Determining an Appropriate Study Population: Challenges in Policy and Practice

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Disclosures

The views expressed do not necessarily represent the views of the National Heart, Lung and Blood Institute, the National Institutes of Health, or the US Department of Health and Human Services.

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Overview

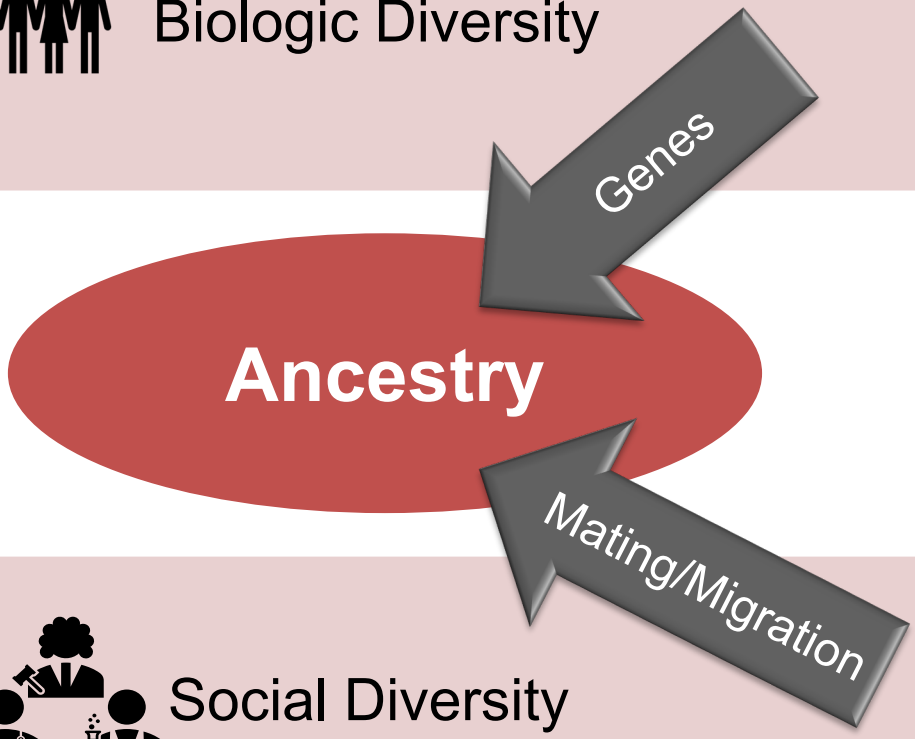
- **Constructs and Complexity**
- Influences on participant inclusion throughout the study life cycle
  - Study design
  - Study implementation
- Case studies

Challenge to appropriate inclusion: Social vs. biological constructs

Biologic Diversity

Genes

Phenotypes (sex, age)



