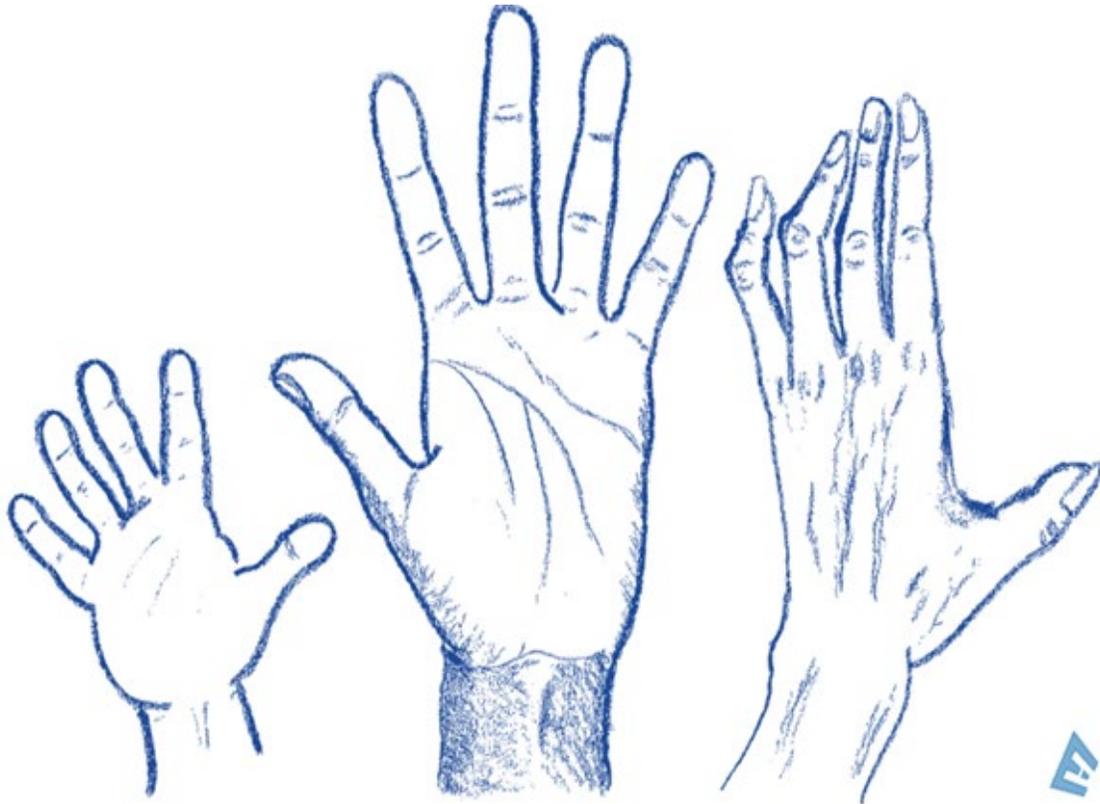


Inclusion Across the Lifespan



September 2, 2020 Workshop

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Disclaimer

The content of this workshop summary reflects the presentations and feedback of the individual participants at the workshop, as well as the individuals and organizations who provided responses to the National Institutes of Health (NIH) Request for Information. Prevailing themes of the workshop are highlighted within the summary and do not necessarily represent the views of the NIH, the U.S. Department of Health and Human Services, or the U.S. Government.

Acknowledgments

The IAL–II Planning Committee would like to thank all of the dedicated researchers and clinicians who participated in this workshop for their tireless efforts to include all people in clinical studies. Additionally, thank you to the panel members for their thoughtful insight in guiding these discussions.

Executive Summary

Background

In 2016, the *21st Century Cures Act* directed the National Institutes of Health (NIH) to collect data on the inclusion of participants in clinical research studies by age and to convene a workshop focused on the inclusion of pediatric and older adult populations in clinical research.¹ The Inclusion Across the Lifespan Workshop (IAL-I) held in June 2017 focused on barriers to and opportunities for inclusion of children and older adults in clinical studies and informed development of the Inclusion Across the Lifespan (IAL) policy that became effective in January 2019.

Following IAL-I, the NIH policy on inclusion of children in clinical research was revised to become the IAL policy to address inclusion at both ends of the age spectrum. Announced in December 2017, the policy applied to all competing grant applications for due dates on or after January 25, 2019. The policy requires applications to include a plan for including individuals across the lifespan and, if excluding based on age, provide justification for the specific age range. Scientific Review Groups assess applications with regard to age-appropriate inclusion or exclusion of individuals in the research project. Progress reports must provide anonymized individual-level data on age at enrollment in units ranging from hours to years and include sex/gender and race/ethnicity data. This enables NIH to examine adequacy of inclusion across a wide range of disease states and to sort data according to what is appropriate for the scientific question a study is attempting to answer.

