



NIH Efforts to Include Older Adults in Clinical Studies

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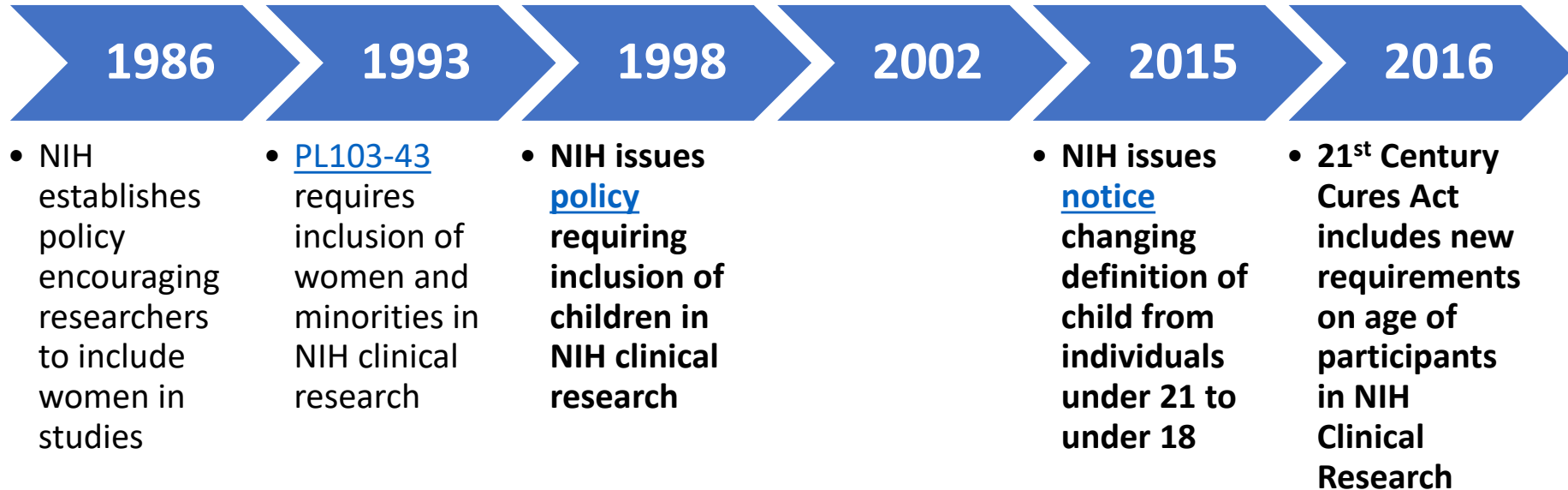


February 23rd, 2021

Inclusion Across the Lifespan

Background

Timeline of NIH Inclusion Policies and Participant Data Collection



H.R.34 - 21st Century Cures Act

114th Congress (2015-2016) | [Get alerts](#)

Required NIH to:

1. Convene a workshop on age groupings and age exclusions in clinical research within 180 days of enactment
 - Post workshop findings on NIH website
2. Publish data on age of participants in NIH clinical research, including pediatric subgroups
3. NIH Director must determine whether the inclusion guidelines on age need revision within 180 days of the workshop



Inclusion Across the Lifespan Workshop

June 1-2, 2017 Bethesda, MD

Purpose: To discuss the challenges and barriers to including children and older adults in clinical research and to identify strategies that would produce more age-inclusive clinical studies.



Baseline NIH Analysis

Older Adults

- Examined the top 10 diseases/disorders that caused hospitalizations &/or affected DALYs in older adults
- Analyzed information on
 - Inclusion/Exclusion Criteria
 - Age Requirement
 - Mean Age/Age Range



Summary of Key Findings in Older Adult Inclusion

- For diseases highly prevalent among older people, clinical trials often excluded subjects based on age
 - 27% of studies had arbitrary upper age caps
- Indirect exclusion factors may apply
 - Co-morbid conditions (hypertension, diabetes, cancer, etc.)
 - Polypharmacy
- Participants in trials may not represent real-world populations with the disease



NIH Inclusion Across the Lifespan Policy

Revision: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects

Notice Number: NOT-OD-18-116

Key Dates

Release Date: December 19, 2017

Related Announcements

[NOT-OD-20-125](#)

[NOT-OD-16-010](#)

[NOT-98-024](#)

[NOT-OD-18-228](#)

[NOT-OD-18-227](#)

[NOT-OD-18-229](#)

Issued by

National Institutes of Health ([NIH](#))

Purpose

This revised Notice replaces [NOT-98-024](#). The purpose of this Notice is to inform the research community that NIH is revising its NIH Policy and Guidelines on the Inclusion of Children. Changes to the policy include (1) the applicability of the policy to individuals of all ages, including children and older adults; (2) clarification of potentially acceptable reasons for excluding participants based on age; and (3) a requirement to provide data on participant age at enrollment in progress reports.



- Stipulates that **participants of all ages must be included in research involving human subjects**, unless there is a scientific or ethical reason for exclusion of any age category.
- Specifically **children (age <18)** and **older adults (age ≥ 65)**.

<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>

Inclusion Across the Lifespan

Policy Implementation

NIH Inclusion Across the Lifespan Policy

- **Applications must:**
 - Submit a plan for including individuals across the lifespan.
 - If excluding based on age, provide justification for the specific age range.
- **Progress reports must:**
 - Report age at enrollment in units ranging from hours to years.
 - Include sex/gender and race/ethnicity data.