Social Diversity

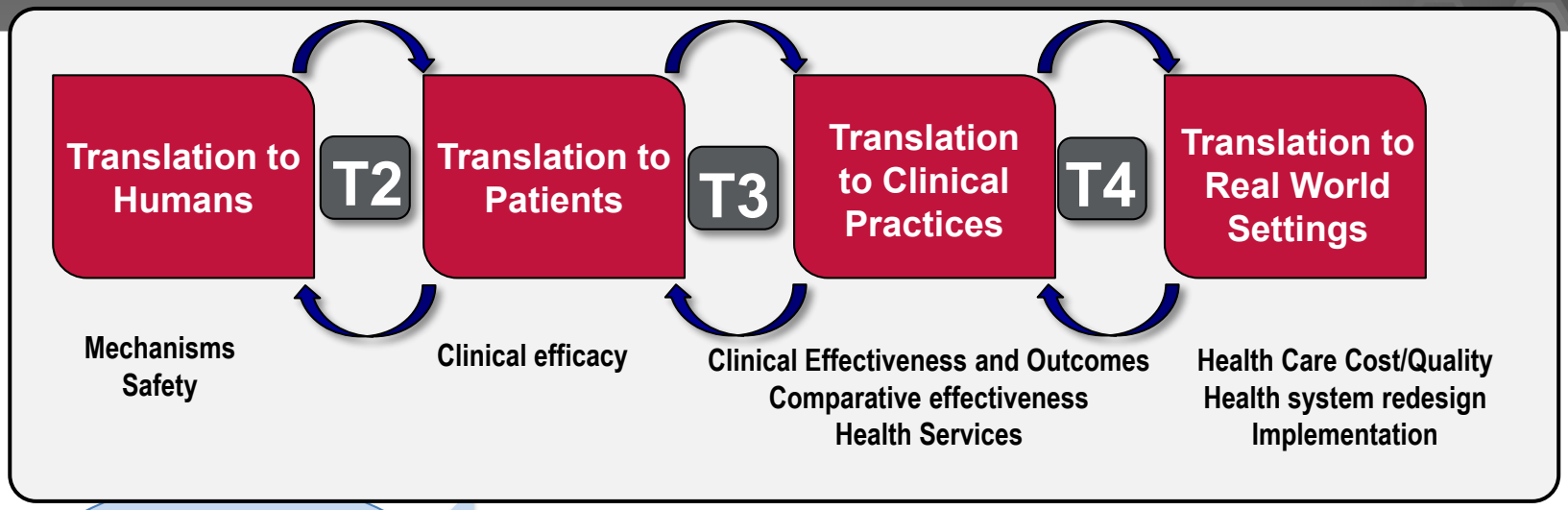
Race/ethnicity

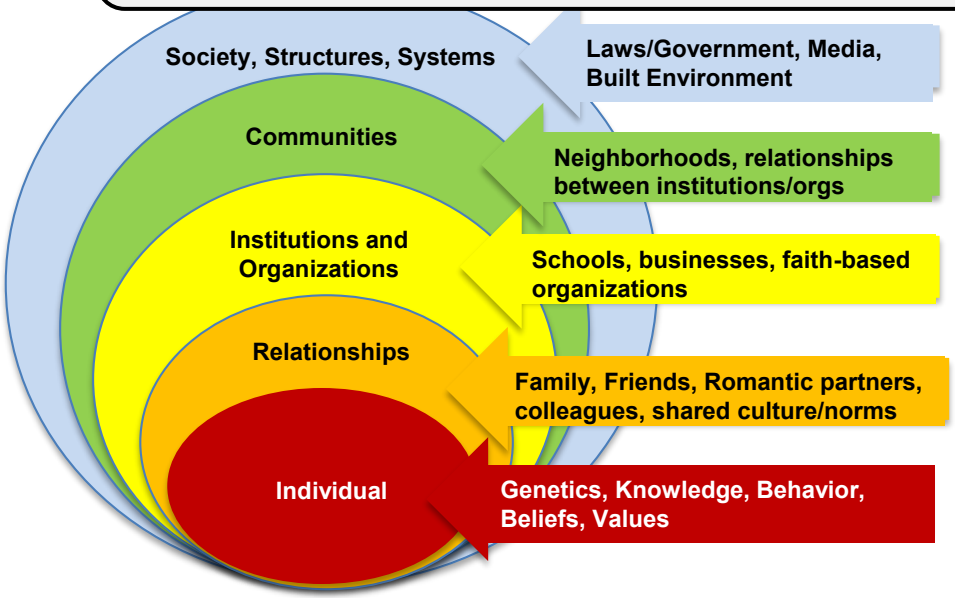
Gender

Environment

Experiences/Exposures

There are levels to this…





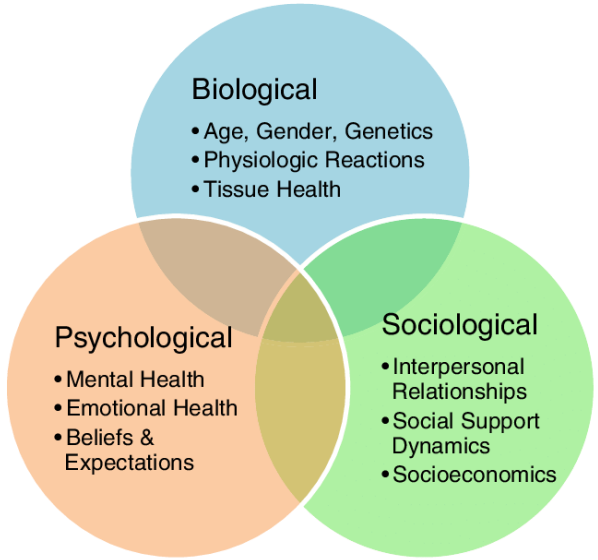


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Image credit: Chiropractic and Manual Therapies. 25. 10.1186/s12998-017-0147-x.

