



Considering Inclusion in Research: Scientific and Policy Perspectives

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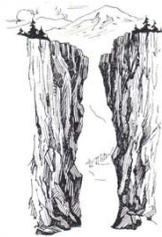
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Outline and Learning Objectives

- The importance of diversity in clinical studies
- Considering inclusion as essential to good science
- NIH Revitalization Act: 1993
- Intersection of good science and policy compliance
- Know the requirements for addressing inclusion of women, minorities, and children in NIH grant applications
- What's on the radar?
- Conclusion

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Obstacles in Translating Discovery to Health



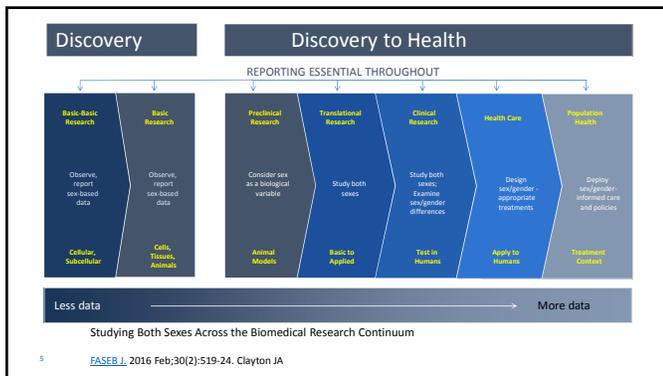
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Benefits from Inclusion



- Advances in knowledge from research
- Incorporating knowledge into education, training
- Implementing new concepts into practice
- Changing standards of practice, public health
- Providing access to sex/gender and ethnic/racial/culturally sensitive and appropriate healthcare
- Need diversified workforce to design studies, recruit participants, implement findings

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Diabetes Prevention Program (DPP) – Lessons Learned:

- (1) a method for ongoing assessment and revision of recruitment strategies is valuable;
- (2) a range of recruitment strategies may be useful;
- (3) the most effective methods for recruiting potential subjects may vary according to the gender, age, and race/ethnicity of those individuals;
- (4) recruitment strategies vary in the amount of staff time required to randomize a participant;
- (5) a stepped screening may make it easier to identify and recruit volunteers who understand the requirements of the study.

our findings suggest that attempts to recruit older adults might concentrate on direct mail, since these individuals may be less likely to participate in screenings and community events or to see posters and newsletters.⁶

6 The Diabetes Prevention Program: recruitment methods and results: Controlled Clinical Trials 23 (2002) 157-172

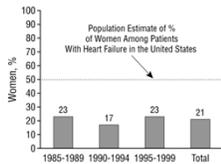
Sex and Gender Differences - Women's Ischemia Syndrome Evaluation (WISE) Study

- 50% of enrollees with symptoms had no blockages
- Impaired microvasculature function not detectable by angiography
- Different methods necessary to diagnose cardiac ischemia in women than in men
- Most common early symptoms in women are sleep disturbance, fatigue, shortness of breath.
- Sex differences in disease symptoms

The Women's Ischemia Syndrome Evaluation (WISE) Study: protocol design, methodology and feasibility report. American College of Cardiology. 1999;33(8):1453-1461. <http://content.onlinejacc.org/article.aspx?articleid=1125777>

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Biased Enrollment Criteria – Selecting out women

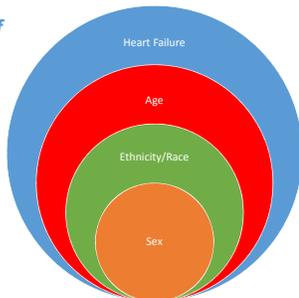


Women were underrepresented in the HF clinical trials when compared with their representation in the general population of HF patients. This study found that enrollment of women was significantly associated with the mean age of participants in HF trials.

Enrollment of women in heart failure randomized controlled trials.

8 Representation of the Elderly, Women, and Minorities in Heart Failure Clinical Trials Arch Intern Med. 2002;162(15):doi:10.1001/archinte.162.15.1682

Heart Failure – Missing Part of the Whole



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Barriers to Recruitment and Retention of Women and Minorities in Clinical Trials

- Fear and distrust of research enterprise
- Lack of knowledge
- Lack of transportation
- Interference with work and/or family responsibilities
- Burden as a result of participation
- Financial costs



Outreach notebook for the inclusion, recruitment and retention of women and minority subjects in clinical research: principal investigators' notebook. National Institutes of Health (U.S.); National Institutes of Health (U.S.). Office of Research on Women's Health, 2002. NIH publication, no. 03-7036.

