



Essential to Rigorous and Relevant Scientific Research and Health Equity

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Learning objectives



LEARN ABOUT

- Inclusion and its importance in clinical research
- Barriers to recruitment of diverse populations for clinical studies
- Factors that facilitate recruitment and retention of diverse populations
- Reasons sex and gender matter in biomedical research



Rigor & relevance

The NIH is mandated by the Public Health Service Act sec. 492B, 42 U.S.C. sec. 289a-2 to ensure the inclusion of women and minority groups in all NIH-funded clinical research in a manner **that is appropriate to the scientific question under study**. The primary goal of this law is to ensure that research findings can be **generalizable to the entire population**.



Who can participate in a clinical study?

The factors that allow someone to participate in a clinical study are called **inclusion criteria**. They are often based on characteristics such as **age, gender, the type and stage of a disease, previous treatment history, and other medical conditions**.

Inclusion achieves more representative studies



- Seeks distribution of participants by sex/gender, race, ethnicity, and age to reflect populations needed to meet study goals
- 42 USC 289a-2 and the 1993 NIH Revitalization Act require researchers to include women and men
- In response to the 21st Century Cures Act, NIH issued the Inclusion Across the Lifespan policy, subsuming its Inclusion of Children policy
 - Requires inclusion **of all ages** – unless there’s scientific or ethical rationale for exclusion

“Insights garnered from this expanded inclusion approach could enhance **reproducibility** and **generalizability** of clinical study findings.”¹

¹ Bernard MA, Clayton JA and Lauer MS. 2018. Inclusion Across the Lifespan: NIH Policy for Clinical Research. *JAMA* 320(15):1535-1536. doi:10.1001/jama.2018.12368



The importance of Inclusion

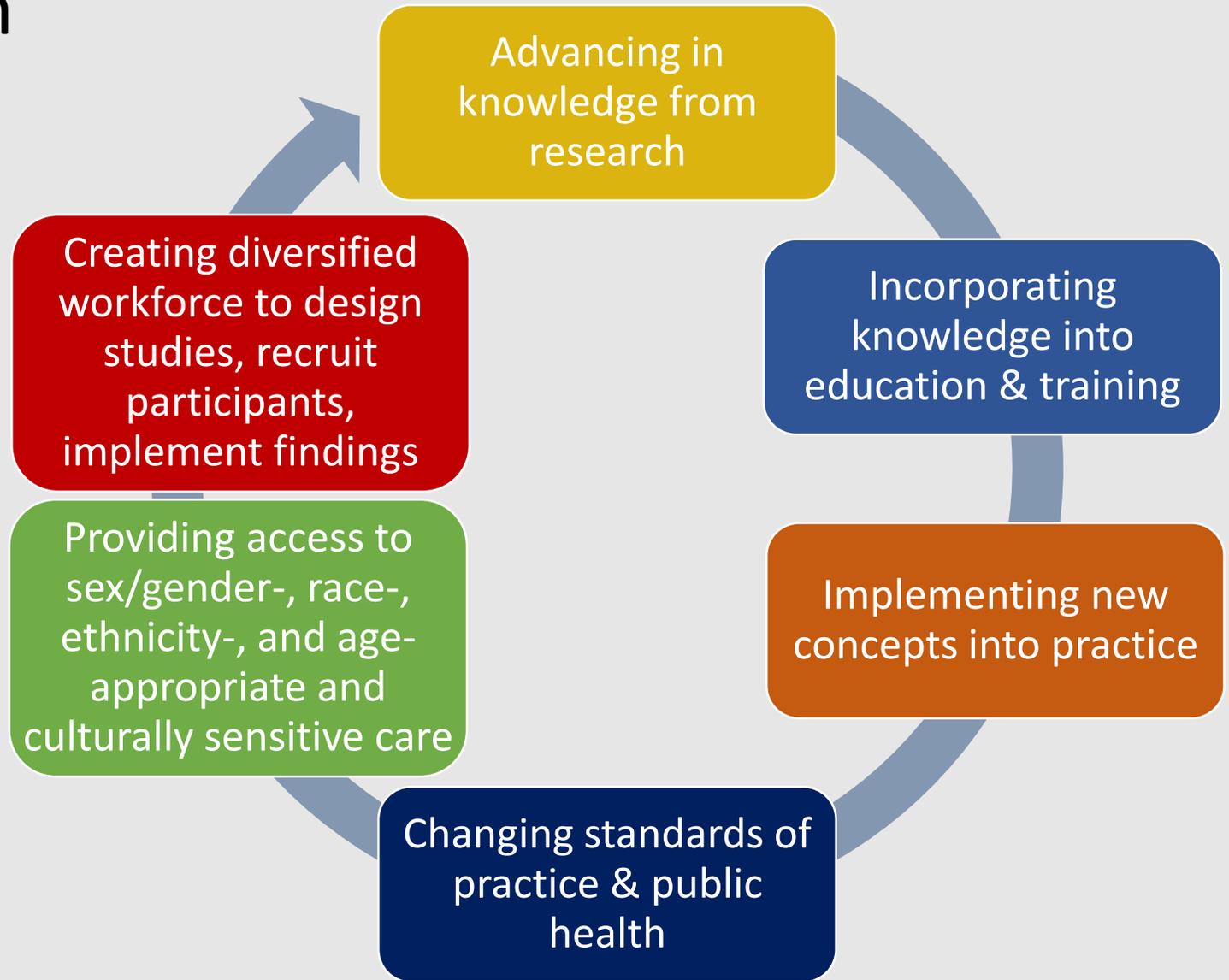
- Captures populations more at risk for certain diseases
- Gives more complete picture of the risk and benefit of intervention
- Addresses differences in clinical outcomes because of biological, cultural, social, or economic factors
- Ensures more equitable distribution of participation in research
- Tests safety and efficacy of treatments in people who will use them

