Optimizing Inclusion: Challenges in Policy and Practice

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Disclosures

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Overview

- Why inclusion matters
- NIH inclusion policies
  - Brief history
  - Challenges to implementation
- Program touch points
  - Pre-application
  - Application/Review
  - Pre-award
  - Post-award
- Case studies

- **Why inclusion matters**
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Why inclusion matters: Do the right thing!

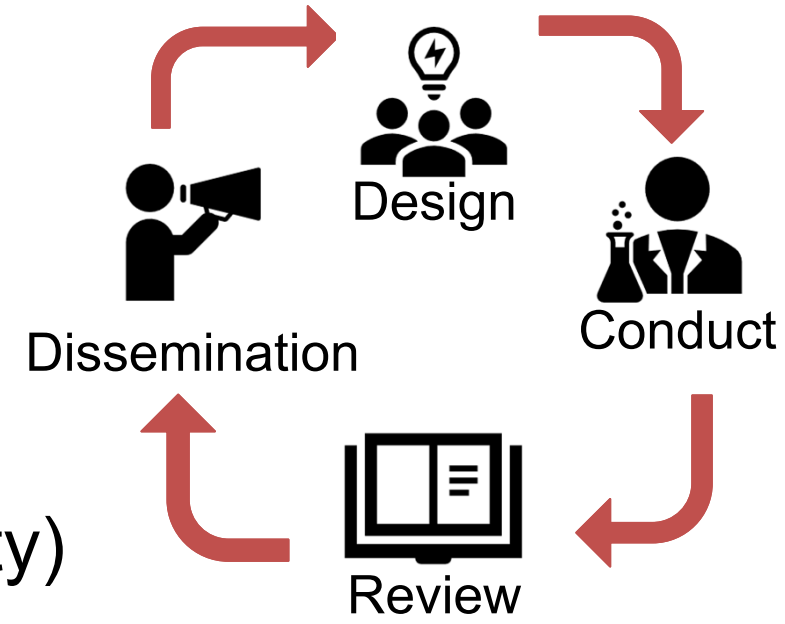
- Do the right thing: JUSTICE
  - Who does this impact?
  - Who is/isn't included?
  - Who benefits/is at risk?
  - Who participates?
  - Who leads?

- Equity in federal investment in research

- Equity in health outcomes

Why inclusion matters: Do things right!

- Doing things right: RIGOR
  - Robust
  - Unbiased
  - Reproducible
  - Transparent



- Results we can trust (validity)

- Results we can use (generalizability)

https://grants.nih.gov/policy/reproducibility/index.htm

- Why inclusion matters
- **NIH inclusion policies**
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Brief history of inclusion policies: Women and Minorities

- NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research
  - NIH Revitalization Act of 1993, PL 103-43 directed the NIH to establish guidelines for inclusion of women and minorities in clinical research
  - Amended in 2017 to include a requirement for applicable NIH-defined Phase III clinical trials to report results of valid analyses by sex/gender, race, and/or ethnicity

https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm
https://grants.nih.gov/faqs#/inclusion-basic-on-sex-gender-and-race-ethnicity.htm