Facilitators to Recruitment and Retention of Women and Minorities in Clinical Trials

- Cultural and linguistic adaptation of recruitment strategies
- Translation of materials into appropriate languages
- Enlisting culturally and linguistically competent research staff
- Including families and communities in a dialogue
- Partnering with community organizations
- Including investigators and staff from the same targeted communities as participants and retaining the same staff and interviewers over time to ensure continuity.+

"... Successful recruitment strategies for African American women should feature community-based, culturally appropriate approaches."*

"...consent should be considered an ongoing process - a dialogue - rather than a discrete act of choice that takes place in a singular moment in time, thus supporting participants in making informed decisions throughout the trial" +

11 * A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. *Am J Public Health*. 2014 February; 104(2): e16-e31.
 + Perceptions of Clinical Research Participation among African American Women. *J Women Health* (Larchmont). 2007 April; 16(3):413-428

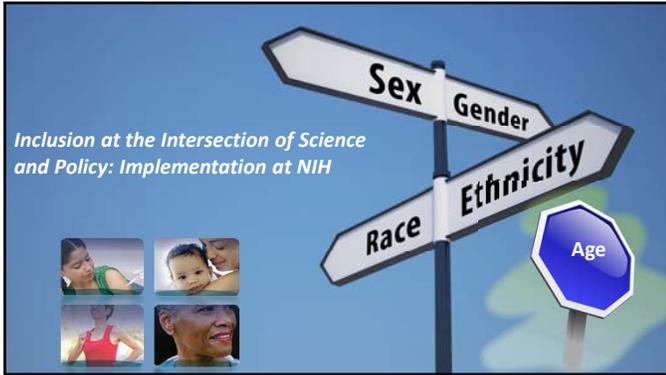
An NIH Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research

- The NIH Outreach Toolkit is intended to help principal investigators and their research teams fulfill their responsibilities to include women in clinical research.



The toolkit includes:

- A review of research on recruitment and outreach best practices
- Information on Federal laws, regulations, and NIH policies on the inclusion of women in clinical research
- Case studies featuring researchers' experience with including women in their studies



NIH Inclusion Policies

- **Inclusion of Women and Minorities**
 - Must be included in NIH-defined clinical research unless exclusion is justified for scientific reasons
 - Justify the proposed sample in the context of who is at risk for the disease/condition and the scientific goals of the specific study
 - Plans for outreach and recruitment
 - Provide Inclusion Enrollment Report form(s) with proposed sex/gender, race, and ethnicity of the sample
 - For Phase III clinical trials, address considerations of trial design and analysis
- **Inclusion of Children**
 - Children must be included in clinical research unless there are scientific or ethical reasons not to do so
 - "Children" are defined by the NIH as individuals <18 years
 - Applicants should justify the proposed age range of the participants, with specific attention to justifying the inclusion/exclusion of individuals under 18

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Defining the Universe

- **What is subject to the statute/policies?**
 - All studies (intramural, extramural, contracts) that meet the NIH definition of clinical research
 - **NIH definition of clinical research:** (1) **Patient-Oriented Research:** Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual (e.g., IRB Exemption 4). Patient-oriented research includes (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical studies, or (d) development of new technologies; (2) **Epidemiologic and Behavioral Studies;** and (3) **Outcomes Research and Health Services Research**
 - Additional requirements for NIH-defined Phase III clinical trials related to unbiased design and assessment of potential differences
- **Bottom line:**
 - If you answer yes to human subjects and not E4, you should address inclusion.

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But what does it mean to include?

- **Purpose Statement:** NIH supported clinical research should address/include the population(s) at risk for the disease or condition under study. The purpose of NIH Inclusion Policies is to ensure that the distribution of study participants by sex/gender, race, ethnicity, and age reflects the population needed to accomplish the scientific goals of the study, rather than enumeration of research participants. All NIH-funded studies that meet the NIH definition for clinical research are subject to NIH Inclusion Policies, regardless of funding mechanism*. (*Funding mechanism includes any activity code associated with extramural grants, R&D contracts, and cooperative agreements as well as intramural projects and R&D contracts)
- **Bottom line:** Thinking more broadly about inclusion → Does the study have the right people for the science?