NIH has taken steps to promote broad inclusion in clinical trials. Although there have been improvements in many areas, it is vital to regularly assess how implementation is proceeding to identify obstacles and any further actions needed to carry out the full intent of the IAL policy. To this end, a follow-up Workshop—Inclusion Across the Lifespan Workshop (IAL-II)—was planned and held on September 2, 2020. The Workshop aimed to achieve several important goals:

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

In preparation for the IAL-II Workshop, NIH issued a [Request for Information \(RFI\) \(NOT-OD-20-044\)](#) to solicit input to inform Workshop planning. Over 40 responses were received from individuals and associations (see Appendix V) and organized into three main themes or topics—inclusion and exclusion criteria; study design and metrics; and recruitment, enrollment, and retention. Based on these responses and other stakeholder input, Workshop organizers established four panels (see Appendix II) to develop sessions on the three themes identified in RFI responses and a fourth topic, data analysis and study interpretation. Panels organized sessions to examine inclusion across phases of clinical study development among pediatric, geriatric, and other special populations (e.g., racial/ethnic minorities, people with disabilities, rural/isolated populations, language-minority individuals, pregnant and lactating women, people with comorbidities, and sexual and gender minorities) and disseminate lessons learned

¹ 21st Century Cures. H.R. 34. 114th Cong. (2016). Retrieved from <https://www.govinfo.gov/content/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf>

about inclusion, similarities and contrasts between the populations, and evidence-based approaches to facilitate compliance with the IAL policy.

Implementation of IAL Policy: NIH Perspective

NIH clinical research is intended to advance the health, well-being, and quality of life of Americans and citizens of the world. NIH aims to ensure the clinical research it supports affords all communities the opportunity to take part in clinical trials to ensure they benefit equally from medical advances.

Current NIH policy mandates that participants of all ages be included in research involving human subjects unless there is a scientific or ethical reason for exclusion. The NIH Center for Scientific Review (CSR) provides training and instructions to peer reviewers to ensure they are aware of the policy. Individual reviewers and review panels determine whether the age range of human subjects is appropriate in the context of the proposed scientific question. Any concerns regarding age must be resolved in collaboration with NIH program staff before an application can be funded. According to CSR, peer reviewers generally appropriately distinguish between acceptable and unacceptable applications with regard to IAL policy. In the first year, the most common IAL-associated reason for flagging applications was the failure to provide a rationale for selection of the target age group, suggesting that it may take time for the research community to understand and appropriately address the new policy requirements. Common data elements (CDEs) for age are of particular relevance to the IAL policy—specifically, in clinical trials; for this reason, the NIH repository of clinical trial information, [ClinicalTrials.gov](https://clinicaltrials.gov), uses common data elements for age to support evaluation and public accountability and to help match patients to trials based on eligibility.

Challenges and Barriers to Inclusion

Researchers may find that including diverse groups in clinical studies is more complicated than expected. Barriers exist across the continuum of study development, implementation, and analysis. While many barriers are common across populations, some subpopulations—including children, older adults, racial/ethnic minorities, pregnant and lactating women, people with disabilities, and sexual minority youth—historically have been especially underrepresented in clinical research due to unique challenges to including these groups. Specific barriers to inclusion that have been cited include:

Ethical and Safety Issues

- Children and pregnant or lactating women often are underrepresented because the level of acceptable risk is lower for these populations. Other ethical and financial concerns may also dissuade some sponsors from including these populations in studies. The paucity of specific data and guidelines has forced providers to extrapolate data from other populations, which is often problematic given physiological and other differences with the groups that have been studied. Studies in pediatric populations have found that extrapolation may be appropriate for efficacy but not for dosing or safety. Extending the age of eligibility is insufficient to make the study population truly representative.
- Often, the older adults who participate in clinical research are not representative of the older adult population due to exclusion of participants with common comorbidities. Similarly, exclusions for comorbidities may result in many racial/ethnic minorities being ineligible.

- Some research on sexual minority youth has been hindered by Institutional Review Board (IRB) reluctance to accept the ability of mature minors to consent to research participation; additional data on consent capacity of mature minors could help address IRB concerns and inform procedures to reduce consent vulnerabilities.

Study Design and Metrics

- Study design and metrics are not always constructed to be optimally inclusive across age groups and populations, which detracts from the applicability and generalizability of results. Some studies are not powered for analysis of all subpopulations. Researchers may consider trial designs that have been successful in recruiting and retaining racial and ethnic minorities such as adaptive and pragmatic trials.
- Complex medication regimens, high numbers of clinic visits, and other features that increase participant burden may disproportionately impede enrollment for certain groups. Many barriers to enrollment—such as inadequate access to transportation—are more pronounced in populations with poor social determinants of health. Many recruitment and retention plans do not adequately account for the needs and limitations of patients and caregivers.
- Research teams may not understand the heightened barriers to participation experienced by some target populations, including children, older adults, and racial/ethnic minorities. Some trials do not have sufficient expertise and do not devote sufficient time or resources to anticipate and respond to recruitment and retention challenges that arise during the study. Target populations may not be aware of or given the opportunity to participate in trials. They also may lack knowledge about clinical trials, have limited English proficiency, and/or harbor mistrust of the medical establishment.