That's why including diverse populations is essential!

Benefits of Inclusion



Photo by Anthony Metcalfe on Unsplash



**Never
asked**

**Fear
and
distrust**

**Expenses
&
logistical
issues**

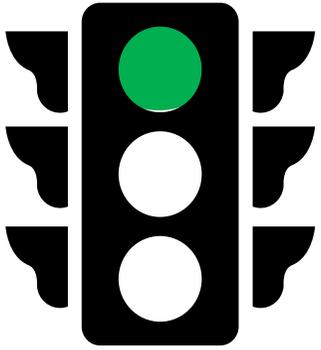
**Lack
of
knowledge**

**Complex
consent
process**

**Work/
family
responsibilities**

**Barriers to participation
of women and minorities**

Ways to recruit and retain women and minorities



- Adapt recruitment strategies for cultural and linguistic backgrounds
- Translate materials into appropriate languages
- Enlist culturally and linguistically competent research staff
- Include families and communities in a dialogue
- Partner with community organizations
- Utilize and retain investigators and staff from the targeted communities – to facilitate acceptance and ensure continuity.¹

“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.”¹

“Successful recruitment strategies for African American women should feature community-based, culturally appropriate approaches.”²

1) George S. et al. 2014. *AMJ Public Health*. 104(2): e16-e31.

2) Smith YR et al. 2007. *J Women’s Health* 16(3):423-428.

Why sex and gender matter in biomedical research

SEX¹

Derived from the chromosomal complement

Every cell has a sex (XX or XY)

- Begins *in utero*
- Affects behavior and perception
- Affects health—from disease risk to treatment response

