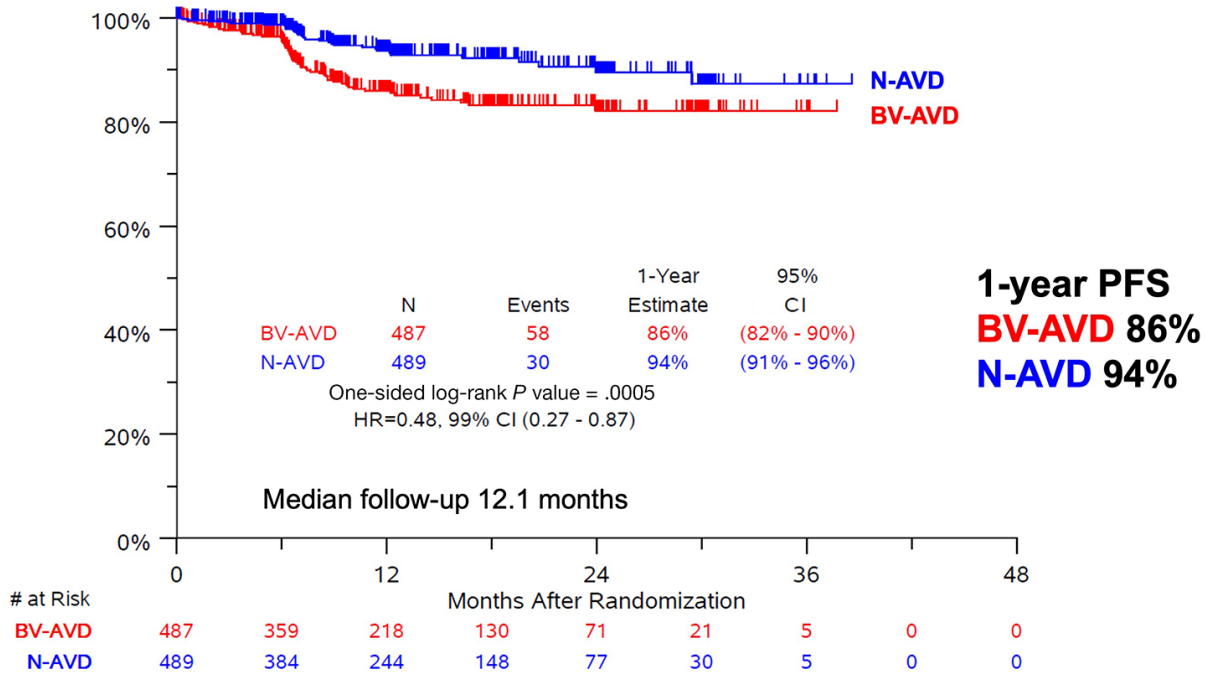
Blacks in pharmaceutical company-sponsored trials compared with SWOG trials 2.9% vs 9.0%



Unger JM, Hershman DL, Osarogiagbon RU, et al. Representativeness of Black patients in cancer clinical trials sponsored by the National Cancer Institute compared with pharmaceutical companies. JNCI Cancer Spectr. 2020;4:pkaa034. doi:10.1093/jncics/pkaa034

What is Possible: SWOG1826

Herrera AF et al. J Clin Oncol 41, 2023 (suppl 17; abstr LBA4)



1-year PFS
BV-AVD 86%
N-AVD 94%

Race		
White	**375 (77%)**	**364 (75%)**
Black	**57 (12%)**	**56 (11%)**
Asian	**11 (2%)**	**17 (3%)**
Other/Unknown	**46 (9%)**	**50 (10%)**
Hispanic	**68 (14%)**	**59 (12%)**

25% of study participants were racial minorities

Authors Conclusion: "REPRESENTATIVE STUDY"

CLINICAL CANCER RESEARCH DISPARITIES IN LYMPHOMA: WHAT CAN "WE" DO?