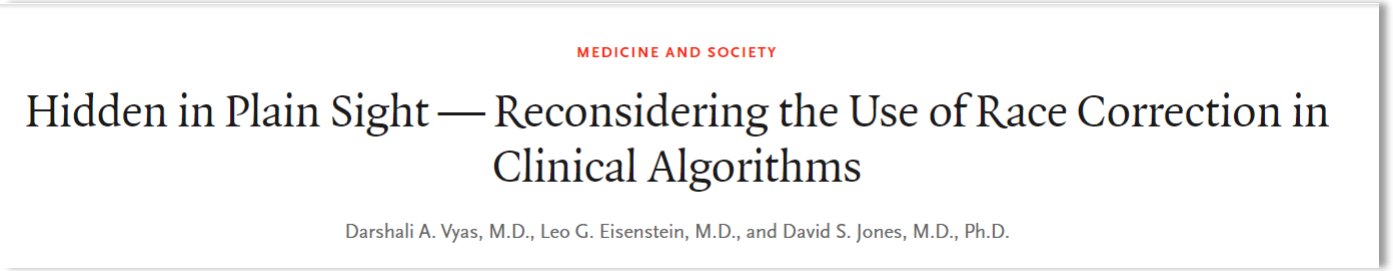
Implications of inadequate inclusion: Hidden in plain sight

MEDICINE AND SOCIETY

Race and Genetic Ancestry in Medicine — A Time for Reckoning with Racism

Luisa N. Borrell, D.D.S., Ph.D., Jennifer R. Elhawary, M.S., Elena Fuentes-Afflick, M.D., M.P.H., Jonathan Witonsky, M.D., Nirav Bhakta, M.D., Ph.D., Alan H.B. Wu, Ph.D., Kirsten Bibbins-Domingo, Ph.D., M.D., José R. Rodríguez-Santana, M.D., Michael A. Lenoir, M.D., James R. Gavin, III, M.D., Ph.D., Rick A. Kittles, Ph.D., Noah A. Zaitlen, Ph.D., et al.

- Lack of diversity in genomic data → gap in access to precision medicine for underrepresented populations
  - Undiscovered/inadequately characterized genotypic and phenotypic variation
  - Potential variation of frequency/effects of genetic variants associated with disease risk may vary across populations



MEDICINE AND SOCIETY

Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms

Darshali A. Vyas, M.D., Leo G. Eisenstein, M.D., and David S. Jones, M.D., Ph.D.

- Clinical algorithms with "race-correction"
  - Best available proxy for ancestry (a determinant of genomic variation)?
  - Proxy for social determinants of health (e.g., environment, discrimination, health care engagement)?

NEJM 2021,384: 474-480
NEJM 2020, 3838:874-882

- Constructs and Complexity
- **Influences on participant inclusion throughout the study life cycle**
  - Study design
  - Study implementation
- Case studies

Study Design: *Study Question and Constructs*

- **Significance of Study Question**
  - Social and scientific value of study question
  - Prior studies regarding the existence of significant differences
  - Importance to and representation of affected population

- **Constructs of interest** (biological, social, or mixed)
  - Theoretical and/or conceptual framework linking participant social, behavioral, and/or clinical characteristics and the topic of study
  - Data collection (appropriate measures)

- **Analysis**
  - Subgroup analysis
  - Impact of participant diversity on power
    - Variability in outcome measurement
    - Variability in magnitude of effect size

https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm

Study Design: *Inclusion and Exclusion Criteria*

- **Justifications for exclusion:**
  - Condition does not occur in the excluded group
  - Topic is not relevant to the excluded group
  - Data/knowledge already available for the excluded group
  - Separate study for the excluded group is warranted or preferable
  - Research involves data from pre-enrolled participants
  - Laws/regulations bar inclusion of individuals in a specific age group in research
  - The study poses unacceptable risk to the excluded group
  - Cost is **NOT** an acceptable exclusion