Data Analysis

- If a clinical trial has an unrepresentative or unbalanced population, it may be difficult to determine whether results are broadly applicable (e.g., differences in sample average treatment effect versus the population average treatment effect). It may be difficult for clinicians and policymakers who lack research experience to fully interpret trial findings. Appropriate statistical methods are necessary to account for imbalances in study population.

Strategies for Promoting Inclusion Across the Lifespan

Presenters, panelists, and meeting participants described strategies for promoting inclusion across the lifespan, including:

- **Ensure that research questions and outcomes reflect community needs and priorities.** Current clinical trials do not always address the needs and concerns of patients and communities. Prioritizing research questions and outcomes most relevant to patients (e.g., quality of life, physical performance) is an important factor in increasing engagement of diverse populations in research. Geriatric assessment (GA) domains can help researchers and providers address outcomes important to older adults.
- **Provide training and resources to researchers.** Investigators should be trained regarding the importance of inclusion, as well as strategies to optimize study design, recruitment, retention, and analysis. Resources and services that promote inclusion also should be developed and

disseminated. Examples include the work of the Recruitment Innovation Center at Vanderbilt University, the [Resource Centers for Minority Aging Research](#) program, and the innovative training program at the University of Colorado Anschutz Medical Campus that provides aging research training to nongeriatrician specialists who conduct research that includes older adults.

- **Avoid unnecessary exclusions that limit representativeness and generalizability.** Careful examination of exclusion criteria is needed to avoid unnecessarily limiting enrollment, especially comorbidities that are common in populations affected by the disease being studied. One strategy used by some trials is use of GA summaries and GA-guided recommendations for trial participants to help predict toxicity and mortality, guide decisions and care management, foster communication, and improve clinical outcomes.²
- **Balance risk of exclusion with risk of participation.** Some populations cannot participate in clinical trials unless their participation involves no more than minimal risk. For inclusion of pediatric subjects, more than minimal risk is acceptable if other criteria are met (e.g., potential for direct benefit, research likely to yield generalizable results, opportunity to address serious problem affecting the health or welfare of children). Revising regulations that limit participation of pregnant women in clinical trials to include measures of minimal risk and allow exceptions for generalizable knowledge when minimum risk is exceeded may enhance the inclusion of pregnant women in research. Industry could be incentivized to include pregnant women in clinical trials through new laws or policies similar to the [Best Pharmaceuticals for Children Act](#). Adequate expertise in special populations on IRBs would better equip IRBs to determine whether populations are capable of providing consent.
- **Ensure that recruitment and statistical analysis plans adequately address subgroup analyses.** Including subgroup analyses requires careful thought during the planning phase. Important considerations include determining how subanalyses will account for within-population variability; enrolling sufficient numbers of subpopulations to generate analyzable, generalizable results; and ensuring that study designs and statistical analysis plans adequately and appropriately describe these analyses. Integration of social determinants of health into analyses may be useful. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines³ for clinical trials protocols are a valuable resource for investigators.
- **Ensure that recruitment and retention plans accommodate the target population.** Intentional planning is needed to minimize barriers to participation. Strategies to increase recruitment and retention include tailoring trial designs and outreach to the needs of the target population, with consideration of ways to minimize participant burden. Frameworks such as the 5-T Framework for Recruiting Older Adults⁴ (Target population, Team, Tools, Time, and Tips to accommodate)

² Soto-Perez-de-Celis, E., Li, D., Yuan, Y., Lau, Y.M., & Hurria, A. (2018). Functional versus chronological age: Geriatric assessments to guide decision making in older patients with cancer. *Lancet Oncology*, 19(6), e305-e316. doi: 10.1016/S1470-2045(18)30348-6.

³ Chan, A.W., Tetzlaff, J.M., Altman, D.G., Laupacis, A., Gøtzsche, P.C., Krleža-Jerić, K., Hróbjartsson, A., Mann, H., Dickersin, K., Berlin, J.A., Doré, C.J., Parulekar, W.R., Summerskill, W.S., Groves, T., Schulz, K.F., Sox, H.C., Rockhold, F.W., Rennie, D., & Moher, D. (2013). SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*, 158(3), 200-207. <https://doi.org/10.7326/0003-4819-158-3-201302050-00583>

⁴ Bowling, C.B., Whitson, H.E., & Johnson, T.M. 2nd. (2019). The 5Ts: Preliminary development of a framework to support inclusion of older adults in research. *Journal of the American Geriatric Society*, 67(2), 342-346. doi: 10.1111/jgs.15785. Epub 2019 Jan 29.

and the Geriatric 5Ms⁵ (Multicomplexity, Mind, Mobility, Medications, and what Matters most) were developed for older adults but also may be helpful for other populations. Increasing diversity among trial investigators and promoting cultural sensitivity may help increase engagement. Patient advocacy groups and community engagement can inform study design and recruitment plans and help build relationships that will support enrollment. Patient navigators may assist with enrollment and adherence.