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NIH Inclusion Re-Engineering Project

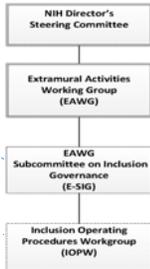
- NIH Inclusion Task Force (2010)
- Reorganized governance structure (2011)
- Business Process Modeling and data system redesign (2011-2014)
 - Identification of pain points in management of inclusion policies
- Release of new Inclusion Management System (IMS) (2014)
 - Data system used to collect and report sex/gender, race, and ethnicity
 - New functionality continues to be added (2015-present)
- Updates to procedures for monitoring inclusion (2013-present)
 - Revise forms for data collection
 - Updated reviewer guidelines and review templates
 - Eliminate exception codes
 - Standardize reporting process



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Inclusion Policy Governance Structure

- **E-SIG Co-Chairs:**
 - Janine Clayton, Director, NIH Office of Research on Women's Health
 - Marie Bernard, Deputy Director, National Institute on Aging
 - Staffed by NIH Inclusion Policy Officer
 - **Membership includes:**
 - NIH Institutes/Centers with small, medium, or large clinical research/clinical trial portfolios
 - Representation from different business areas: extramural, intramural, contracts, review, legal, technical/system
 - **Function:**
 - To provide guidance and oversight regarding inclusion policies and procedures
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- **Chair:** NIH Inclusion Policy Officer and IC Member
 - **Trans-NIH membership**
 - Four breakout groups: Policy/Data, Training, System Users, and Clinical Research Review Group
 - **Functions:**
 - To provide input and feedback to the E-SIG on inclusion business process/policy
 - To enhance communication between E-SIG, NIH Office of the Director, and ICs



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What's required for inclusion in a competing NIH application?

- Remember the "universe" to determine whether inclusion applies to your application
 - ◊ NOTE: Follow the scenarios described in Human Subjects' protection section to further understand what's expected for different scenarios
- Plans for inclusion of women and minorities
 - Includes addressing plans for valid analysis if conducting an NIH-defined Phase III clinical trial
- Plans for the inclusion of children
- Inclusion enrollment report
 - Planned or Cumulative (actual) information depending on the study design
- Missing plans may be subject to application return



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Peer Review of Inclusion

- Each reviewer will assess the inclusion plans
 - Plans for inclusion
 - Justification in the context of the science
 - http://grants.nih.gov/grants/peer/guidelines_general/Review_Human_Subjects_Inclusion.pdf
- Peer review group will determine overall rating of "acceptable" or "unacceptable"
- Summary Statement:
 - INCLUSION OF WOMEN, MINORITIES, AND/OR CHILDREN: UNACCEPTABLE (U CODE)
 - Unacceptable (U) code is a bar to award



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Common Inclusion Concerns Identified in Peer Review

- Inadequate information describing the sex/gender, race, ethnicity, and/or age(s) of the sample
- Inadequate justification for proposed sample
 - Sex/gender, race, ethnicity, and/or age(s) breakdown not appropriate for the scientific goals of the study or not adequately justified
- Unrealistic sampling
 - Appropriate from scientific perspective but not realistic
 - Collaborations and outreach plans may help



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"Just-in-Time" Requirements

- **After peer review, for grants likely to be funded:**
 - Work with Institute/Center staff to resolve unacceptable inclusion concerns, usually involves a written response to IC
 - Provide inclusion enrollment report(s) if missing or need update as a result of peer review and/or programmatic adjustments



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*After the Award...
Now What?*



- **Funded investigators provide cumulative inclusion enrollment (e.g., actual enrollment) information at least annually or as frequently as specified by the funding Institute/Center**
- **For NIH-defined Phase III Clinical Trial– report any analysis or findings related to outcomes by sex/gender, race, and ethnicity if available**
- **Note progress (or challenges) in recruitment as needed in the progress report**

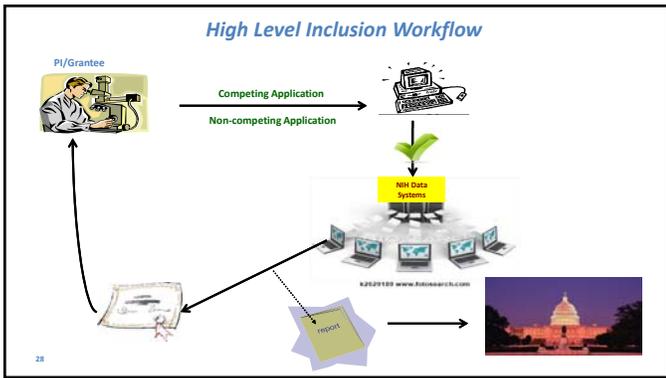
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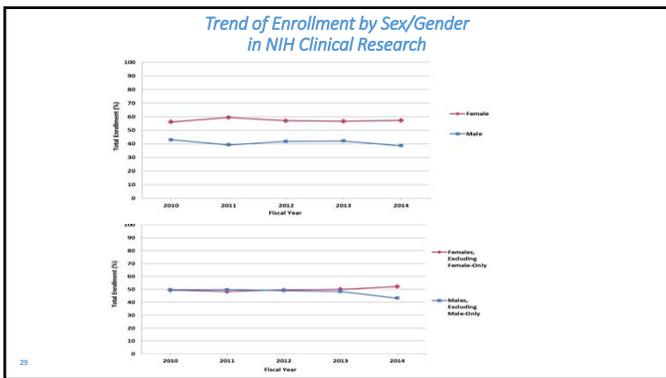
Other Important Inclusion Information