https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm

Study Design: *Inclusion and Exclusion Criteria*

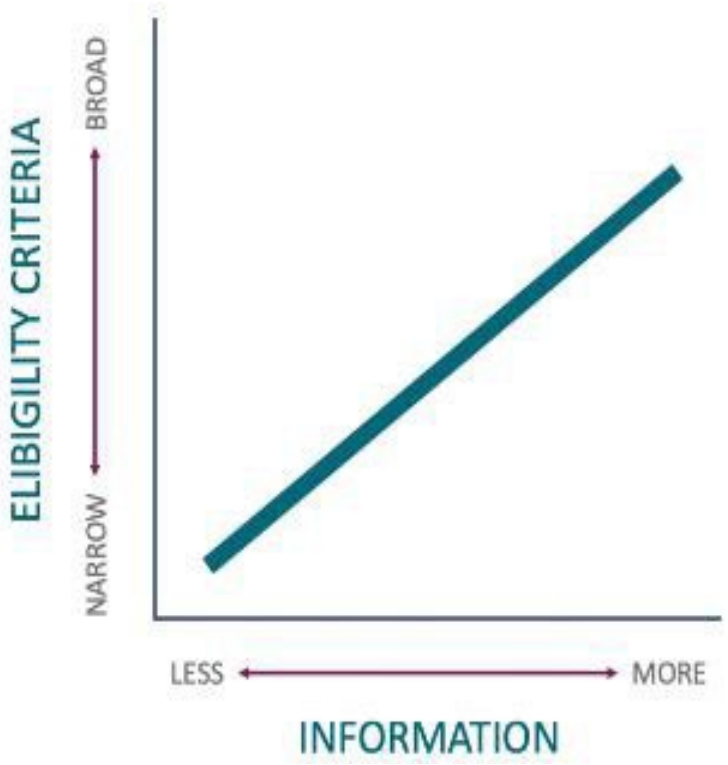
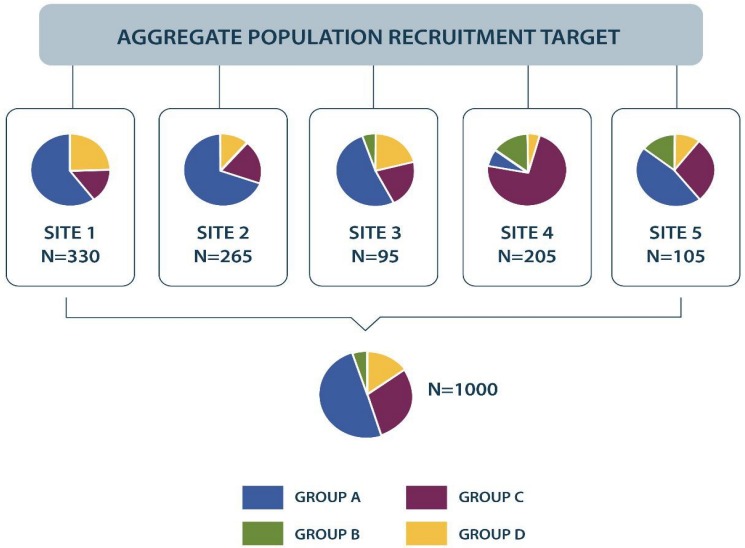


Image Credit: mrctcenter.org/diversity-in-clinical-trials
18 November 2020 Leaning In Webinar Series

- Narrow eligibility criteria = greater similarity
  - Optimizes results consistency
  - Reduces “noise”
- Permissive eligibility criteria = greater diversity
  - Increases heterogeneity of results, **BUT**
  - Potentially reveals differential effects on outcomes, thus increasing generalizability of results

Study Design: *Study Operations*

- Site selection, recruitment capacity
- Personnel
- Recruitment/outreach strategies
- Participant burden
- Retention strategies
- Timeline, budget



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https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm
https://orwh.od.nih.gov/toolkit/recruitment

Study Design: *Troubleshooting*

- Anticipate and provide justification and/or mitigation plan for common concerns, such as:
  - How study participant demographics vary from general population with the disease/condition to be studied
  - Impact that low inclusion may have on scientific aims
  - How the benefits of unique information provided by the proposed study outweigh potentially low inclusion for a subpopulation
  - How prior literature, pilot studies, community experience informs assumptions about recruitment and retention goals *specific to the condition, intervention, and target population*
  - Feasibility (or not) of including additional sites, and/or participants and the impact this may have on study aims
  - Plans (if any) for conducting subset analyses to identify areas for future research