Acceptable vs. Unacceptable Justifications for Exclusion

Acceptable

- **Scientific justifications, e.g.:**
 - The condition does not occur in the excluded group.
 - Knowledge is already available in the excluded group.
 - A separate study for the excluded group is warranted and preferable.
- **Ethical justifications, e.g.:**
 - Laws/regulations bar the inclusion of individuals in the age group.
 - The risk to the excluded group is unacceptable; therefore, their inclusion is unethical.

Unacceptable: Cost, convenience, lack of explanation for the chosen age range, concerns about noisy data

IAL Implementation: Outcomes to Date

- Since the IAL policy was implemented in 2017, **only ~3% of the 46,794 applications proposing human subjects research have been rated as unacceptable** in light of their proposed inclusion plans.
- Reviewers have **appropriately distinguished** between acceptable and unacceptable IAL justifications.
- However, applications for research with children and older adults have **a higher proportion of “Unacceptable” codes.**

Inclusion Across the Lifespan

IAL-II Workshop & Objectives

NIH's Second IAL Workshop, IAL-II, Held Virtually on September 2nd, 2020



A screenshot of a virtual meeting slide. At the top, there is a small video feed of a woman with glasses speaking. Below the video feed is a white rectangular area containing the following text:

Inclusion of Older Adults in Clinical
Research

Cynthia M. Boyd, MD MPH
Professor of Medicine, Epidemiology and Health Policy & Management
Johns Hopkins University

Below the text is a dark grey bar with the text "INCLUSION OF OLDER ADULTS IN" in white. At the bottom left of the slide is the NIH logo. At the bottom center is the text "NIH Inclusion Across the Lifespan-II" with a small icon of three hands to the right.

A recording of the event is available at the following link:

<https://videocast.nih.gov/watch=38384>

IAL-II Objectives

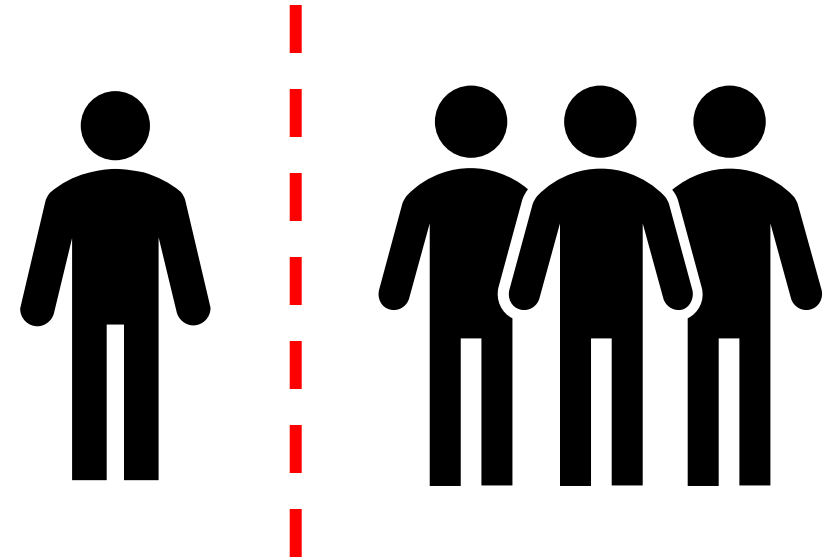
- **Examine the science of inclusion** across relevant populations.
- Share **evidence-based, practical approaches to facilitate compliance** with the IAL policy.
- Conduct **open scientific discussion** of evidence-based approaches.
- **Share resources to facilitate inclusion** across the lifespan.

Inclusion Across the Lifespan

Lessons Learned from IAL-II

Topic Area 1: Inclusion / Exclusion Criteria

- The Inclusion/Exclusion Criteria Panel was tasked with examining **inclusion and exclusion criteria** and how to **ensure representativeness of study populations** in clinical trials.



- Considerations for several populations were discussed, including older adults.