Brief history of inclusion policies: Inclusion across the Lifespan

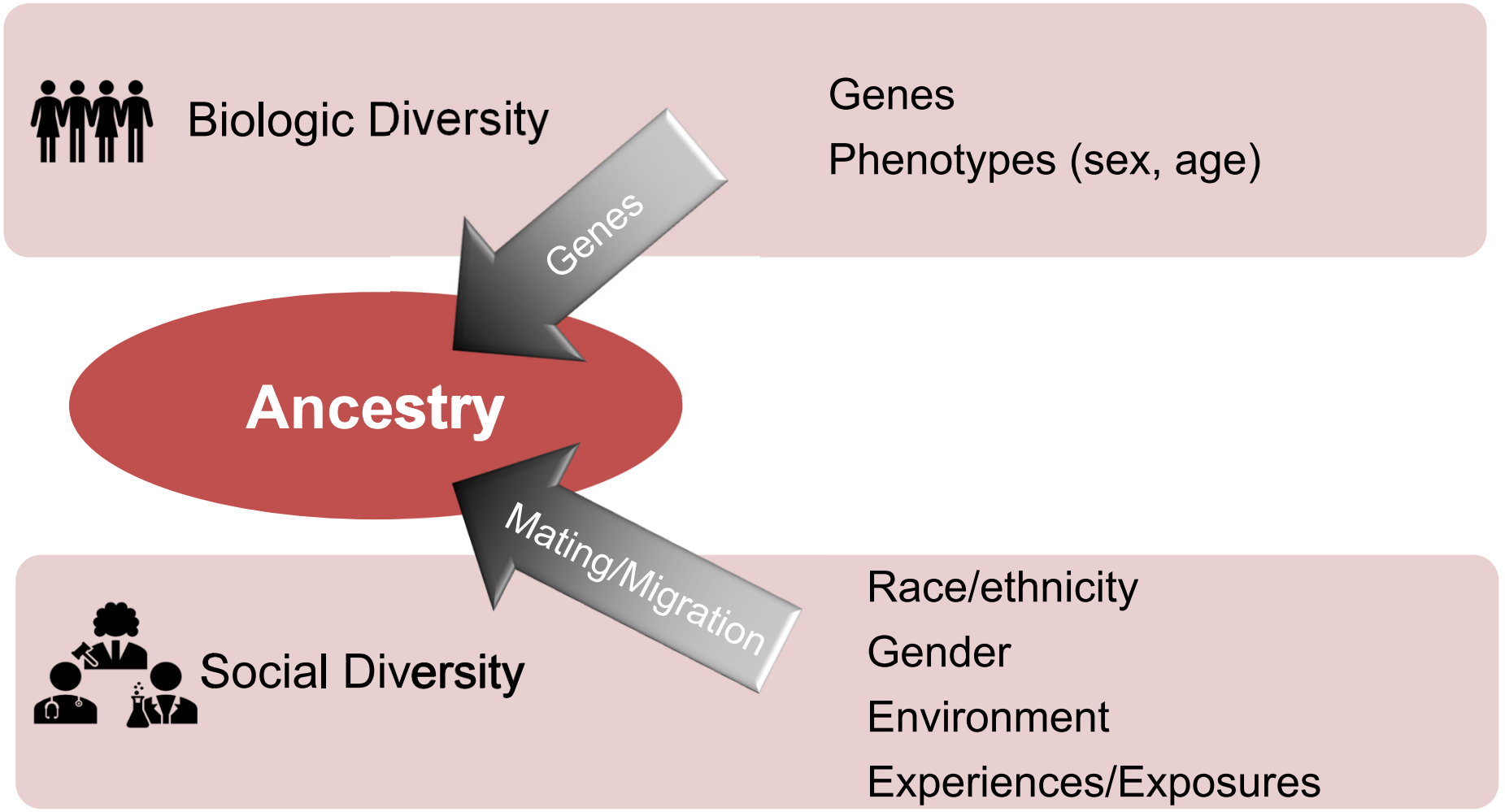
- NOT-OD-18-116 NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects
  - Initiated beginning with competing grant applications due on/after January 25, 2019
  - Principal investigators (PIs) must make efforts to include all age groups, especially children (<18 years) and older adults (≥65 years) so that study populations are representative of the target patient population.

Brief history of inclusion policies: NIH and Institute/Center inclusion reporting

- NIH Revitalization Act of 1993 requires NIH-level and IC-level reporting of inclusion data to Congress on a biennial basis
  - Reports provide enrollment data by sex/gender, race, and ethnicity.
  - Includes grants and contracts with human subjects; excludes analyses of existing data sets

- New requirements in the 21st Century Cures Act, 2016:
  - Triennial reporting
  - Report inclusion data by Research, Condition, and Disease Categories (RCDC) codes.