How to eat an elephant 101

https://www.amazon.com/s?k=how+to+eat+an+elephant&adgrpid=1330409634619376&hvadid=83150925195629&hvbmt=be&hvdev=c&hvlocphy=94504&hvnetw=o&hvqmt=e&hvtargid=kwd-83150948973642%3Aloc-190&hydadcr=21902_13365855&tag=mh0b-20&ref=pd_sl_13t3pie7ry_e

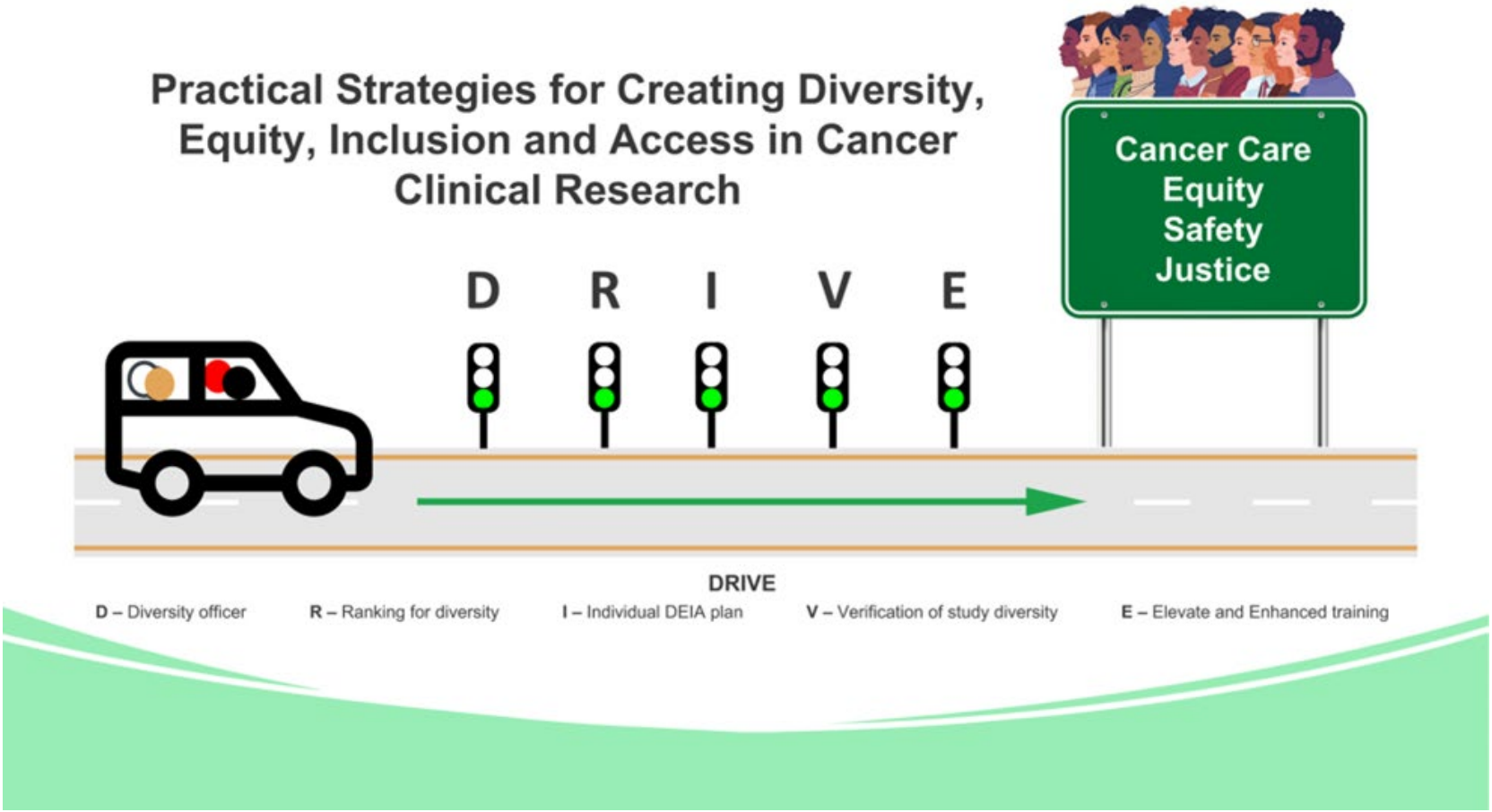
Food and Drug Omnibus Reform Act of 2022 ("FDORA")

- Legislation Requiring Guidance on Clinical Research Diversity and Modernization
- Sponsors are required to submit to FDA "diversity action plans" for Phase III and Pivotal trials for drugs and devices, unless otherwise waived or excepted
- FDA is tasked with updating guidance on diversity action plans for clinical studies and hosting public stakeholder workshops focused on enhancing clinical study diversity.
- Within one year, the FDA is to, as applicable, issue or revise guidance on the appropriate use of decentralized clinical studies:

1. Recommendations for incorporation of data collection methodologies using digital health technologies in clinical trials to collect data remotely;
2. Considerations for privacy and security protection for clinical trial data, including compliance with "HIPAA" and the Common Rule;
3. Recommendations regarding data and information needed to demonstrate that a digital health technology is fit-for-purpose for a clinical trial;
4. Recommendations for increasing access to, and the use of, digital health technologies in clinical trials to facilitate inclusion of diverse and underrepresented populations;
5. Recommendations on the use of clinical trial designs that involve concurrent conduct of different or multiple clinical trial phases;
6. Recommendations for how to streamline trial logistics to facilities for efficient collection and analysis of data, including through interim analyses; and
7. Recommendations for communications between sponsors and the FDA on the development of seamless, concurrent, or other adaptive clinical trial designs.

https://www.ropesgray.com/en/newsroom/alerts/2023/01/congress-enacts-legislation-requiring-guidance-on-clinical-research-diversity-and-modernization. Assessed April 1, 2023, 5:18PM

DRIVE



Birhiray MN, Birhiray RE. Practical strategies for creating diversity, equity, inclusion, and access in cancer clinical research: DRIVE. Blood Adv. 2023 Apr 25;7(8):1507-1512. doi: 10.1182/bloodadvances.2022008220. PMID: 36005840; PMCID: PMC10139854..

DRIVE

A new paradigm for establishing diversity in clinical trials

Maya N. Birhiray, MS
and Ruemu E. Birhiray, MD

Diversity Officer

All clinical trials must include a Diversity Officer who is tasked just like a DSMB in safety to ensure a diversity plan is established, maintained, and 5 modified during the course of each study to meet its accrual goals of inclusion and diversity.

- ✓ Diversity goals are tailored to the disease demographics

Ranking

Create a Ranking System for measuring the relative diversity of enrolled subjects in a clinical trial that are published with each trial.

- ✓ (0-5) based on achieving diversity goals
- ✓ Ideally rankings would be viewed as a major factor in judging the quality of the trials

Individual Responsibility

Create an Individual/Personal diversity plan to ensure your minority patients are enrolled or participating in clinical research.

- ✓ As individuals, we all have responsibility to ensure equal treatment and representation for our fellow human beings
- ✓ Not just an issue for minorities
- ✓ Economic impact: studies that aren't designed to look at all people can fall short of reporting possible adverse reactions. In turn, increased medical costs that ultimately are born by all of us

Verify

Verify and ensure that podium presentations at major conferences are preferentially given to clinical trials meeting diversity goals.

- ✓ Studies that meet the highest standards of diversity goals would be labeled as VERIFIED
- ✓ VERIFIED studies would be a focal point for presentations (ASH, ASCO, etc.) and a factor in new treatment approvals by the FDA or that country's regulatory body

Elevate

Elevate and Encourage, train, and recruit minority investigators and team members to participate in all clinical trials.

- ✓ Ensure that the entire clinical team is diverse
- ✓ Investigators, patient coordinators, navigators, data safety monitoring board, steering committees of clinical trials

Birhiray MN, Birhiray RE. **Practical strategies for creating diversity, equity, inclusion, and access in cancer clinical research: DRIVE. Blood Adv. 2023 Apr 25;7(8):1507-1512. doi: 10.1182/bloodadvances.2022008220. PMID: 36005840; PMCID: PMC10139854.**

Diversity Officer

- NIH commissioned GREENBERG REPORT, 1967: Established DSMBs to oversee and ensure safety and the validity of an ongoing clinical trials
- “The problem to be studied is an important one that must be resolved (a) from a purely scientific point of view, and or (b) for the benefit of mankind through improved methods of prevention, diagnosis and or therapy”

SAFETY = DIVERSITY

- Major corporations: Chief Diversity Officer; Strategist to promote DEIA
- All clinical trials must include a **Principal Diversity Officer (PDO)** who is tasked just like a **DSMB** in safety to ensure a diversity plan is established, maintained, and modifiable during the study to meet accrual goals of inclusion and diversity
- Trial sites should create an **Institutional Diversity Officer** to liaise with the PDO and promote local diversity strategies