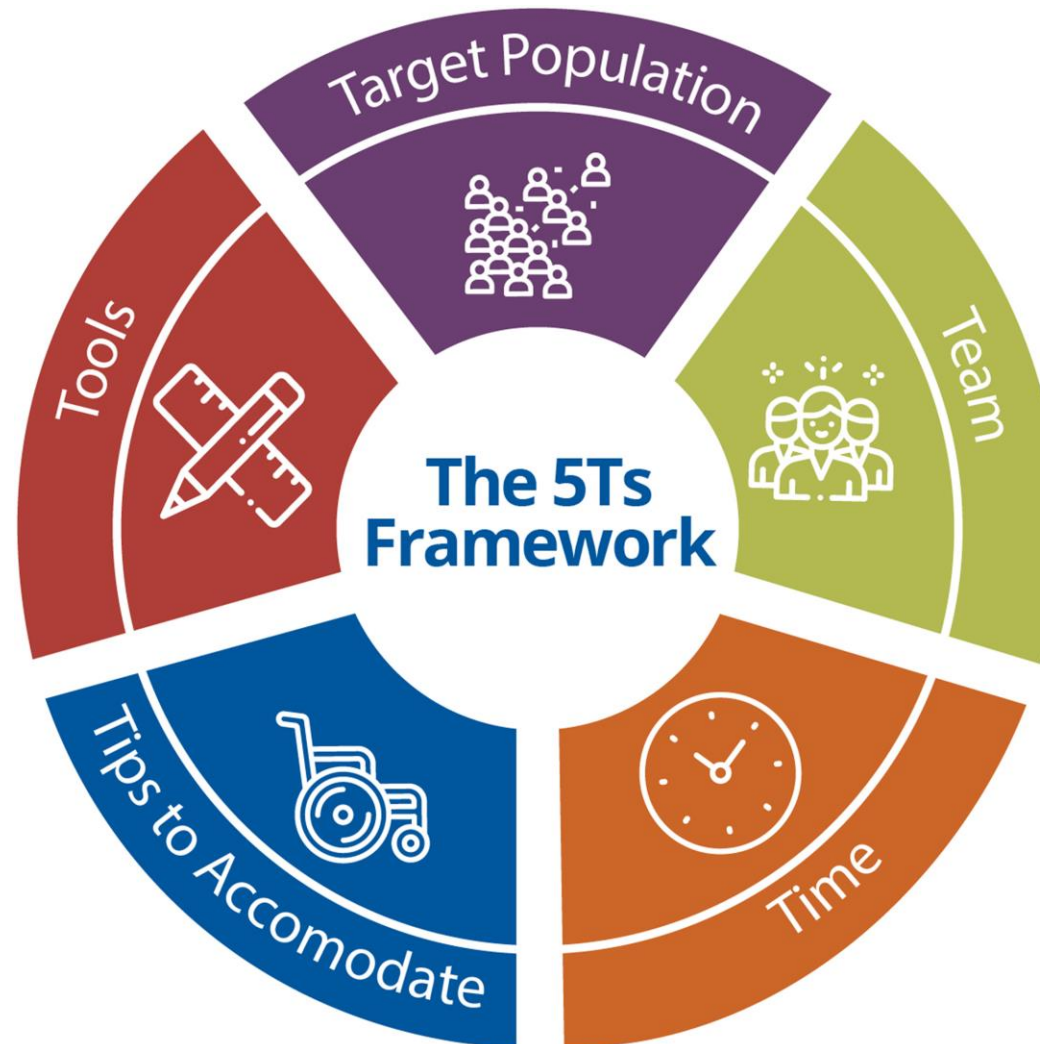
Extending the Age of Eligibility is Not Enough to Ensure That Older Adults Are Represented

- Despite progress, clinical trial participants are often **younger and have fewer chronic conditions than the population affected by the disease** being studied.
 - May not represent older adult populations.
 - Extending the age of eligibility is **not sufficient**.

Thoughtful & Deliberate Planning Can Enhance Recruitment and Retention of Older Adults

The 5Ts:

A Framework to Support Inclusion of Older Adults in Research



Bowling, C. B., Whitson, H. E., & Johnson, T. M. (2019). *Journal of the American Geriatrics Society*, 67 (2), 342-346. doi:10.1111/jgs.15785

Minorities in Particular May Be Excluded From Clinical Trials Due to Coexisting Conditions

- In a study of 235 African American cancer patients, **exclusion criteria rendered the majority of participants ineligible for clinical trial participation, and 17% ineligible due to comorbidities.**

Adams-Campbell, L. L., et al. (2004). *Journal of Clinical Oncology*, 22 (4). 730-734.

Table 3. Overall and Disease-Specific Causes for Exclusion of African-Americans From Clinical-Trial Enrollment at HUCC (N = 235)

Exclusions	No. of Patients	%
Overall		
No available protocol	55	24.2
Comorbidities	39	17.1
Multiple primary cancers	10	4.4
Premature death	16	7.0
Poor performance status	8	3.5
Prior chemotherapy	8	3.5
Noncompliance	7	3.1
HIV positivity	5	2.2
Concurrent radiation	5	2.2
Disease-related*		
Serum testosterone > 50 ng/dL (prostate cancer)	5	15.6
Low Gleason score (<8; prostate cancer)	8	25.0
< 6 positive nodes (breast cancer)	4	3.0

Abbreviation: HUCC, Howard University Cancer Center.

*n = 32 for prostate cancer, and n = 132 for breast cancer.

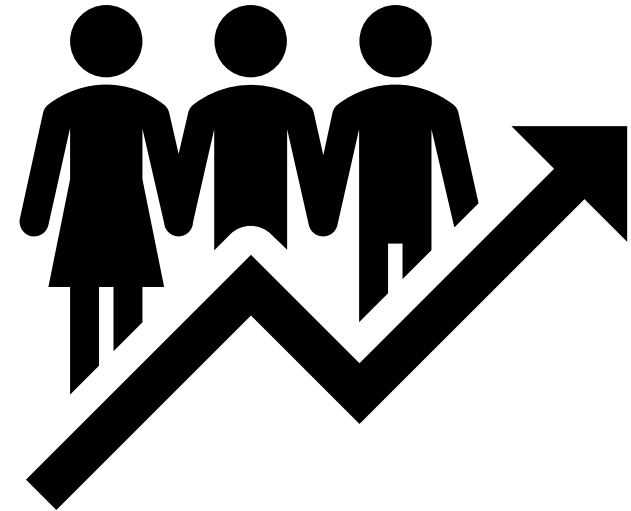
Topic Area 1: Inclusion / Exclusion Criteria

TAKEAWAYS:

- Extending the age of eligibility is not enough to ensure that older populations are represented.
- Exclusions that limit representativeness and generalizability should be avoided.
- Risk of exclusion should be considered relative to risk of participation.
- Understand and accommodate target populations.