Challenge to implementing inclusion policy: Social vs. biological constructs



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

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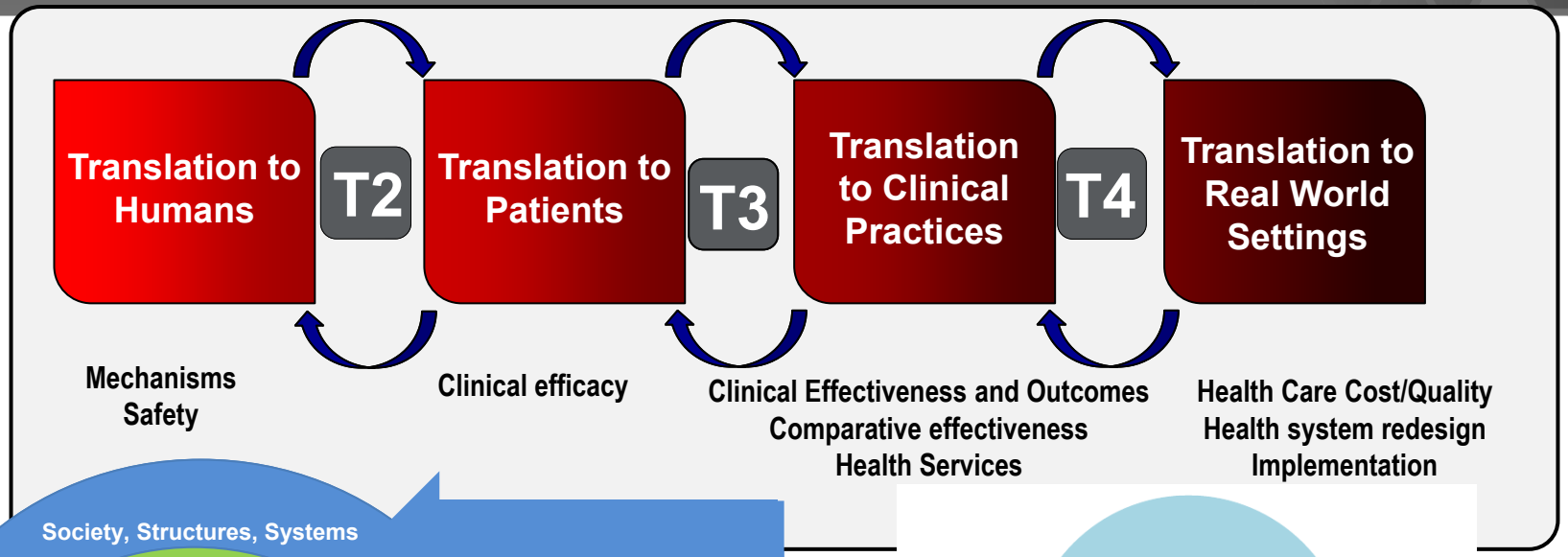
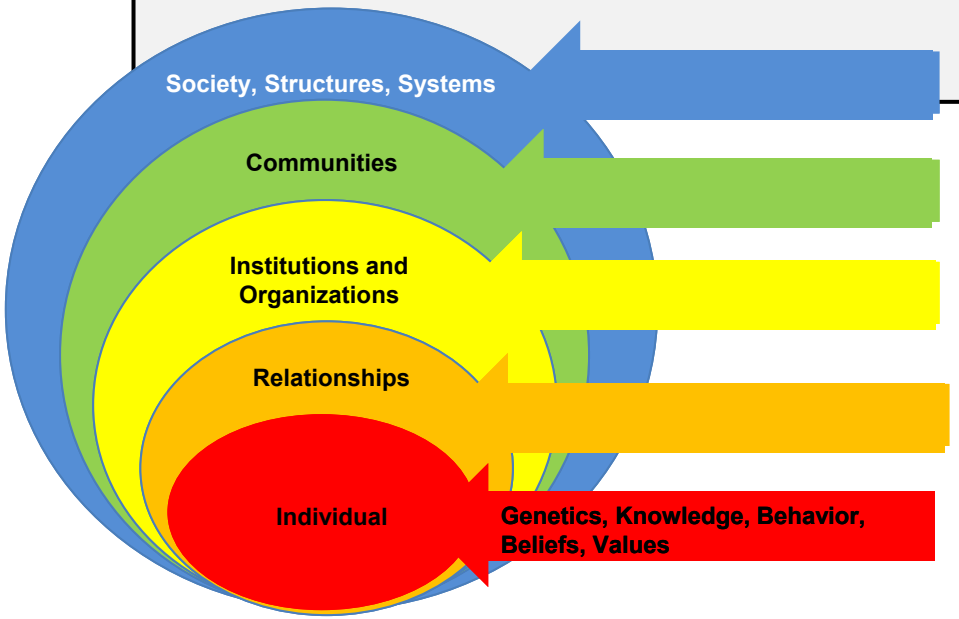
There are levels to this…