GENDER²

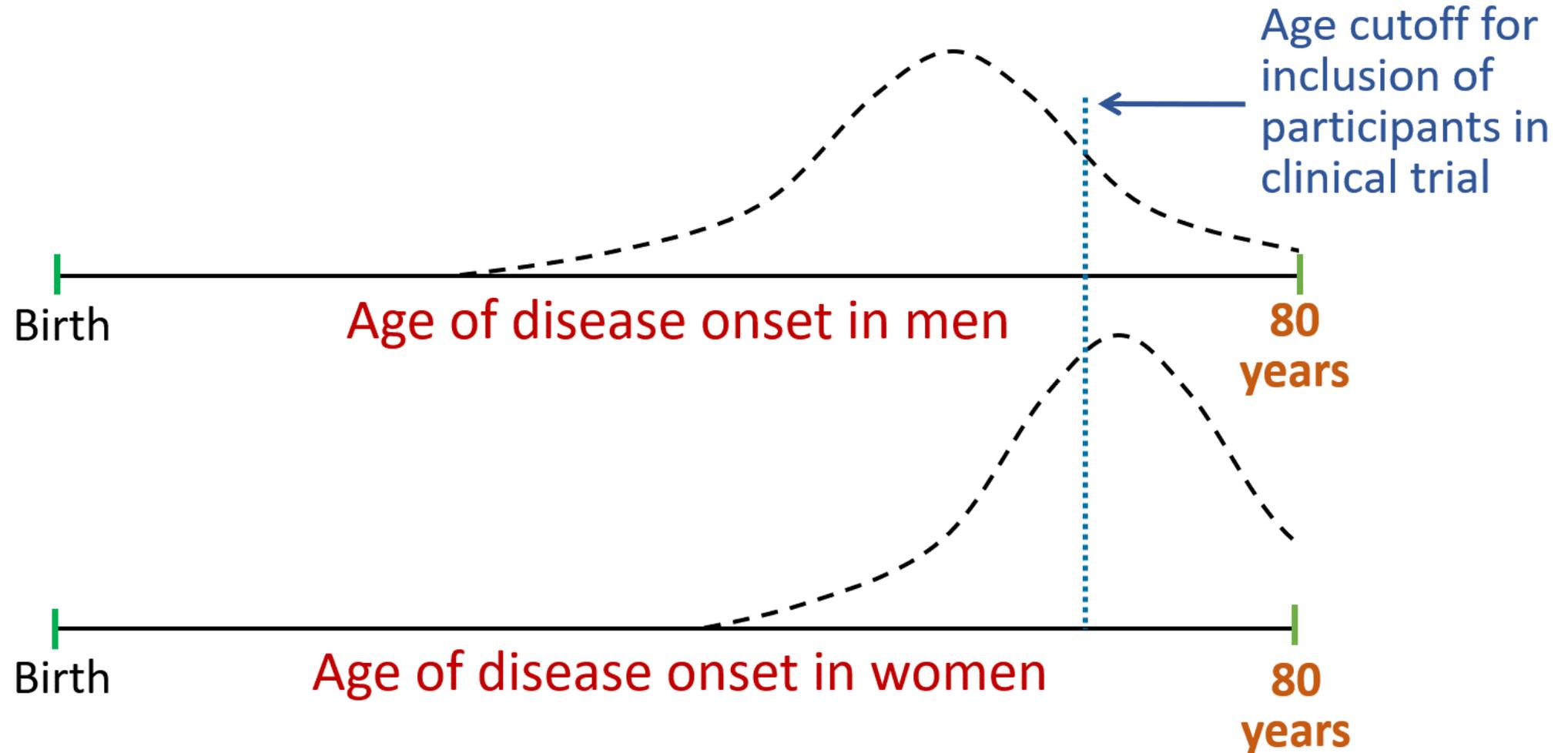
Multidimensional psychosocial construct that integrates roles, behaviors, expressions, and identities of girls, women, boys, men, and gender-diverse people

- Influences how people perceive themselves and others and how they act and interact
- Begins after birth
- Affects behavior and health
- Lacks agreed-upon definition in U.S.

¹Exploring the Biological Contributions to Human Health: Does Sex Matter, IOM Report , 2001

²<https://orwh.od.nih.gov/sex-gender/sexgender-influences-health-and-disease/infographic-how-sexgender-influence-health>

Is study population representative of those with disease or condition in wider population?



Case studies on Inclusion practices

User's Note: For case studies illustrating the effectiveness of various inclusion practices, visit <http://bit.ly/ORWHCaseStudies>. Topics include:

- “Facebook Advertising to Recruit Young, Urban Women into an HIV Prevention Clinical Trial”
- “Cervical Cancer Prevention”
- “Treatments for Menopause Symptoms
- “Caries Prevention in Young Children”
- “Diabetes Prevention”

S A B V

Why study sex as a biological variable?