Topic Area 2: Study Design & Metrics

- The Study Design and Metrics Panel was tasked with **identifying ways to construct clinical trial design and metrics to be more inclusive across all ages.**



- The panel examined challenges that investigators face when designing studies and how these challenges can impact clinical trials.

Intentional Planning Is Needed to Minimize Barriers to Recruitment and Enrollment

- Develop enrollment **early in the trial planning process**; eligibility criteria **should align with these**.
- **Engage patients and communities** in study design and recruitment planning.
- Build relationships with community stakeholders to **build trust and awareness and address challenges and barriers**



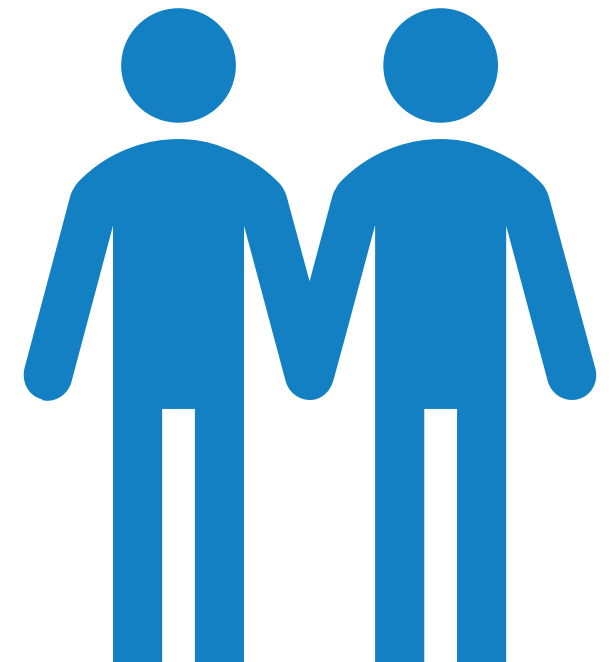
A Success Story: The Diabetes Telephone Study

- In the Diabetes Telephone Study, **deliberate planning** and **active stakeholder engagement** were used to address factors related to awareness, opportunity, and acceptance in order to improve retention of underrepresented groups.
- Yielded the following results:
 - Participation rate: 83%
 - Retention rate: 93%
- Participants also tended to be older, and 43% were nonwhite

A Success Story: The Diabetes Telephone Study

The following strategies were used to enhance inclusion of underrepresented populations in the Diabetes Telephone Study:

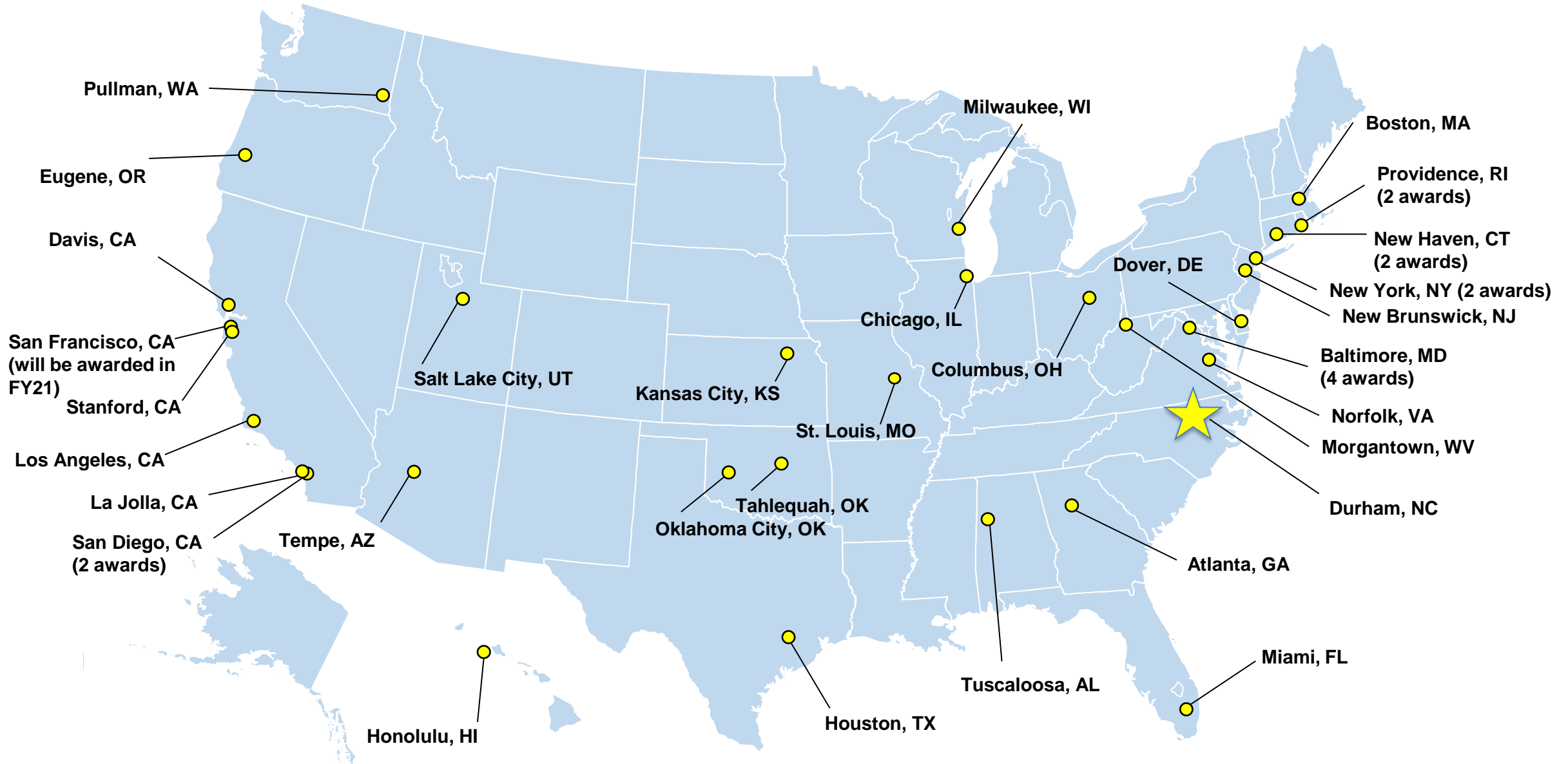
- **Stakeholder engagement:**
 - Effort made to reach groups which may not otherwise have been aware of the trial.
- **Limited exclusion criteria:**
 - People with multiple chronic conditions, disabilities, and minor cognitive impairment were included.
- **Participant involvement:**
 - Both patients and clinicians were involved in the intervention design, which likely facilitated acceptance.



