Optimizing Inclusion: Challenges in Policy and Practice

Nicole Redmond, MD, PhD, MPH
Physician
Clinical Applications and Prevention Branch
Division of Cardiovascular Sciences

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

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

[Links to NIH guidelines and FAQs]

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

Biologic Diversity

Genes
Phenotypes (sex, age)

Ancestry

Mating/Migration

Race/ethnicity
Gender
Environment
Experiences/Exposures

Social Diversity
Implications of inadequate inclusion: Hidden in plain sight

- 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

- 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)?

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.

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.

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NEJM 2021, 384: 474-480
NEJM 2020, 3838:874-882
There are levels to this…

Translation to Humans
Mechanisms Safety

Translation to Patients
Clinical efficacy

Translation to Clinical Practices
Clinical Effectiveness and Outcomes
Health Services

Translation to Real World Settings
Health Care Cost/Quality
Health system redesign
Implementation

Society, Structures, Systems
Communities
Institutions and Organizations
Relationships
Individual
Genetics, Knowledge, Behavior, Beliefs, Values

Biological
• Age, Gender, Genetics
• Physiologic Reactions
• Tissue Health

Psychological
• Mental Health
• Emotional Health
• Beliefs & Expectations

Sociological
• Interpersonal Relationships
• Social Support Dynamics
• Socioeconomics

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 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

- 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

- Cost is **NOT** an acceptable exclusion

Image Credit: mrctcenter.org/diversity-in-clinical-trials
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the excluded group

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

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https://mrctcenter.org/diversity-in-clinical-trials/

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

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

Why inclusion matters

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  - Challenges to implementation

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Case studies
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

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

Driving Inclusion in Clinical Research
Second Wednesday monthly
11AM -12PM ET
LEARNING IN: A WEBINAR SERIES

Practical Approaches to Improving Diversity in Clinical Trials
Wednesdays
11AM -12noon ET
LEARNING IN: A WEBINAR SERIES

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 NIH resources 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
## Definitions

<table>
<thead>
<tr>
<th>Genetics</th>
<th>Study of heredity; function and composition of single genes</th>
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<tbody>
<tr>
<td>Genomics</td>
<td>Study of genes, their functions, inter-relationships and related techniques</td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td>Study of how genes affect a person’s response to particular drugs</td>
</tr>
<tr>
<td>Geographic Ancestry</td>
<td>Geographic locations of family origins</td>
</tr>
<tr>
<td>Genetic Ancestry</td>
<td>Method of quantifying ancestral background statistically by understanding genome history; different genomic segments may have their own ancestral history</td>
</tr>
<tr>
<td>Race</td>
<td>Sociocultural construct; not biologically distinct entities; genetically admixed populations</td>
</tr>
<tr>
<td>Precision Medicine</td>
<td>Identification of which approaches effective for which patients based on genetic, environmental, and lifestyle factors</td>
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</tbody>
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February 10, 2021
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