Diversity Officer: RESPONSIBILITIES

- Prospectively develop an achievable, flexible, and monitorable DEIA Plan trials in accordance with FDA guidance on clinical trial diversity.
- Establish an infrastructure to monitor and adjust recruitment efforts prospectively.
- Identify impediments to meeting accrual goals at the micro- and macro-levels with proposed solutions
- Develop language and culturally appropriate study materials to promote minority accrual.
- Identify potential scientific questions and study design solutions based on trial barriers, modifications, and results, and improve methods of research in keeping with the Greenberg report's report .
- Advise study sponsor(s), principal investigators, steering committees, and DSMB on potential challenges and solutions.
- Liaise and communicate with other Diversity Officers (e.g., institutional diversity officers) to improve and remove barriers to diverse study enrollment and promote steps for the achievement of DEIA goals.

Diversity Officer: QUALIFICATIONS

a. Training in cancer research. Examples include persons with MD, PhD, AP/NP, PharmD degrees.

b. Training in cultural awareness, humility, sensitivity, appropriateness, and diversity.

c. An understanding of historical factors precluding potential enrollment in clinical trials. including, but not limited to, the Tuskegee syphilis study, Nuremberg code,

d. Training in leadership, negotiation, and communications skills.

e. Training and understanding of current recommendations and guidance on strategies to promote clinical trial diversity.

f. To avoid conflicts of interest, diversity officers must be independent of study principal investigators.

Diversity Officer: TRAINING

a. Clinical study design and statistics.

b. Historical issues relating to diversity: slavery, racism, sexism, gender, and sexuality, including but is not limited to: the Tuskegee syphilis study, the Walter Reed Yellow Fever experiments, the Terre Haute experiments, and the background and development of the Nuremberg Code.

c. Medical ethics and regulatory law and practice relating to clinical research.

d. Cultural sensitivity, humility, and awareness training.

e. The interplay between safety and diversity and an understanding of the Greenberg report and Declaration of Helsinki.

f. The economic impact and implications of clinical research diversity, the economic promoters and inhibitors of research participation in diverse communities.

g. Social construction, (based on the notion that human definition and interpretation is shaped by cultural and historical contexts) including cultural factors and drivers in diverse communities.

h. The regulatory requirements that impact clinical trial diversity.

i. Leadership and negotiation related to clinical trial development and conduct.

j. Additional elements of the training of diversity officers should include the recommendations of the AAMC Report on The Role of the Chief Diversity Officer in Academic Health Centers

R: RANKING: "Informational tool"

DRIVE RANK SCORE	Study racial or nationality enrollment of the sum of all minority groups relative to the epidemiology of the disease§.
0	≤20% of the sum of all minority groups relative to the epidemiology of the disease.
1	21-40% the sum total of all minority groups relative to the epidemiology of the disease and at least one minority groups* not reaching 50% relative to the epidemiology of the disease.
2	21-40% the sum of all minority groups relative to the epidemiology of the disease and at least one minority group* reaching 50% relative to the epidemiology of the disease.
3	41-60% the sum of all minority groups relative to the epidemiology of the disease and at least two minority groups reaching 60% relative to the epidemiology of the disease.
4	61-80% the sum of all minority groups relative to the epidemiology of the disease and at least three minority groups reaching 60% relative to the epidemiology of the disease.
5	80% the sum of all minority groups relative to the epidemiology of the disease and at least three minority groups reaching 80% relative to the epidemiology of the disease.

§: Studies will be ranked at the next lower rank if all criteria for next higher rank are not reached.

*Minority groups in the US are self-defined by the participants and are listed as follows: African American or Black, Native American, Asian, Hispanic, and race. In other countries, minorities should be defined as appropriate, based on societal norms and internationally medically acceptable groups/nationalities.

Birhiray, MN and Birhiray, RE. Creating diversity, equity, inclusion, and access in cancer clinical research: DRIVE Rank and Drive Score. ASCO abstract, e13636, 2022.

I: INDIVIDUAL PLAN; What is your SCORE?

- The modern Hippocratic oath begins with **"I"**
- Diversity can only be achieved when each individual team member and corporation embraces DEIA efforts.
- An individual's diversity plan is central to this altruistic and self-preserving desire.
- The individual diversity plan should include:

➢ To understand and address unconscious bias and develop strategies to overcome these issues in the immediate environment, community, and practice.