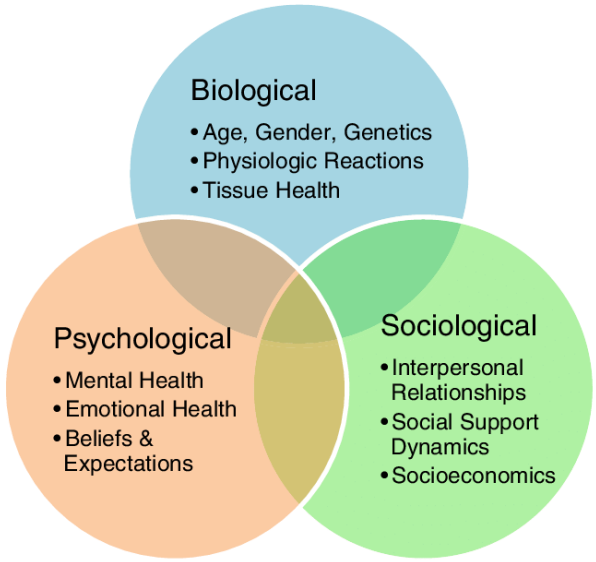


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Image credit: Chiropractic and Manual Therapies. 25. 10.1186/s12998-017-0147-x.

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Inclusion touch-points for program staff
Pre-application consultation

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

- **Constructs of interest** (biological, social, or mixed)
  - Theoretical and/or scientific linkages between sex/gender, race/ethnicity, and the topic of study
  - Data collection (appropriate measures)
  - Subgroup analysis
  - Impact of participant diversity on power
    - Variability in outcome measurement
    - Variability in magnitude of effect size

Inclusion touch-points for program staff
Pre-application consultation

- **Inclusion/exclusion criteria:**
  - Condition does not occur in the

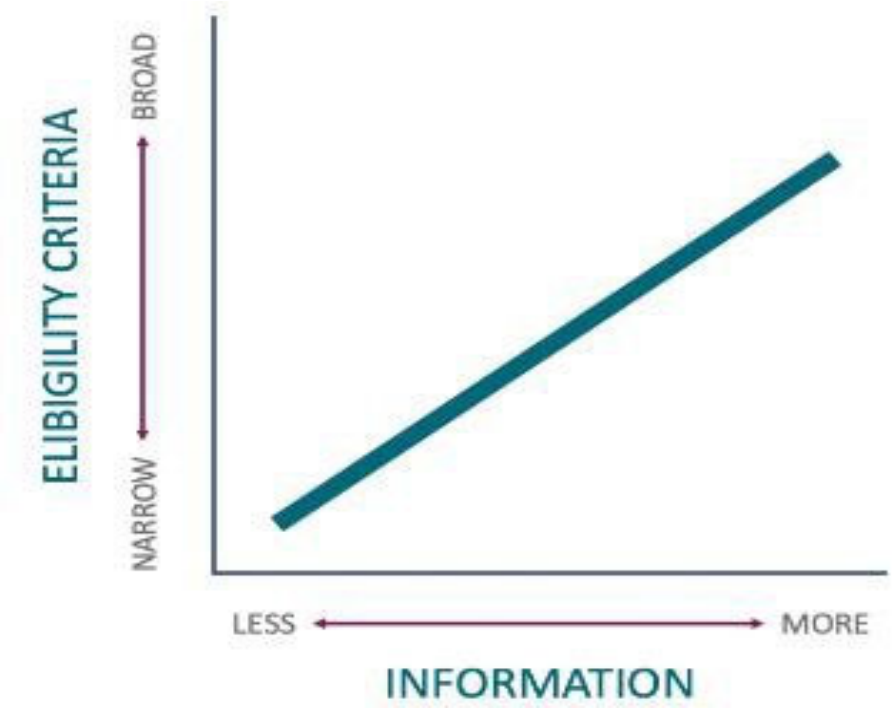


Image Credit: mrctcenter.org/diversity-in-clinical-trials
18 November 2020 Leaning In Webinar Series