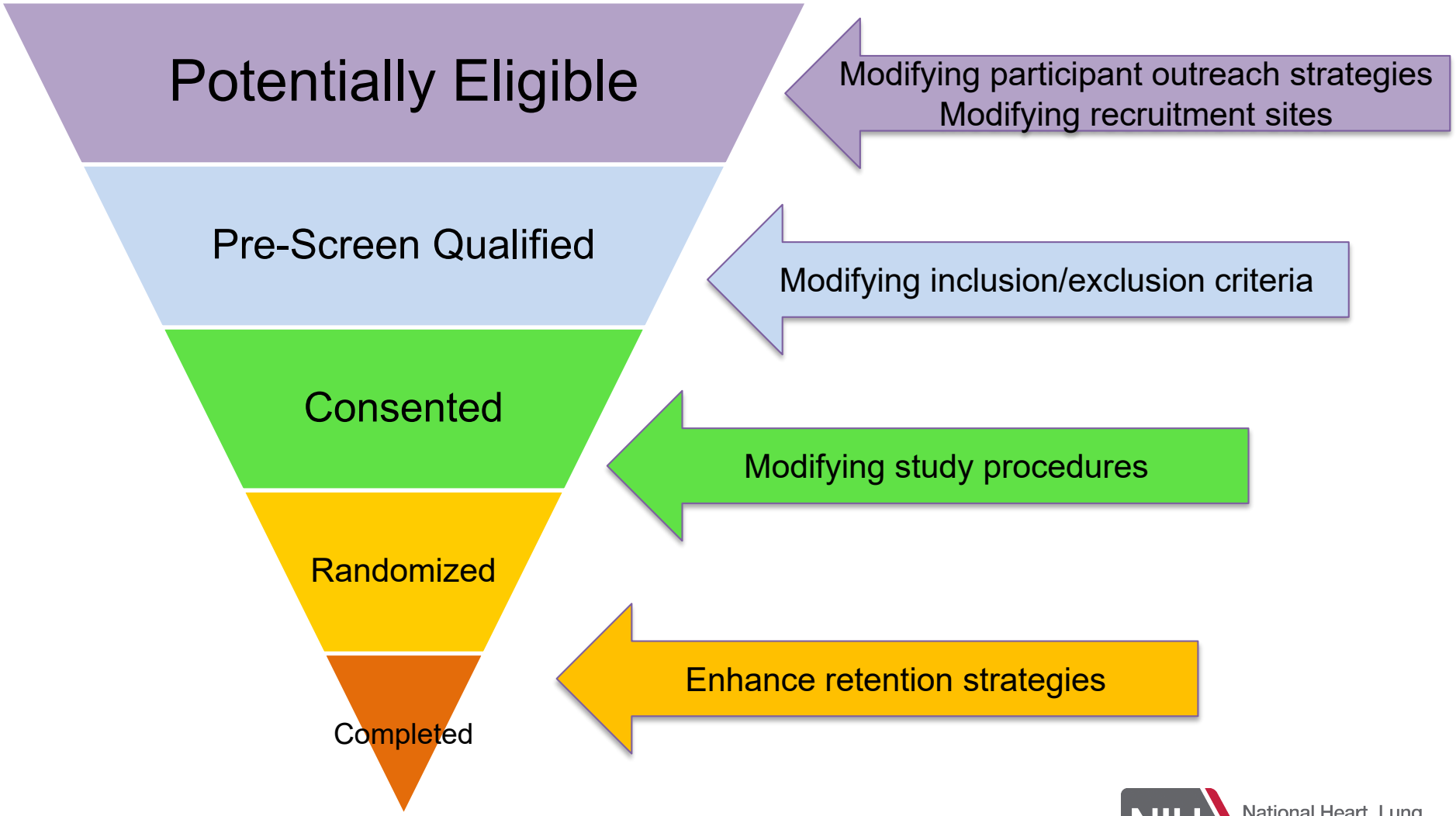
Study Implementation

- **Adherence to NIH Inclusion Policies**
  - Section 2 of the Human Subjects and Clinical Trials (HSCT) Information form must include at least one Inclusion Enrollment Report (IER).
    - Eligibility Criteria
    - Age Limits (Minimum Age and Maximum Age)
    - Inclusion of Individuals Across the Lifespan
    - Inclusion of Women and Minorities
    - Recruitment and Retention Plan

- **Periodic Accrual Monitoring: NHLBI's Human Subjects (Milestone) Accrual Policy/Milestone accrual plan (MAP)**
  - PI and NHLBI staff (and DSMB/OSMB if applicable) agree on benchmarks for participant numbers based upon a recruitment period initiation date, projected recruitment time duration, and final recruitment target.
  - Quarterly accrual reporting

- **Research performance progress report (RPPR)**
  - Compare planned vs. actual enrollment by inclusion categories
  - Address inadequate enrollment issues, mitigation plans prior to renewal

Study Implementation: *Prepare to Pivot*



- Constructs and Complexity
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- **Case studies**

Case studies: *Study Planning*

- Pharmacokinetics study
  - NIH Inclusion policy based on race/ethnicity, not ancestry
  - Can genetic diversity still be adequate in racially homogenous cohort?