➢ Implement a cultural competency plan with cultural humility and remove communication barriers. Cultural competency is defined as healthcare providers' ability to function effectively in the context of cultural differences.

➢ Self-education on the historical, structural, and systemic effects of racism, redlining, and economic factors precluding or preventing enrollment in clinical trials with their applicability to one's community.

➢ Develop a diverse workforce and research teams and enhance organizational DEIA plans.

V: Verify

- Studies that meet the highest standards of diversity goals would be labeled as VERIFIED
- VERIFIED studies would be a focal point for presentations (ASH, ASCO, etc.) and a factor in new treatment approvals by the FDA or that country's regulatory body

E: ELEVATE

- TEAM DIVERSITY enhances communication
- Establish Scholarships, grants and funding mechanisms to train minority/diverse investigators and non-minority investigators practicing in minority communities
- Enhanced funding and training of potential investigators in historical Black colleges and medical schools
- Training should include physicians, advanced providers, nurses, social workers, pharmacists, navigators, medical assistants, students and other members of the clinical and research team

Where can we be? Generalizability and Transportability of Clinical Results and Social Justice

Structural Racism are due to normalized racist practices: #leavenopatientbehind

- **Generalizability:** Concerns making inference on the average treatment effect from a possibly biased sample of the target population back to the full target population.
- **Transportability:** Refers to making inference on the treatment effect for a target population when the study sample and target population do not overlap (partially or entirely)

https://www.pinterest.co.uk/jencortedcon/equity-and-equality/

Calip GS, Royce TJ. External validity of lymphoma clinical trials. Blood. 2023 Aug 31;142(9):757-759.

DEI in Clinical Trials: "What Can we do?"

- **ANNUAL MEDICAL SOCIETY MEETINGS: We all can ADVOCATE!!!!!**
- Rank all abstracts for diversity: **DRIVE SCORE**
- Use diversity score rank as factor for determining PODIUM and Plenary Session presentations
- "ANNUAL HONORIFIC AWARD" to highlight the study with highest diversity RANK presented
- **JOURNALS:**
- Ensure Editorial Board and PEER reviewer diversity
- Select publications based on DIVERSITY SCORES
- Include a diversity statement for all major clinical trials
- **SCIENOMIC INDICES**: DRIVE SCORE availability in clinical informational searches

DIVERSITY STATEMENT IN THE NEJM

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer

Turner NC et al. DOI: 10.1056/NEJMoa2214131

CLINICAL PROBLEM

Among patients with hormone receptor–positive advanced breast cancer without human epidermal growth factor receptor 2 (HER2) overexpression, disease progression is common during or after first-line treatment with endocrine therapy, which often consists of an aromatase inhibitor, combined with an inhibitor of cyclin-dependent kinase 4 and 6 (CDK4/6). Appropriate endocrine-based treatment in patients who have progression while receiving such therapy is unclear.

LIMITATIONS AND REMAINING QUESTIONS

- Few Black patients were included in the trial, so the generalizability of the trial findings to Black patients is limited.
- Whether the relatively low incidence of hyperglycemia was due to the intermittent administration of capivasertib is uncertain.

FUTURE DIRECTIONS

- Consensus recommendations:
- **“Indianapolis Black Paper”**
- Use Artificial Intelligence to evaluate clinical research data and ranking
- RANKINGS:
- **I-RANK:** Individual Investigator Diversity Rank Sore
- **RANK SCORE:** Study Diversity Rank
- **C-RANK (CORPORATE RANK):** Corporate Aggregate Diversity Score
- VERIFICATION

HIPPOCRATIC OATH: "First do no harm"

UBUNTU: "I am because you are"

"Our lives begin to end the day we become silent about things that matter."

Dr. Martin Luther King, Jr

March 8, 1965, Selma, Alabama

"Out of the mountain of despair, a stone of hope"

“This is our hope. This is the faith that I go back to the South with. With this faith, we will be able to hew out of the mountain of despair a stone of hope. With this faith we will be able to transform the jangling discords of our nation into a beautiful symphony of brotherhood. With this faith we will be able to work together, to pray together, to struggle together, to go to jail together, to stand up for freedom together, knowing that we will be free one day.”

Dr. Martin Luther King; "I Have a Dream" speech on Aug. 28, 1963, as part of the March on Washington