To build a knowledge base that better informs the design of clinical research and trials in humans



To deliver personalized care based on studies of both sexes

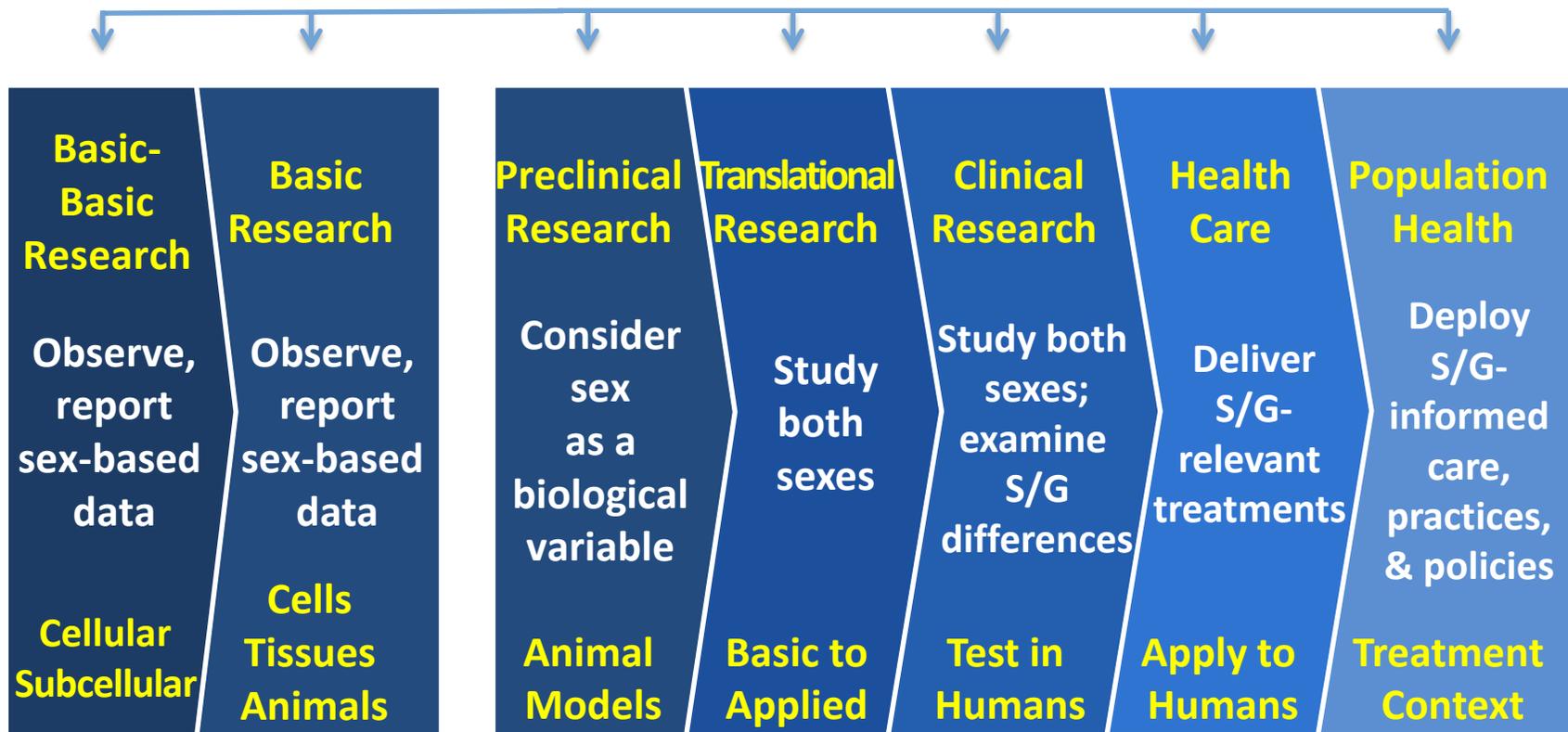


To maximize return on investment

Discovery

Turning Discovery into Health

REPORTING ESSENTIAL THROUGHOUT



Less data

More data

SABV is an integrating approach for investigations across the biomedical research continuum

Studying Both Sexes Across the Biomedical Research Continuum

Case Study:

Women's Ischemia Syndrome Evaluation (WISE)

Multicenter prospective study of 936 women referred for coronary angiography to evaluate ischemic heart disease (IHD), the leading cause of death among women.