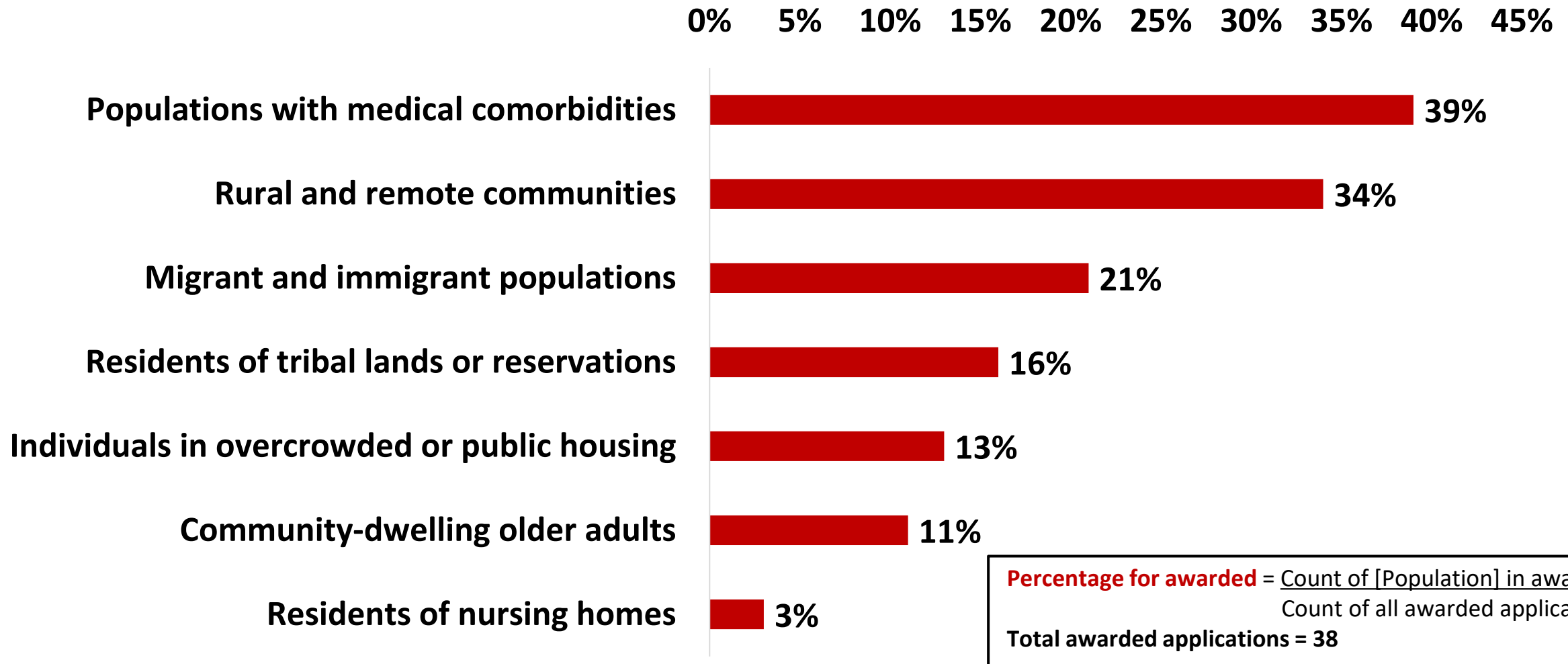
Rapid Acceleration of Diagnostics (RADx)

- ➔ **RADx Tech (\$500M)**: Highly competitive, three-phase challenge to identify, at an accelerated pace, the best candidates for at-home or point-of-care tests for COVID-19.
- ➔ **RADx Underserved Populations (RADx-UP; \$500M)**: Community-engaged projects focused on implementation strategies to enable and enhance COVID-19 testing in underserved and vulnerable populations.
- ➔ **RADx-Radical (RADx-Rad; \$200M)**: Development and advancement of novel, non-traditional testing approaches or new applications of existing approaches.
- ➔ **RADx Advanced Technology Platforms (RADx-ATP; \$230M)**: Rapid scale-up of advanced technologies to increase testing pace and enhance/validate throughput; creation of ultra-high throughput machines and facilities.
- ➔ **Data Management Support (\$70M)**: Building an infrastructure to support coordination of the data management needs of COVID-19 efforts.