- **Regularly assess recruitment and retention and make modifications as needed.** Periodically assessing recruitment and retention throughout the course of the trial may help identify unexpected barriers and opportunities for improvement. Communication between sites of multisite trials may facilitate exchange of ideas. Institution-wide tracking systems and ClinicalTrials.gov are useful for collecting key recruitment metrics.
- **Learn from successes and failures of past trials.** Clinical trialists can learn from the successes and failures of past trials. Examples of recruitment and retention of traditionally hard-to-reach subgroups include the [Systolic Blood Pressure Intervention Trial \(SPRINT\)](#)⁶ that successfully recruited minority and frail older adults. The Marfan Trial⁷ and the Fontan Udenafil Exercise Longitudinal (FUEL) trial⁸ developed strategies for promoting recruitment of and adherence among pediatric populations. The Diabetes Telephone Study⁹, the [Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults \(PREVENTABLE\) trial](#), and SPRINT actively engaged community stakeholders, members of the affected populations, and healthcare providers.
- **Develop standards to communicate applicability and limitations of trial results.** The applicability and limitations of trial results should be stated clearly to ensure they are interpreted correctly and used in meaningful ways. Applicability to types of populations, providers, communities, and settings of care should be provided. Standards for recording this information would be helpful, particularly in communicating results to policymakers and clinicians.
- **Ensure that journal articles include accurate and complete methods.** Publications are essential for dissemination of results. Inclusion of complete and accurate methods in publications is essential for peer review and appropriate interpretation of results.
- **Increase patient access to clinical trials.** Trial access for older cancer patients and others could be increased by expanding access to large academic research centers or expanding research

⁵ Molnar, F. & Frank, C.C. (2019). Optimizing geriatric care with the GERIATRIC 5Ms. *Canadian Family Physician*, 65(1), 39.

⁶ Ramsey, T.M., Snyder, J.K., Lovato, L.C., Roumie, C.L., Glasser, S.P., Cosgrove, N.M., Olney, C.M., Tang, R.H., Johnson, K.C., Still, C.H., Gren, L.H., Childs, J.C., Crago, O.L., Summerson, J.H., Walsh, S.M., Perdue, L.H., Bankowski, D.M., Goff, D.C., SPRINT Study Research Group. (2016). Recruitment strategies and challenges in a large intervention trial: Systolic Blood Pressure Intervention Trial. *Clinical Trials (London, England)*, 13(3), 319-330. <https://doi.org/10.1177/17407745166631735>.

⁷ National Library of Medicine. (2015). Comparison of Two Medications Aimed at Slowing Aortic Root Enlargement in Individuals with Marfan Syndrome—Pediatric Heart Network. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT00429364>.

⁸ Frischhertz, B.P., Wagner, J.B., McHugh, K.E., McCrindle, B.W., Shillingford, A.J., Sabati, A.A., Yetman, A.T., Pediatric Heart Network Investigators. (2020). Results of the FUEL Trial. *Circulation*, 141(8), 641-651. <https://doi.org/10.1161/CIRCULATIONAHA.119.044352>

⁹ Adams, A.S., Bayliss, E.A., Schmittiel, J.A., Altschuler, A., Dyer, W., Neugebauer, R., Jaffe, M., Young, J.D., Kim, E., Grant, R.W., Diabetes Telephone Study Team. (2016). The Diabetes Telephone Study: Design and challenges of a pragmatic cluster randomized trial to improve diabetic peripheral neuropathy treatment. *Clinical Trials*, 13(3), 286-293. doi: 10.1177/17407745166631530. Epub 2016 Mar 31.

opportunities in community-based practices. Pediatric cancer patients have high clinical trial participation rates because most of them receive care at National Cancer Institute (NCI)-designated cancer centers.

- **Leverage existing data and modeling to supplement randomized controlled trials.** Large-sample pragmatic trials have the potential for maximizing diversity and inclusivity in study samples. Electronic medical records (EMRs) also include a wealth of information on large, diverse patient populations. Multidisciplinary teams can help utilize EMR data for research. Big data initiatives such as the [Big Data to Knowledge](#) program are creating tools and resources to leverage large datasets. Physiologically based modeling tools and simulations also may be able to predict the pharmacokinetic and pharmacodynamic features of a drug in different populations, which could inform clinical trials.

Recurrent Themes

Several common themes were identified over the course of the Workshop. The following is a synthesis of these recurrent themes.