- IHD presents treatment challenge because of lack of evidence-based management
- Study aim: Improve diagnostic testing and explore female-specific pathophysiology¹

- Sex differences exist in IHD presentation and pathophysiology
- Different methods needed to diagnose cardiac ischemia in women than in men
- Results of 10-year follow-up:
 - 1 in 5 died (184) – for a **20% all-cause mortality rate**
 - Of these, 115 (12%) were cardiac deaths² – 36 of which (31%) were women without obstructive CAD
- Lacking obstructive CAD is often seen as clinically benign
 - “Women are most often provided reassurance rather than cardiovascular therapy.”²
 - Clinical trials are needed for guidance on women without obstructive CAD

FINDINGS

¹ Bairey Merz CN et al. 1999. *J Am Coll Cardiol*. 3(6):1453-61.

² Kenkre TS et al. 2017. *Circ Cardiovasc Qual Outcomes*. 10 (12).

Putting WISE findings in perspective

10-year est. mortality rate for women aged 50 to 59 at baseline scoring low on a mortality index during similar time period **2.8%**

WISE all-cause mortality rate among those with obstructive CAD ($\geq 50\%$ stenosis) **36%**

WISE all-cause mortality rate among those without obstructive CAD at baseline **13%**

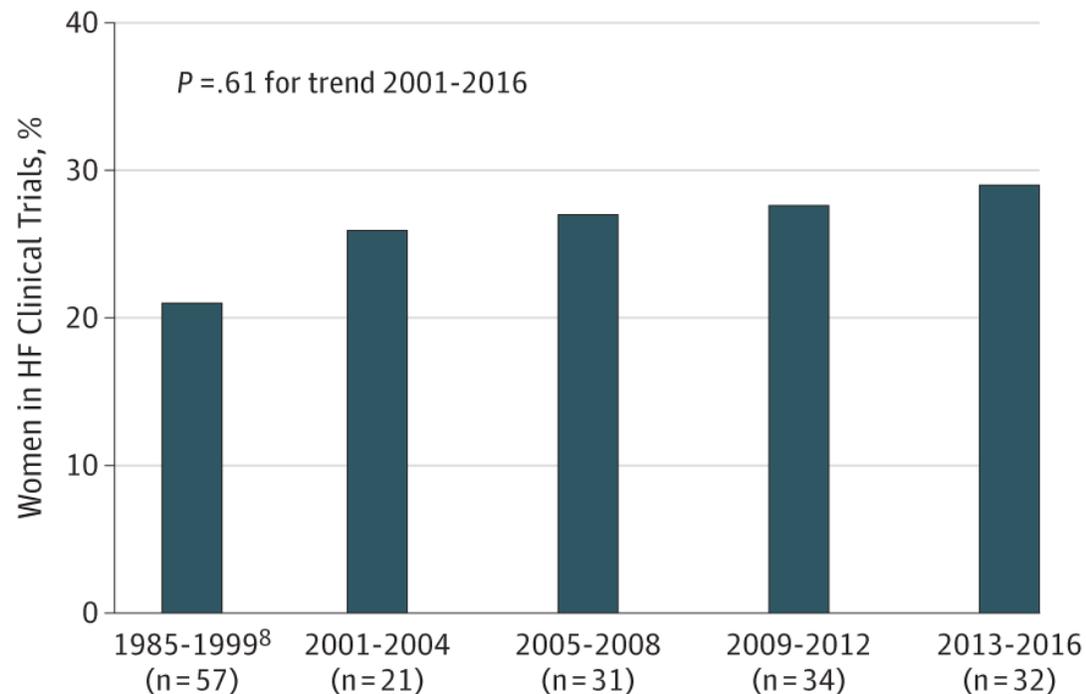
Proposed American College of Cardiology/American Heart Assoc. Guidelines threshold for initiating lipid-lowering therapy **7.5%**

Case Study:

Contemporary heart failure clinical trials

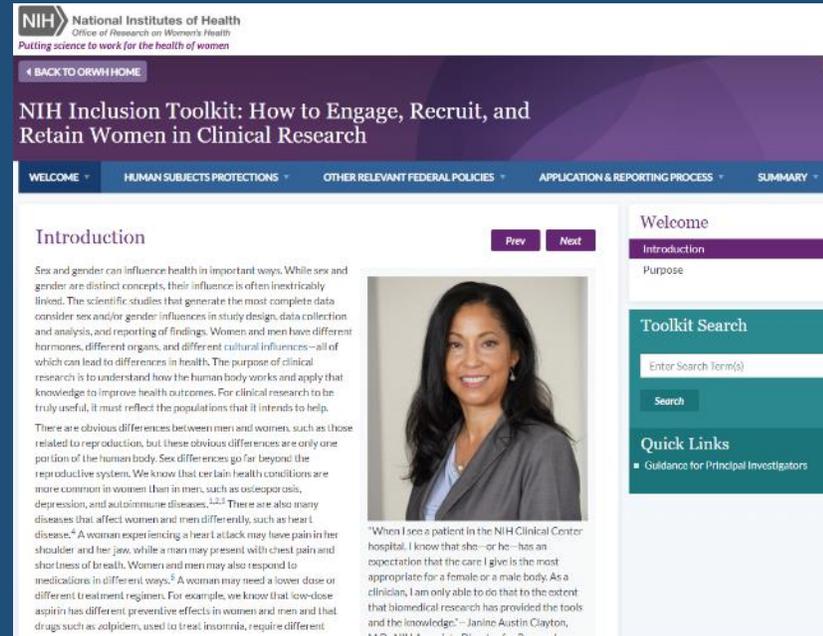
Objective: Determine enrollment patterns by age, sex, and race/ethnicity to compare demographic makeup with that of U.S. epidemiologic studies of specific heart failure (HF) types, among other things.

B Proportion of women



- Women were **underrepresented** in cumulative clinical trials (27%) when compared with their representation in general population of HF patients (~50%)
- Enrollment of women was significantly associated with the mean age of participants in HF trials