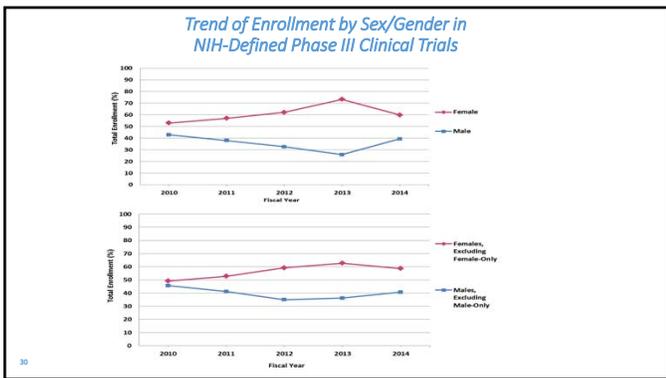
- **Defining sex/gender, race, and ethnicity**
 - Sex at birth vs. gender identity: What's important for your scientific question?
 - Race/Ethnicity
 - Required to use the OMB standards (Directive 15, revised in 1997)
 - Ethnic Categories
 - Hispanic or Latino
 - Not Hispanic or Latino
 - Racial Categories (select all that apply)
 - American Indian or Alaska Native
 - Asian
 - Black or African American
 - Native Hawaiian or Other Pacific Islander
 - White
 - More than one race (use this when more than one selected)
- **Collecting and reporting information from participants**
 - NIH report format for investigators, not participants
 - Usually based on self-identification
 - How you ask is important!
 - Ask ethnicity first, then race
- **US vs. Non-US research**
 - Inclusion policy applies to both
 - Considering race and ethnicity in a foreign context

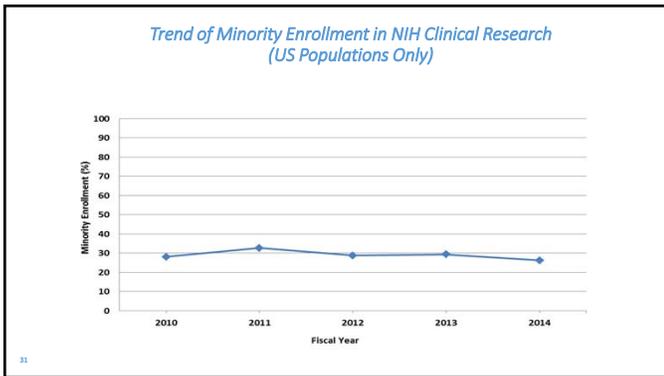


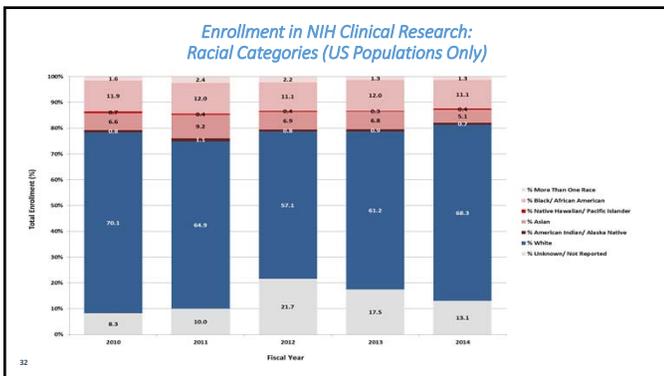
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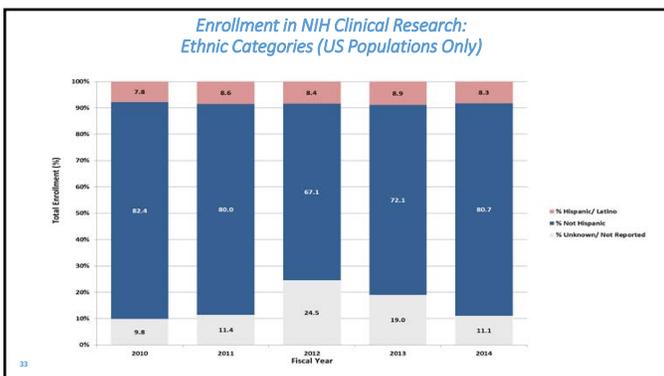