- **There is diversity within pediatric and older populations.** Pediatric and older populations include racial/ethnic and gender subgroups and are diverse in other respects. Age is not synonymous with size, maturity, cognitive status, or vulnerability. Recruiting patients in a given age group does not guarantee that the diversity of that population will be represented. Pediatric subjects of the same age may differ significantly with respect to size, physiologic maturity, and diet. Older patients vary substantially in health and cognitive measures. Measures of cognition and function supersede chronological age in many cases; it is important to have measures to capture these differences at either end of the lifespan.
- **COVID-19 trials illustrate persisting inclusion challenges.** As trials for COVID-19 vaccines and therapeutics are under way, trial participants should be representative of the populations at highest risk and those most likely to receive the intervention. Although older adults and children likely will be priority populations for these interventions, only a small number of COVID-19-related trials are open to children, and the median age of participants in SARS-CoV-2 vaccine trials is 33 to 43 years. Investigators of COVID-19 trials also may need to invest in communication to counteract widespread disinformation in the public domain.
- **Social determinants of health may influence trial participation and outcomes.** Social factors (e.g., employment status, socioeconomic status) may influence access to clinical trials. Health-related risk factors (e.g., smoking) vary among racial/ethnic groups. These factors may influence recruitment, retention, and outcomes. Tools such as the neighborhood disadvantage Area Deprivation Index¹⁰ can help incorporate these factors into research.
- **Collaboration can help address common challenges.** Many challenges to inclusion are similar across populations. Increasing communication and interaction among researchers in different areas will lead to synergistic development of strategies to overcome these challenges.

¹⁰ University of Wisconsin, School of Medicine and Public Health, Department of Medicine. (2020). About the Neighborhood Atlas®. Retrieved from <https://www.neighborhoodatlas.medicine.wisc.edu/>.

Next Steps

Researchers need to work together and with NIH, industry, patients and caregivers, patient advocacy groups, and other stakeholders to address barriers to inclusion across the lifespan. Changes are needed across the continuum of research, from development of relevant research questions to high-quality study design, appropriate inclusion/exclusion criteria, thoughtful and nimble recruitment and retention efforts, and clear interpretation of applicability and generalizability of results.

Whenever new policies are established, it is vital to check in on how implementation of those policies is proceeding, what obstacles may have been encountered, and any further actions that might be needed to carry out the full intent of those policies. The research community, in partnership with NIH, should plan regular evaluations of progress on the implementation of NIH IAL policies via monitoring reports and outreach activities, including future workshops, designed to identify and persistent barriers to inclusion and foster creative and innovative ways to address them.

Summary of Presentations and Discussions

Implementation of the Inclusion Across the Lifespan Policy: Center for Scientific Review and National Library of Medicine Perspectives

Speaker: Noni Byrnes, PhD, Director, Center for Scientific Review, National Institutes of Health (NIH)

- From the grant review perspective, Inclusion Across the Lifespan (IAL) policy implementation includes reviewer training, instructions to reviewers and review panel chairs, and postreview labeling of applications.
- Postreview feedback in the form of summary statements provides useful information to applicants about compliance with the IAL policy.
- Most of the applications coded as unacceptable lacked a rationale for the age group proposed for the study.

Speaker: Patricia Brennan, RN, PhD, Director, National Library of Medicine, NIH

- The [ClinicalTrials.gov](https://clinicaltrials.gov) repository supports research insights and public accountability and assists with matching patients to trials.
- Two of the age options available during study registration on ClinicalTrials.gov—age, continuous and age, customized—make it more difficult to understand study performance in terms of inclusion across the lifespan and reduce comparability across studies.

Topic Area 1: Inclusion/Exclusion Criteria

Co-Chairs: Florence Bourgeois, MD, MPH, Harvard Medical School, and Cynthia Boyd, MD, Johns Hopkins Bloomberg School of Public Health

Panelists: Lucile L. Adams-Campbell, PhD, Georgetown University; George Saade, MD, University of Texas Medical Branch; Celia Fisher, PhD, Fordham University; William Dale, MD, PhD, City of Hope

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, and several cross-cutting themes were identified.

Populations

- **Pediatric populations.** Underrepresentation of pediatric patients in clinical trials has resulted in a lack of evidence-based guidelines for care, forcing providers to extrapolate findings in other populations. There are ethical, legal, and financial barriers to conducting trials in children. The level of acceptable risk is much lower for pediatric populations than for adults.
- **Older adults.** Clinical trial participants often are younger and have fewer chronic conditions than the population affected by the disease being studied. Although there has been an increase in enrollment of older adults in trials in recent years, many older adults are ineligible due to coexisting conditions, which is detrimental to the representativeness and applicability of the research. Recruitment, enrollment, and retention of older adults to trials would be enhanced through thoughtful and deliberate approaches and accommodations. Geriatric assessment (GA) domains to identify vulnerability in older patients should be included in clinical assessment tools and decision-making models in clinical trials and as part of comprehensive care.