Sites for RADx-UP Phase 1 Awards



Percent of RADx-UP Projects Addressing Vulnerable Populations



NIH Community Engagement Alliance (CEAL) Against COVID-19 Disparities

CEAL seeks to address and ameliorate the disproportionate impact of the COVID-19 pandemic on health disparity populations by:

1. Conducting community outreach to **raise awareness about COVID-19**, to **address misinformation and mistrust** about the pandemic, and to **combat it**.
2. Working to ensure that clinical trials for COVID-19 prevention and treatment **include racially and ethnically diverse communities most affected by the pandemic**.

<https://covid19community.nih.gov/>



NIH Community Engagement Alliance (CEAL) Against COVID-19 Disparities

- In September, NIH awarded **\$12 million to support CEAL research teams in 11 states** (Alabama, Arizona, California, Florida, Georgia, Louisiana, Michigan, Mississippi, North Carolina, Tennessee and Texas).
- These funds **will support outreach and engagement efforts in ethnic and racial minority communities** disproportionately affected by the COVID-19 pandemic.

<https://www.nih.gov/news-events/news-releases/nih-funds-community-engagement-research-efforts-areas-hardest-hit-covid-19>

NEWS RELEASES

Wednesday, September 16, 2020

NIH funds community engagement research efforts in areas hardest hit by COVID-19



The National Institutes of Health today announced a \$12 million award for outreach and engagement efforts in ethnic and racial minority communities disproportionately affected by the COVID-19 pandemic. The award to RTI International, a non-profit research institution, will support teams in 11 states established as part of the NIH Community Engagement Alliance (CEAL) Against COVID-19 Disparities. These teams have received initial funding to immediately create CEAL programs, and RTI will serve as the Technical and Administrative Support and Coordination (TASC) center.

The CEAL research teams will focus on COVID-19 awareness and education research, especially among African Americans, Hispanics/Latinos, and American Indians — populations that account for over half of all reported cases in the United States. They also will promote and facilitate the inclusion and participation of these groups in vaccine and therapeutic clinical trials to prevent and treat the disease.

The communities of special focus include counties in Alabama, Arizona, California, Florida, Georgia, Louisiana, Michigan, Mississippi, North Carolina, Tennessee and Texas.

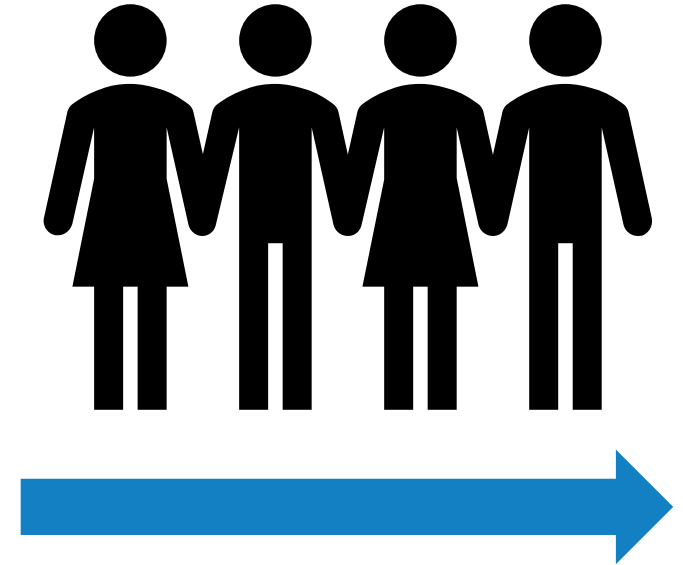
Topic Area 2: Study Design & Metrics

TAKEAWAYS:

- Intentional planning is needed to minimize barriers to recruitment and enrollment.
- Priority populations should be included in phase III trials.
- Research questions and outcomes should reflect community needs and priorities.

Topic Area 3: Recruitment, Enrollment, & Retention

- The Recruitment, Enrollment, and Retention Panel was tasked with **discussing considerations related to identification, enrollment, and retention of children and older adults in clinical trials.**



- The panel discussed these considerations and provided evidence-based recommendations.

Older Adult Populations Are Diverse

- Sociodemographic characteristics such as age, race, ethnicity, and gender intertwine with health status and other factors
- These intersecting factors **create special needs for recruiting and retaining older adults.**
- Recruiting and enrolling patients in a given age group **does not mean that the diversity of the population will be represented.**