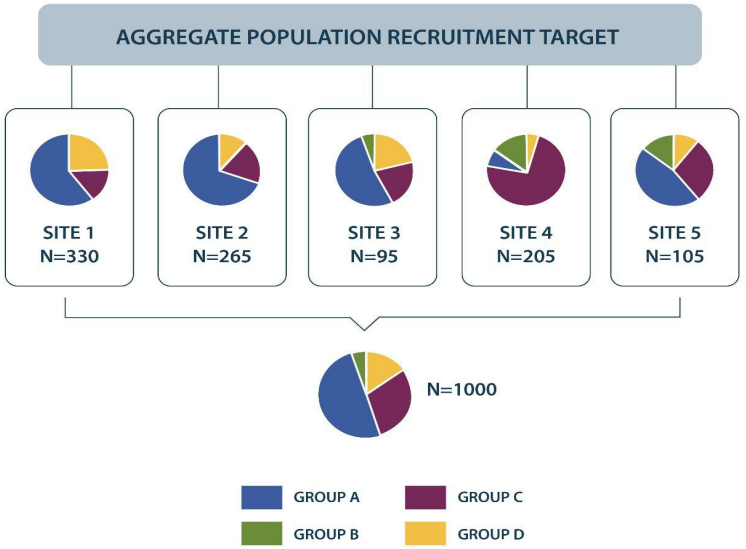
    the excluded group
  - Cost is **NOT** an acceptable exclusion

- 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

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

Inclusion touch-points for program staff
Pre-application consultation

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



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

NIH National Institutes of Health
Office of Research on Women's Health
Putting science to work for the health of women

https://orwh.od.nih.gov/toolkit/recruitment

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

Inclusion touch-points for program staff Application/Review

- **Application**
  - 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

- **Review**
  - Scientific Review Groups (SRGs) will assess each application/proposal as being "acceptable" or "unacceptable"
  - Reviewer inclusion concerns must be resolved prior to issuance of Notice of Award (NoA)

Inclusion touch-points for program staff Post-review/Pre-award

- Investigators should provide a justification that addresses reviewer concerns, such as:
  - How study participant demographics vary from general population with the disease/condition to be studied
  - Impact that low inclusion has on scientific aims
  - Feasibility (or not) of including additional datasets, sites, and/or participants and the impact this may have on study aims
  - How the benefits of unique information provided by the existing cohort/dataset and why this outweighs low inclusion
  - Plans (if any) for conducting subset analyses to identify areas for future research

Inclusion touch-points for program staff
Post-award monitoring

- 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 monitoring
  - PI reports overall accrual
  - NHLBI Clinical Dashboard for monitoring
  - Zones based on % of benchmark accrual for a given time point within study
    - **Green ≥75%**
    - **Yellow 50-75%**
    - **Red <25% of the benchmark at the 25% or 50% time point; <50% at 75% time point**

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

https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/accrual-of-human-subjects-milestones-policy