- **Minorities.** Many minorities and others with poor social determinants of health are interested in participating in trials. “Cookie-cutter” exclusion criteria, particularly those related to comorbidities, result in many minority populations being ineligible for trials.
- **Pregnant and lactating women.** Physiological changes during pregnancy and lactation affect pharmacokinetics of drugs, so findings cannot reliably be extrapolated from nonpregnant women. Barriers to inclusion of pregnant women in clinical trials are similar to those for inclusion of children. Risk assessments tend to overemphasize risk to the fetus. Regulations need to include measures of minimal risk and allow exceptions for generalizable knowledge when minimum risk is exceeded.
- **Sexual minority youth.** Extrapolation of data from adult studies does not address developmental challenges related to adherence and uptake among adolescents. Although the Office of Human Research Protections and U.S. Food and Drug Administration consider mature minors to be adults, some Institutional Review Boards (IRBs) have been reluctant to waive guardian permission for mature minors to participate in research studies, in part due to concerns about youth capacity to consent. This is a barrier for research on adolescents, particularly for HIV research involving adolescent males who have sex with males. Additional data on consent capacity of mature minors could help address IRB concerns and inform procedures to reduce consent vulnerabilities. Guidance also is needed on compliance with new Common Rule requirements for identifying key consent information and whether adolescents can be considered reasonable persons with the right to consent to research independently.

Cross-Cutting Themes

- **In the race to develop therapies for COVID-19, generating high-quality evidence to guide treatment of children is necessary and feasible.** However, as of August 27, 2020, only 164 of 1,761 interventional studies were open to children.
- **Review and reporting processes can maximize the impact of the IAL policy.** Successful implementation of IAL starts with the application. Applications must clearly describe and provide rationale for inclusion/exclusion criteria in the context of the study question. Review panels must have the appropriate expertise to evaluate the criteria. In particular, review panels must decide whether inclusion of certain populations (e.g., children, older adults) is justifiable and scientifically meaningful and whether the proposed enrollment plan is rigorous and feasible. NIH currently reports aggregate data on enrollment of relevant age categories in its triennial report. Providing study-level data via [NIH RePORTER](#) or [ClinicalTrials.gov](#) could facilitate more frequent analyses and help identify opportunities to improve inclusion.
- **Exclusions that limit representativeness and generalizability should be avoided.** Exclusion criteria should be examined carefully to ensure they do not unnecessarily limit enrollment. Efforts should be made to avoid exclusions based on comorbidities that are common in the population affected by the disease being studied.
- **Risk of exclusion should be considered.** For many populations, the risk of research participation has been given more weight than the risk of exclusion from research. Improving the composition of IRBs or using centralized IRBs with strong, relevant expertise would help.

- **Extending the age of eligibility is not enough to ensure that older populations are represented.** Efforts must be made to make the trial population mirror the population affected by disease to the extent possible. This often will entail revisiting inclusion/exclusion criteria other than age (e.g., comorbidities).
- **Understand and accommodate target populations.** Increasing diversity among trial investigators and promoting cultural sensitivity will help increase engagement with minority populations. Outreach and trial designs should be tailored to the needs of the target population. Studies involving older adults may need to allow more time for visits or provide transportation. Patient navigators may help enrollment and adherence.

Topic Area 2: Study Design and Metrics

Co-Chairs: Jerry Gurwitz, MD, University of Massachusetts Medical School, and Peter Peduzzi, PhD, Yale School of Public Health

Panelists: Alyce S. Adams, PhD, Kaiser Permanente Northern California; Danny Benjamin, MD, PhD, Duke Clinical Research Institute; Supriya Mohile, MD, University of Rochester

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.

Key Points:

- **Priority populations should be included in phase III trials.** Phase III trial participants should be representative of the population affected by the disease and of high-priority populations in particular. Generalizable findings will not be obtained if trial participants are homogeneous. Although older adults are considered a priority population for SARS-CoV-2 vaccination, the participants in trials of these vaccines are much younger.
- **Intentional planning is needed to minimize barriers to recruitment and enrollment.** Enrollment goals should be developed early in the trial planning process, and eligibility criteria should be aligned with these goals. Researchers should engage patients and communities in study design and recruitment planning. Building relationships with community stakeholders, particularly those in communities of color, can help build trust and awareness and address challenges and barriers. Barriers to recruitment and retention of underrepresented groups in trials include lack of actionable information, lack of opportunity, mistrust, costs, and fear of harm.
- **Extrapolation should be used cautiously and thoughtfully.** Extrapolation of findings from one population to another can be a powerful tool, but it is not always appropriate. Studies have found that dosing and safety findings in adults should not be extrapolated for use in pediatric patients; separate studies must be done in children to ensure appropriate dosing and safety. However, extrapolation sometimes can be used to predict efficacy. When used appropriately, extrapolation of efficacy can avoid the need to conduct expensive phase III trials in a new population, freeing up resources for other important public health questions.
- **Research questions and outcomes should reflect community needs and priorities.** Currently, clinical trials often do not address the needs and concerns of patients and communities. Research questions most relevant to patients should be prioritized, and outcomes important to patients

should be measured (e.g., quality of life, physical performance). GA domains can help researchers and providers address outcomes important to older adults.