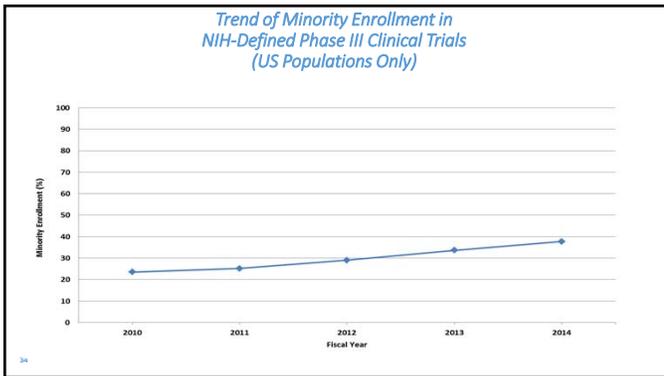


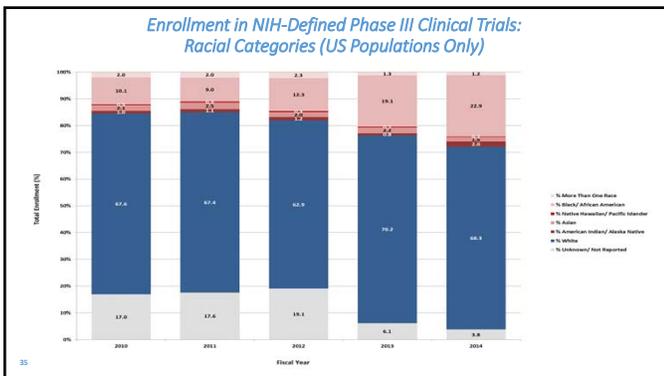


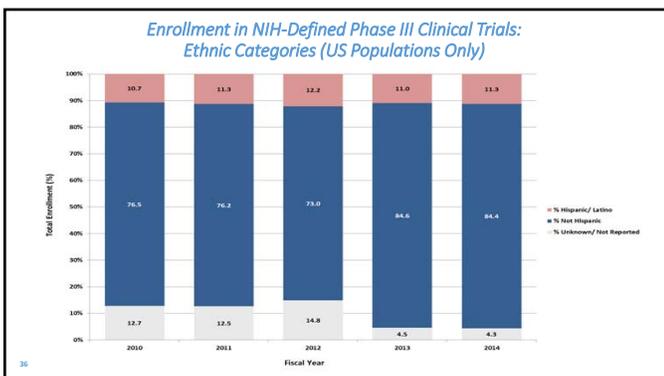














What's on the radar?

*Broader Context:
Congressional Interest in Inclusion*

- **Minority enrollment in clinical trials**
 - Recent articles highlight inclusion policy and peer review concerns
- **Inclusion of different age groups**
 - Language in 21st Century Cures bill (House)
 - Development of trans-NIH workshop
- **Inclusion of women**
 - Longstanding concern
 - FDA/Ambien
 - GAO study on the inclusion of women in clinical trials



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GAO Study on Women in Clinical Trials Recommendations

- Recommendation 1:
Make IC-level enrollment data readily available through public means, such as its regular biennial report to Congress on the inclusion of women in research, or through its website
- Recommendation 2:
Examine approaches for aggregating more detailed enrollment data at the disease and condition level, and report on the status of this examination to key stakeholders and through its regular biennial report to Congress on the inclusion of women in research
- Recommendation 3:
Ensure that program officers have a means of recording their monitoring of awardees plans for and progress in conducting analysis of potential sex differences;
- Recommendation 4:
On a regular basis, systematically collect and analyze summary data regarding awardees' plans for analysis of potential sex differences, such as the proportion of trials being conducted that intend to analyze differences in outcomes for men and women
- Recommendation 5:
Report on this summary data and analysis in its regular biennial report to Congress on the inclusion of women in research

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Summary/Conclusions

- NIH has made progress on addressing inclusion in clinical research
- More to be done
 - Analysis and results reporting
 - Further understanding of inclusion in our research portfolio
- Primary aim of policy is to collect scientific information leading to changes in standard of care
- We have gained knowledge broadly applicable to health care



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Questions?



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