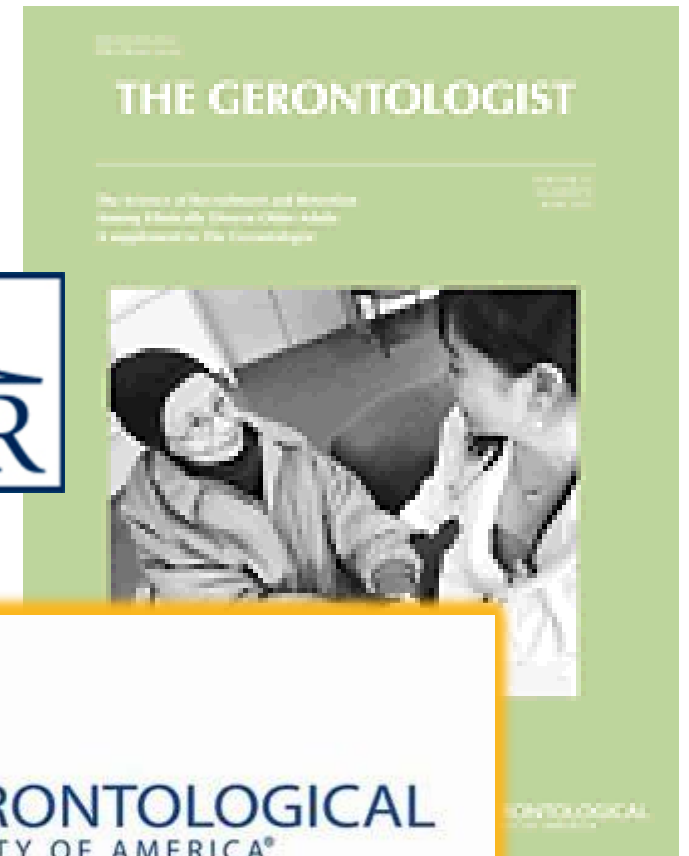
Researchers Should Undergo Relevant Training

- **Training topics should include:**
 - The importance of inclusion
 - Development of eligibility criteria
 - Tips for recruiting and retaining priority populations



Researchers Should Utilize Existing Resources on Recruitment, Enrollment, and Retention

- Research Centers for Minority Aging Research (RCMAR)
- 2011 supplement of *The Gerontologist*
- 2019 GSA preconference presentation, “Strategies for Successful Recruitment and Retention of Minority Elders.”



Does intensive blood pressure control compared with standard control reduce the occurrence of morbidity and mortality?

Randomized Controlled Trial Target Systolic Blood Pressure

Intensive Treatment
Goal SBP < 120 mmHg
(n= 4,278)

Standard Treatment
Goal SBP < 140 mmHg
(n= 4,285)

Lessons Should Be Gleaned from the Successes or Failures of Past Trials

- **SPRINT achieved the following:**
 - 101% of recruitment goal (9,361 participants)
 - 28% age 75+
 - 26% of whom were Black or Hispanic.
 - 33% of whom met criteria for frailty.
 - Average Montreal Cognitive Assessment score 22/30.



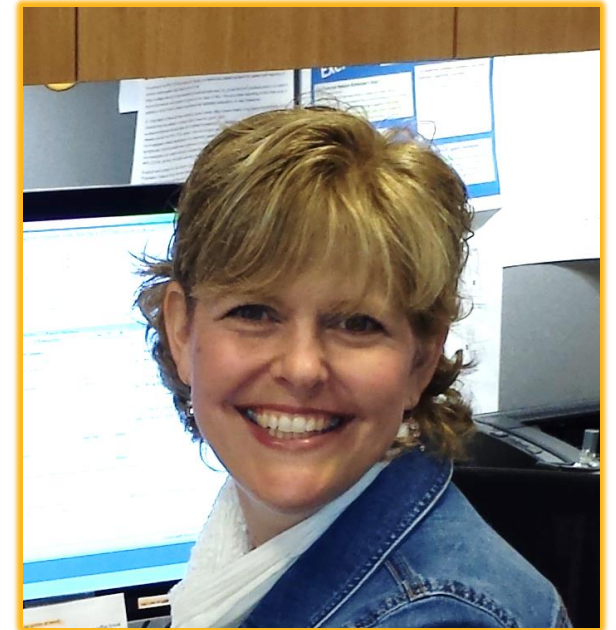
Lessons Should Be Gleaned from the Successes or Failures of Past Trials

- Adopted a **planful and deliberate study design** (e.g., cognitive impairment outcomes included in trial design from beginning).
- **Mass mailings targeted by age and zip code** achieved the greatest yield for recruitment purposes.



NIA Clinical Research Operations and Management System (CROMS)

- NIA recently announced the development of the new **Clinical Research Operations and Management System (CROMS)**.
- CROMS will provide NIA the capability **to track, report, and manage extramural clinical research data, activities, and enrollment in real time**, facilitating a more efficient and seamless research experience for NIA staff and awardees.
- Initial focus in FY 2021 will be on **grants supporting AD/ADRD clinical trials, followed by rollout to all NIA grants supporting human subjects research.**



NIA CROMS Contact:
[Dr. Holly Massett](#)

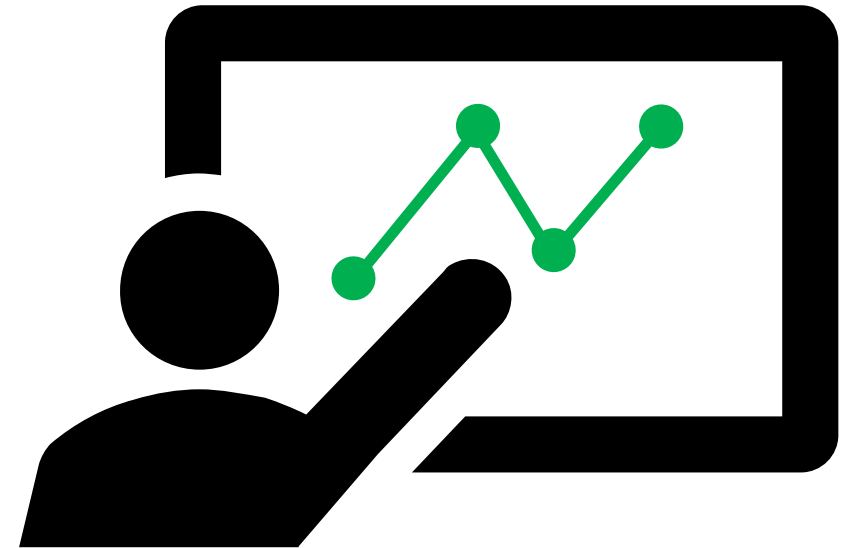
Topic Area 3: Recruitment, Enrollment, & Retention

TAKEAWAYS:

- Older adult populations are diverse.
- Investigators should undergo relevant training.
- Researchers should utilize existing resources on recruitment, enrollment, and retention.
- Lessons should be gleaned from the successes and failures of past trials.