Topic Area 3: Recruitment, Enrollment, and Retention

Co-Chairs: Michelle S. Hamstra, MS, Cincinnati Children's Hospital Medical Center, and Steven Wallace, PhD, University of California, Los Angeles

Panelists: Raegan Durant, MD, MPH, University of Alabama at Birmingham; Wendy Kohrt, PhD, University of Colorado-Anschutz Medical Campus; Mark Supiano, MD, University of Utah School of Medicine; Consuelo Wilkins, MD, MSCI, Vanderbilt University Medical Center

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. Presenters examined pediatric and geriatric recruitment and retention considerations and provided concrete, evidence-based approaches that may be useful for Workshop attendees.

Key Points:

- **There is diversity within pediatric and older populations.** Pediatric and older populations include racial/ethnic and gender subgroups and are diverse in other respects. Recruiting patients in a given age group does not mean the diversity of that population will be represented. Measures of cognition and function supersede chronological age in many cases; it is important to have measures to capture these differences at either end of the lifespan.
- **Strategies to improve recruitment and retention should be adopted.** These include establishing a robust and representative team; identifying potential barriers; budgeting for recruitment and retention activities; creating an intentionally inclusive plan; and periodically evaluating the plan and making adjustments to improve it. Working with partners—including industry and advocacy organizations—can help with recruitment and retention.
- **Multiple strategies are needed to promote adherence.** Different strategies are needed for different populations. Strategies may include investing in resources; minimizing staff turnover to maintain rapport with participants; maximizing collaboration with providers, family members, and other sites; and using patient advocacy resources.
- **Researchers should utilize existing resources on recruitment, enrollment, and retention.** Resources on recruitment, enrollment, and retention of older adults in clinical research include the Research Centers for Minority Aging Research program, a special 2011 supplement of *The Gerontologist*, and the 2019 Gerontological Society of America preconference, Strategies for Successful Recruitment and Retention of Minority Elders.
- **Lessons should be gleaned from past trials.** Clinical trialists should learn from the successes and failures of past trials. The Systolic Blood Pressure Intervention Trial (SPRINT) was successful in recruiting several traditionally hard-to-reach subgroups, including minority and frail older adults.
- Trial investigators, particularly those conducting trials that include populations for whom they lack expertise, should undergo training. Training should include information on the importance of inclusion, guidance on development of eligibility criteria, and tips for recruiting and retaining priority populations. The Recruitment Innovation Center at Vanderbilt offers a course on enhancing minority recruitment on Coursera.

- **Strategies to increase access to clinical trials should be pursued.** Unlike pediatric cancer patients, who are largely treated at NCI-designated cancer centers, most adults receive care from community oncologists. Trial access for older adult patients can be increased by expanding research opportunities in community-based practices or by increasing access to NCI-designated cancer centers.
- **Investigators conducting COVID-19 studies must be prepared to address disinformation being disseminated during the pandemic.** Vanderbilt Recruitment Innovation Center consultations with COVID-19 studies identified this as a critical information need for potential participants.

Topic Area 4: Data Analysis and Study Interpretation

Co-Chairs: Heather Allore, PhD, Yale School of Medicine, and Valentina Shakhnovich, MD, Children's Mercy Kansas City

Panelists: Robert Golub, MD, Deputy Editor, *Journal of the American Medical Association*; Karen Bandeen-Roche, PhD, Johns Hopkins Bloomberg School of Public Health; and Jay Magaziner, PhD, MSHyg, University of Maryland School of Medicine

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

Key Points:

- **Age groups encompass substantial variability.** Many analyses group subjects by age, but this fails to account for wide variation of health and health-related factors within an age group. This is true for both pediatric and older populations. Pediatric subjects of the same age may differ significantly with respect to size and physiologic maturity. Changes in diet and drug formulations over the course of infancy and childhood may affect outcomes. Among older adults, functional measurements (e.g., frailty, resilience) may be more informative than age for some analyses.
- **Age is not synonymous with vulnerability.** Although vulnerability of potential subjects at the extreme ends of the age span must be considered, vulnerability and unacceptable 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.
- **Race/ethnicity and social factors impact health and risk.** Health-related risk factors (e.g., smoking, disability) vary among racial/ethnic groups. It may be important to take race/ethnicity and social determinants of health into account in analyses. Tools such as the area deprivation index can help incorporate these factors into research.
- **Study design and planning are critical.** Careful thought must be given to how subpopulations will be included and analyzed in research studies during the planning phase. Study designs and statistical analysis plans must adequately and appropriately describe planned subgroup analyses. Sufficient numbers of subpopulations of interest must be enrolled in order to generate analyzable and generalizable results. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for clinical trial protocols are a valuable resource for investigators.