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Case studies

- 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 studies

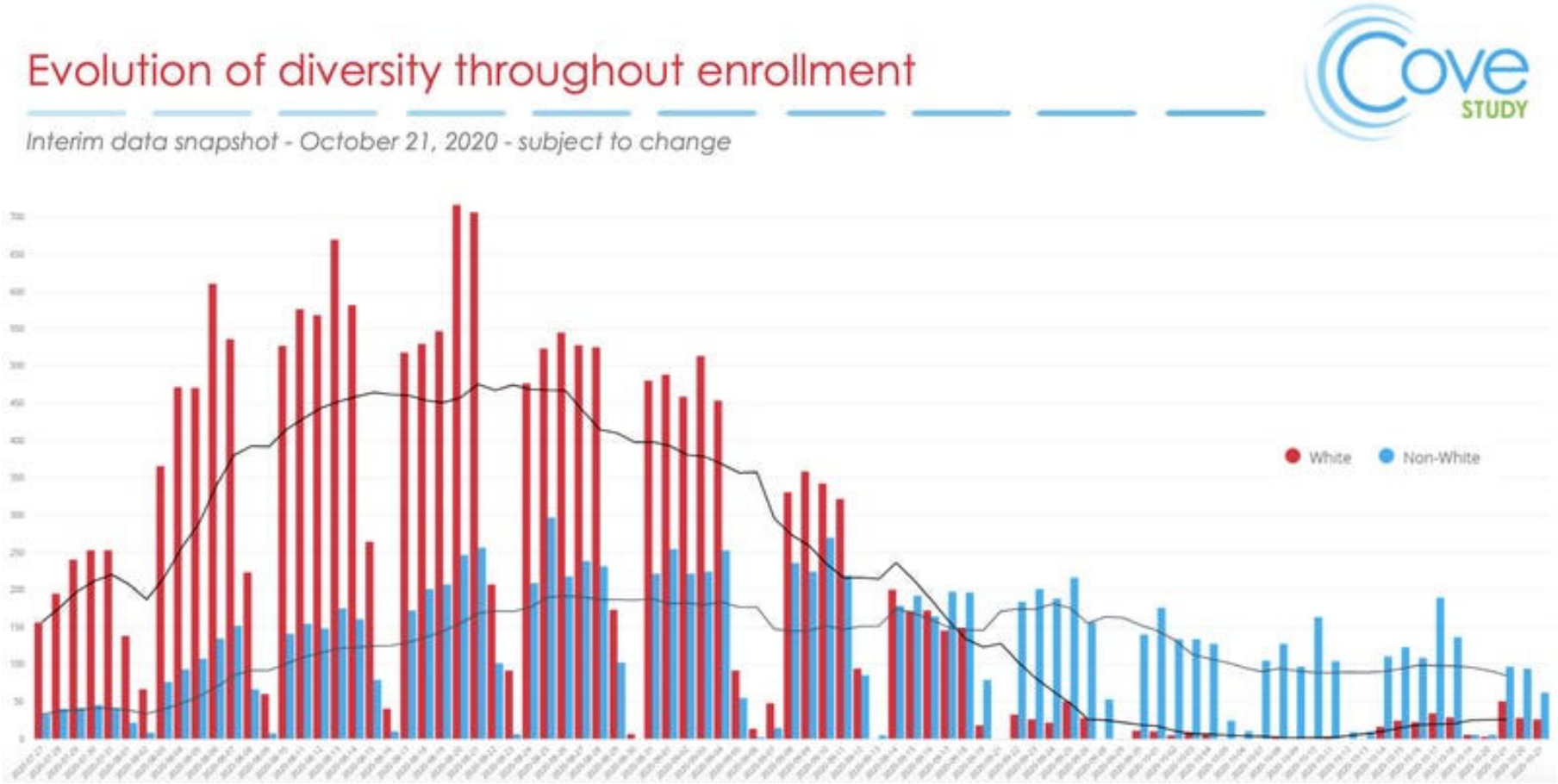


Image source: https://www.businessinsider.com/moderna-completes-coronavirus-vaccine-study-enrollment-with-diversity-2020-10

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

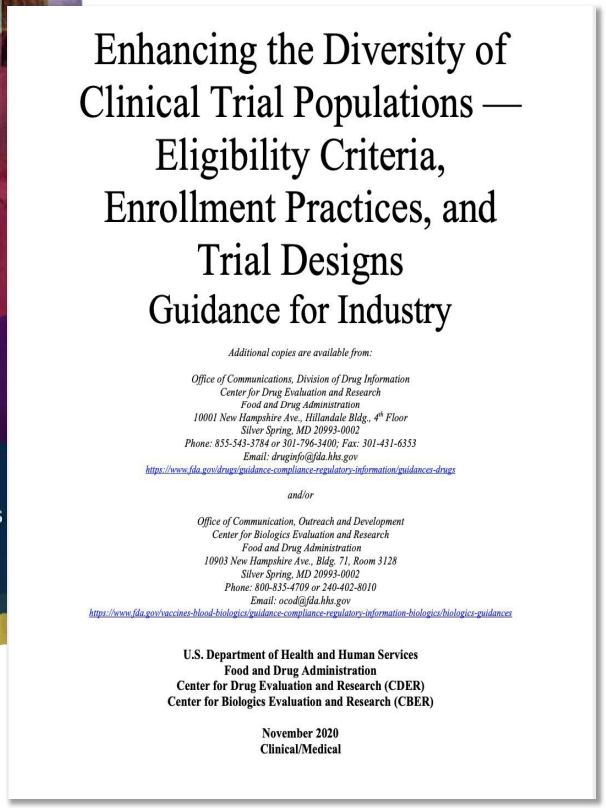
For Program Staff

- 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


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

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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

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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Additional NIH resources for program staff

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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