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

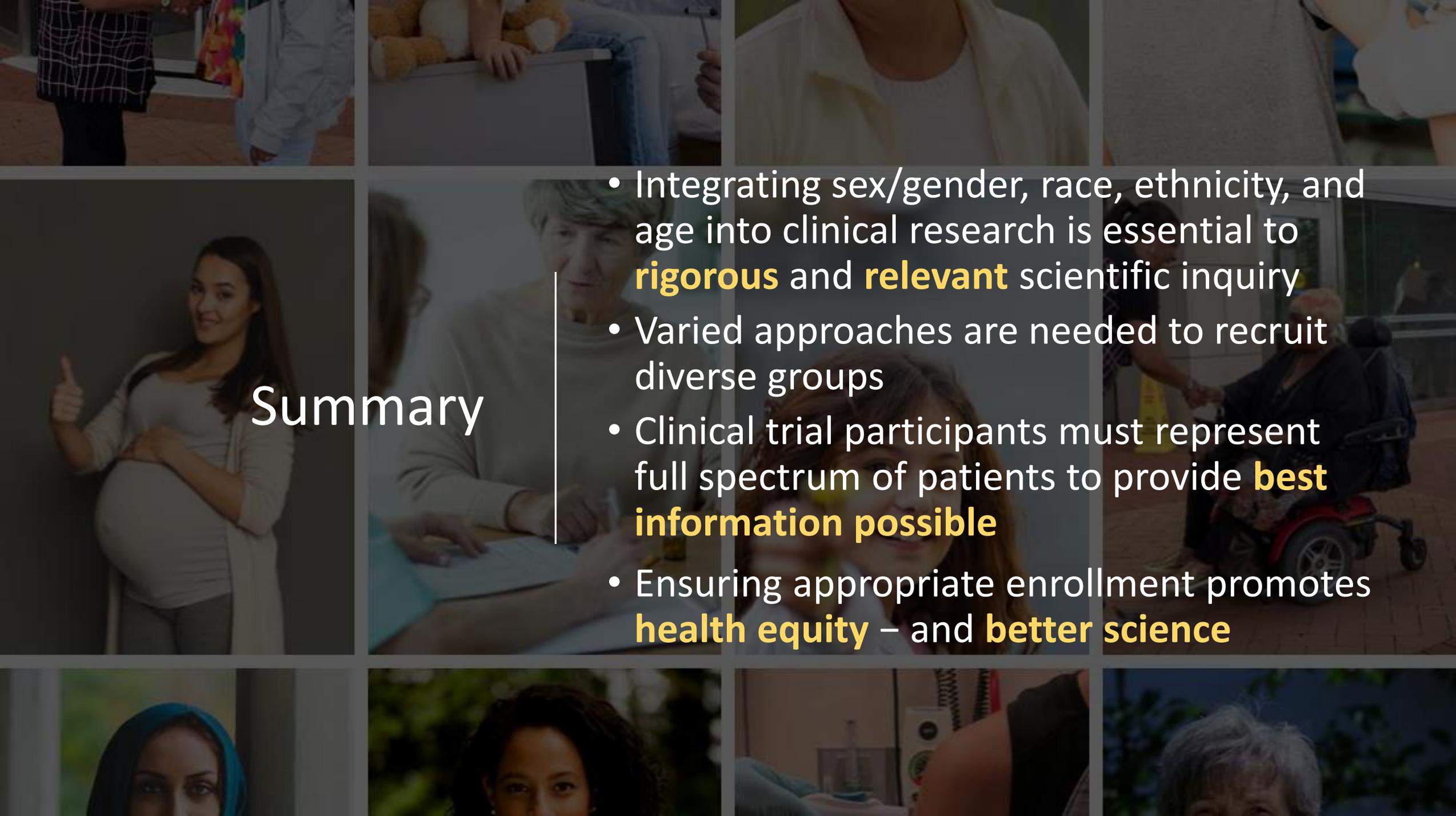


The screenshot shows the NIH Inclusion Toolkit website. At the top, it features the NIH logo and the text "National Institutes of Health Office of Research on Women's Health Putting science to work for the health of women". Below this is a navigation bar with a "BACK TO ORWH HOME" button and a main title: "NIH Inclusion Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research". A secondary navigation bar includes links for "WELCOME", "HUMAN SUBJECTS PROTECTIONS", "OTHER RELEVANT FEDERAL POLICIES", "APPLICATION & REPORTING PROCESS", and "SUMMARY". The main content area is titled "Introduction" and includes a "Prev" and "Next" button. The text discusses the importance of sex and gender in clinical research, noting that men and women have different hormones, organs, and cultural influences, which can lead to differences in health. It also mentions that certain health conditions are more common in women than in men, such as osteoporosis, depression, and autoimmune diseases. A quote from Janine Austin Clayton, M.D., is included: "When I see a patient in the NIH Clinical Center hospital, I know that she—or he—has an expectation that the care I give is the most appropriate for a female or a male body. As a clinician, I am only able to do that to the extent that biomedical research has provided the tools and the knowledge." A sidebar on the right contains a "Welcome" section with a "Purpose" link, a "Toolkit Search" box with a search input field and a "Search" button, and a "Quick Links" section with a link to "Guidance for Principal Investigators".

Helps PIs and their research teams fulfill their responsibilities to include women in clinical research

- Research on recruitment and outreach best practices
- Related Federal laws, regulations, and NIH policies
- Case studies

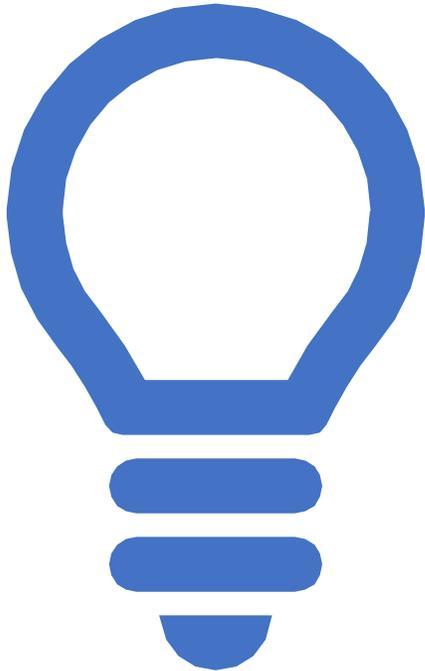
<http://orwh.od.nih.gov/toolkit>



Summary

- Integrating sex/gender, race, ethnicity, and age into clinical research is essential to **rigorous** and **relevant** scientific inquiry
- Varied approaches are needed to recruit diverse groups
- Clinical trial participants must represent full spectrum of patients to provide **best information possible**
- Ensuring appropriate enrollment promotes **health equity** – and **better science**

Inclusion Resources



- Inclusion of Women and Minorities
https://grants.nih.gov/grants/funding/women_min/women_min.htm
- Inclusion Across the Lifespan
<https://grants.nih.gov/grants/funding/lifespan/lifespan.htm>