- Black women age 30-45 and CV outcomes
  - Justifications for “middle age” age limit?
  - Biological—“perimenopause”? other clinical criteria?
  - Social—life experiences? Program eligibility? Prior data?

Case study: *Study Implementation*

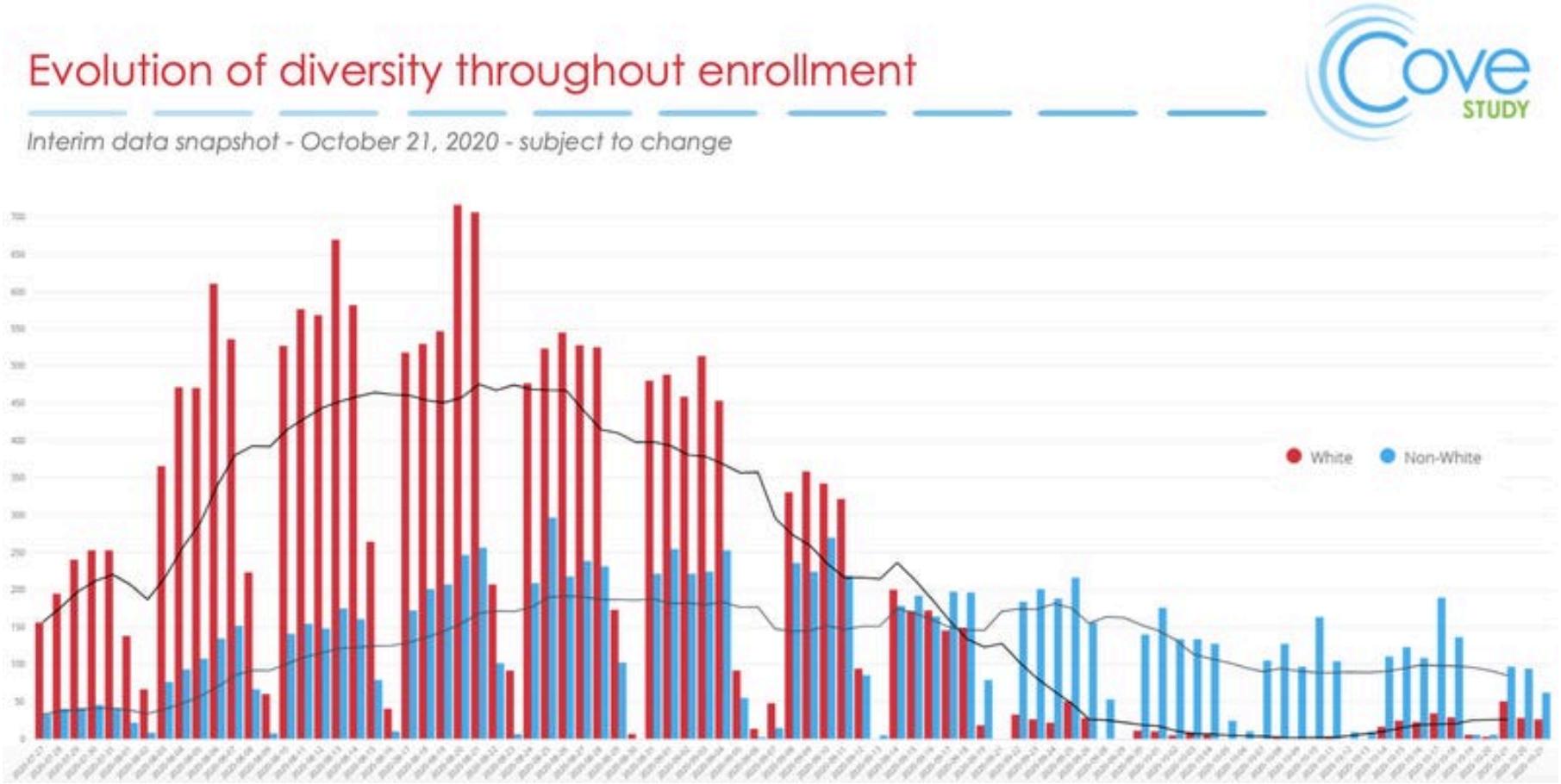

Image source: https://www.businessinsider.com/moderna-completes-coronavirus-vaccine-study-enrollment-with-diversity-2020-10

