Determining an Appropriate Study Population: Challenges in Policy and Practice

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NIH 2023 Workshop on Inclusive Participation in Clinical Research

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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
- Social Diversity

- Genes
  - Phenotypes (sex, age)

- Ancestry

- Race/ethnicity
- Gender
- Environment
- Experiences/Exposures

- Mating/Migration
There are levels to this:

- **Translation to Humans**
  - Mechanisms
  - Safety

- **Translation to Patients**
  - Clinical efficacy

- **Translation to Clinical Practices**
  - Clinical Effectiveness and Outcomes
  - Comparative effectiveness
  - Health Services

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

Levels include:

- **Individual**
  - Genetics
  - Knowledge
  - Behavior
  - Beliefs
  - Values

- **Relationships**
  - Family
  - Friends
  - Romantic partners
  - Colleagues
  - Shared culture/norms

- **Institutions and Organizations**
  - Schools
  - Businesses
  - Faith-based organizations

- **Communities**
  - Neighborhoods
  - Relationships between institutions/orgs

- **Society, Structures, Systems**
  - Laws
  - Government
  - Media
  - Built Environment

**Translation to**

- **Humans**
- **Patients**
- **Clinical Practices**
- **Real World Settings**

**Mechanisms**

- Safety

**Clinical efficacy**

- Clinical Effectiveness
- Comparative effectiveness

**Health Care Cost/Quality**

- Health system redesign
- Implementation

**Laws/Government, Media, Built Environment**

**Translation to**

- Humans
- Patients
- Clinical Practices
- Real World Settings

**T1**

- Genetic
- Knowledge
- Behavior
- Beliefs
- Values

**T2**

- Family
- Friends
- Romantic partners
- Colleagues
- Shared culture

**T3**

- Schools
- Businesses
- Faith-based organizations

**T4**

- Neighborhoods
- Relationships between institutions/orgs

**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.
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)?
• 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

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

Study Design: Inclusion and Exclusion Criteria

- 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

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

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

An NIH Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research

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

- Potentially Eligible
  - Pre-Screen Qualified
  - Consented
  - Randomized
  - Completed

- Modifying participant outreach strategies
  - Modifying recruitment sites
- Modifying inclusion/exclusion criteria
- Modifying study procedures
- Enhance retention strategies

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National Heart, Lung, and Blood Institute
- Constructs and Complexity
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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

Evolution of diversity throughout enrollment

Interim data snapshot - October 21, 2020 - subject to change

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)
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

Practical Approaches to Improving Diversity in Clinical Trials
Wednesdays
11AM – 12noon ET

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


mrctcenter.org/diversity-in-clinical-trials
## Definitions

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<th>Term</th>
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<tbody>
<tr>
<td>Genetics</td>
<td>Study of heredity; function and composition of single genes</td>
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<tr>
<td>Genomics</td>
<td>Study of genes, their functions, inter-relationships and related techniques</td>
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<tr>
<td>Pharmacogenomics</td>
<td>Study of how genes affect a person’s response to particular drugs</td>
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<td>Geographic Ancestry</td>
<td>Geographic locations of family origins</td>
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<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>
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<tr>
<td>Race</td>
<td>Sociocultural construct; not biologically distinct entities; genetically admixed populations</td>
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<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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