Topic Area 4: Data Analysis & Study Interpretation

- The Data Analysis and Study Interpretation Panel was tasked with discussing **how study design, data analysis, and interpretation and dissemination of results should occur** with consideration of the populations and subpopulations included in a trial.



Age groups vary – Vulnerability is not defined by age

- Grouping by age may fail to account for wide variation of health and health-related factors within age groups.
- For older adults, functional measurements (e.g., frailty, resilience) may be more informative than age.
- Vulnerability and risk should not be based solely on age.
- Potential risks of participation should be balanced with the ethical consequences of excluding certain populations from research.

Sociodemographic Factors Impact Health and Risk

- Take socioeconomic variables such as race and ethnicity into account
- Tools such as the **Area Deprivation Index (ADI)**, a set of 17 education, employment, housing quality, and poverty measures, may be useful.



- The ADI has been validated and is available in the **Neighborhood Atlas®** at the following link:
neighborhoodatlas.medicine.wisc.edu/

Journal Editors Can Improve Presentation of Information, But Not Study Design Flaws

- Journal editors and peer reviewers **cannot address shortcomings in trial design**, particularly for randomized controlled trials.
- Subgroup analyses need to be **built into study designs and analytical plans** to ensure that results will be meaningful.
- Journal articles **must include complete and accurate methods**. This helps reviewers evaluate studies and ensures appropriate interpretation of results.

Topic Area 4: Data Analysis & Study Interpretation

KEY TAKEAWAYS RELEVANT TO OLDER ADULTS:

- Age groups encompass substantial variability, while age is not synonymous with vulnerability.
- Race/ethnicity and social factors impact health and risk.
- Study design and planning are critical.
- Journal editors can improve presentation of information but not study design.

IAL Resources

- **NIH Office of Extramural Research Inclusion Across the Lifespan Compliance Page:**
<https://grants.nih.gov/policy/inclusion/lifespan.htm>
- **Inclusion Across the Lifespan II Workshop Summary:**
<https://grants.nih.gov/faqs#/inclusion-across-the-lifespan>
- **Guidance for Peer Reviewers:**
https://grants.nih.gov/grants/peer/guidelines_general/Review_Human_Subjects_Inclusion.pdf

Ways to Stay Informed and Connected



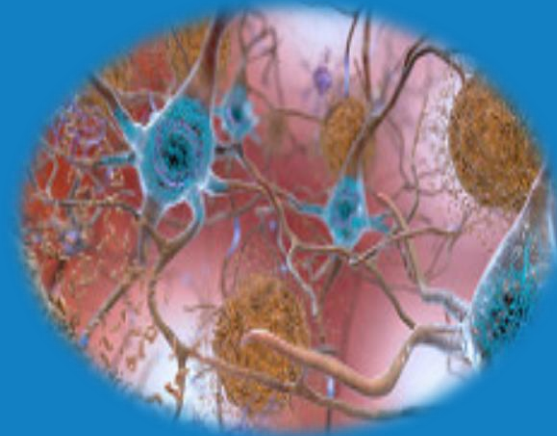
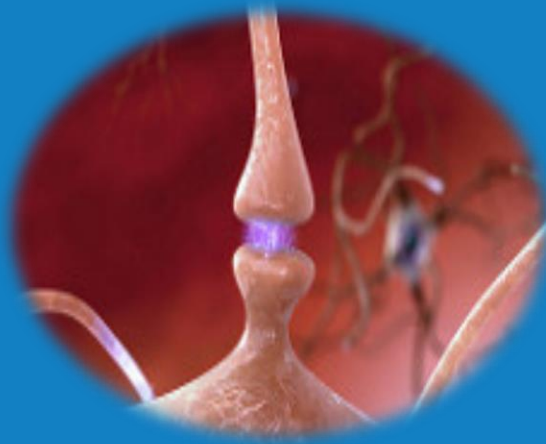
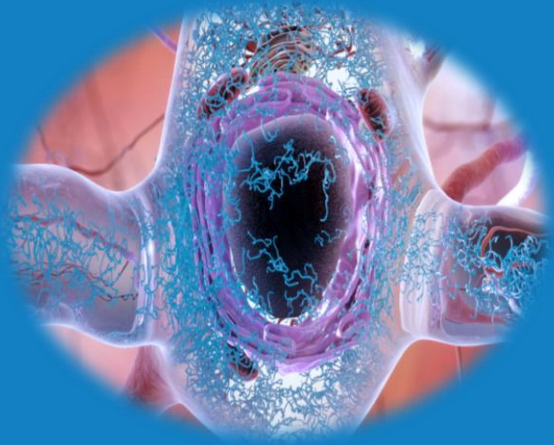
Search all active NIA funding opportunities:
<https://www.nia.nih.gov/research/funding>



Review the latest approved concepts:
<https://www.nia.nih.gov/approved-concepts>



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