Summary

- Carefully consider your study question and conceptual framework
  - Selection of measures
  - Intervention design
- Understand the impact of your study design on participant selection, enrollment, and retention
  - Trade-offs
  - Feasibility
  - Resources (e.g., personnel, timeline, budget)

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NIH resources for investigators and program staff

- NIH Inclusion Policies for Research Involving Human Subjects
  - 45 CFR 46 Subpart B – Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research
  - 45 CFR 46 Subpart D – Additional Protections for Children Involved as Subjects in Research
- NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research
  - NIH Grants Policy Statement, Section 4.1.15.8: Inclusion of Women and Minorities as Subjects in Clinical Research and Reporting Sex/Gender, Racial, and Ethnic Participation
- NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects
  - NIH Grants Policy Statement, Section 4.1.15.7: Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects
- Guidelines for the Review of Inclusion on the Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research

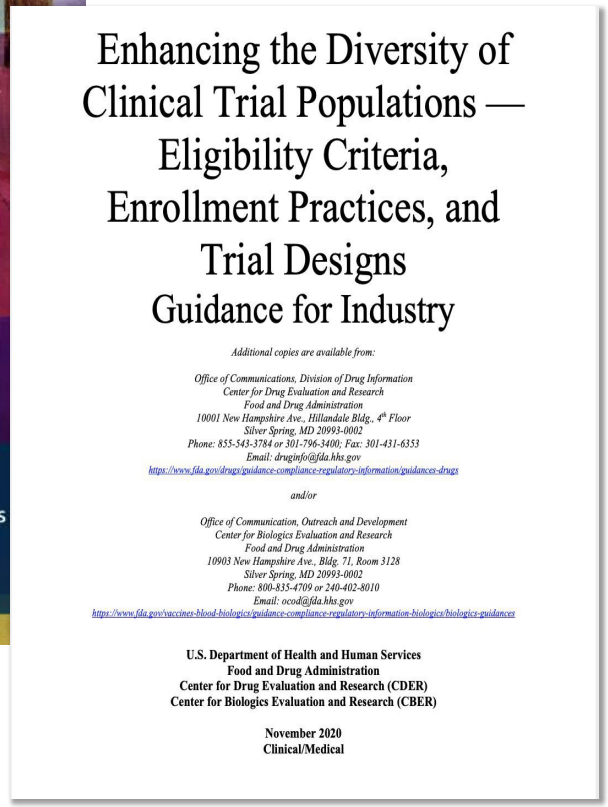
For Program Staff

- NIH OER Inclusion FAQs
- NIH Extramural Intranet Inclusion General Staff FAQs
- Inclusion and the RPPR: A Quick Guide for Program and Grants Management Staff

External resources for investigators and program staff

Recording available	Community Awareness, Access, Knowledge
Recording available	Workforce Development
Recording available	Study Design, Eligibility, Site Selection & Feasibility
Recording available	Study Conduct (Recruitment, Retention)
Recording available	Data Standards and Analysis
Recording available	Stakeholder Roles and Responsibilities
February 10, 2021	Role of Data in Diversity: Genetics & Real World Data

mrctcenter.org/diversity-in-clinical-trials



https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial

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Definitions

Genetics	Study of heredity; function and composition of single genes
Genomics	Study of genes, their functions, inter-relationships and related techniques
Pharmacogenomics	Study of how genes affect a person's response to particular drugs
Geographic Ancestry	Geographic locations of family origins
Genetic Ancestry	Method of quantifying ancestral background statistically by understanding genome history; different genomic segments may have their own ancestral history
Race	Sociocultural construct; not biologically distinct entities; genetically admixed populations
Precision Medicine	Identification of which approaches effective for which patients based on genetic, environmental, and lifestyle factors