- **Standards for reporting trial results are needed.** The applicability and limitations of trial results should be clearly stated to ensure they are interpreted correctly and used in meaningful ways. Applicability to types of populations, providers, communities, and settings of care should be provided. Standards for recording this information would be helpful, particularly in communicating results to policymakers and clinicians.
- **Statistical methods and data harmonization can facilitate informative analyses.** Statistical methods can help account for some population differences and data gaps, but they cannot overcome study design deficits. Meta-analyses and data harmonization efforts allow evaluation of outcomes of interest across studies. These types of approaches enable life course analyses that integrate biological and social processes over time.
- **Big data initiatives, electronic medical records (EMRs), and modeling can complement clinical trials.** Big data initiatives such as the Big Data to Knowledge (BD2K) program can maximize the utility of existing data. EMRs also have potential to provide information on large groups of heterogeneous populations, although it can be challenging to clean and validate data for research use. Interdisciplinary teams can help address these challenges. Physiologically based modeling tools and simulations also may be useful for predicting outcomes for different populations, possibly to inform clinical trial design.
- **Journal editors can improve presentation of information but not study design.** Journals link researchers and consumers of research (i.e., other researchers, clinicians, patients). Editors can advise on optimal presentation of information in articles, but they have limited ability to influence analytical approaches, particularly for randomized controlled trials. Inclusion of complete and accurate methods in publications is critical for peer review and appropriate interpretation of results.
- **Synergy among researchers can help address challenges across the lifespan.** Many of the inclusion challenges are similar for pediatric and older populations. Increasing communication and interaction among pediatric and geriatric researchers will lead to synergistic development strategies to overcome these challenges.

Appendix I. Inclusion Across the Lifespan Planning Committee Members

Committee Co-Chair: James Griffin, PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Committee Co-Chair: Barbara Radziszewska, PhD, National Institute on Aging (NIA)

Committee Co-Chair: Samir Sauma, PhD, NIA

Dara R. Blachman-Demner, PhD, NIH Office of Behavioral and Social Sciences Research (OBSSR)

Dawn Corbett, MPH, NIH Office of Extramural Research (NIH OER)

Elonna Ekweani, JD, NIH Office of Research on Women's Health (NIH ORWH)

Valery Gordon, PhD, MPH, National Center for Advancing Translational Sciences (NCATS)

Joyce Hunter, PhD, National Institute on Minority Health and Health Disparities (NIMHD)

Brian Johnson, PhD, National Cancer Institute (NCI)

Lisa Kaeser, JD, NICHD

Katherine Kavounis, MPH, National Heart, Lung, and Blood Institute (NHLBI)

Jaron Lockett, PhD, NIA

Samia Noursi, PhD, NIH ORWH

Mercy Prabhudas, PhD, MBA, National Institute of Allergy and Infectious Diseases (NIAID)

Sheila Prindiville, MD, MPH, NCI

Susan Schafer, RN, MS, NIAID

Katrina Serrano, PhD, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Erica Spotts, PhD, OBSSR

Appendix II. Panel Co-Chairs

Four Panels were formed to examine specific topics related to inclusion. The co-chairs who led each effort are listed below.

Topic 1: Inclusion/Exclusion Criteria

Co-Chairs:

Florence Bourgeois, MD, MPH, Harvard Medical School

Cynthia Boyd, MD, Johns Hopkins Bloomberg School of Public Health

Topic 2: Study Design and Metrics

Co-Chairs:

Jerry Gurwitz, MD, University of Massachusetts Medical Schools

Peter Peduzzi, PhD, Yale School of Public Health

Topic 3: Recruitment, Enrollment, and Retention

Co-Chairs:

Michelle S. Hamstra, MS, Cincinnati Children's Hospital Medical Center

Steven Wallace, PhD, University of California, Los Angeles

Topic 4: Data Analysis and Study Interpretation

Co-Chairs:

Heather Allore, PhD, Yale School of Medicine

Valentina Shakhnovich, MD, Children's Mercy Hospital Kansas City

Appendix III. Presentation Summaries

As part of the Inclusion Across the Lifespan Workshop (IAL-II), experts presented background information and the results of analyses. This appendix includes a brief summary of each presentation.

Opening Remarks

Marie A. Bernard, MD, Deputy Director, National Institute on Aging (NIA), National Institutes of Health (NIH)

In 2016, the *21st Century Cures Act* directed the NIH to collect data on the inclusion of participants in clinical studies by age and to convene a workshop focused on the inclusion of pediatric and older adult populations in clinical research. The 2017 Inclusion Across the Lifespan Workshop (IAL-I) addressed challenges and opportunities for including children and older adults in clinical research strategies that would produce more age-inclusive clinical studies.

Following IAL-I, NIH revised its policy on inclusion of children in clinical research to become the Inclusion Across the Lifespan policy to address inclusion at both ends of the age spectrum. Announced in December 2017, the policy applied to all competing grant applications for due dates on or after January 25, 2019. Applications must include a plan for including individuals across the lifespan and, if excluding based on age, provide justification for the specific age range. Progress reports must provide anonymized individual-level data on age at enrollment in units ranging from hours to years and include sex/gender and race/ethnicity data. This enables NIH for the first time to examine adequacy of inclusion across a wide range of disease states and have the ability to sort data according to what is appropriate for the scientific question a study is attempting to answer.

IAL-II goals include:

- Sharing evidence-based approaches to facilitate full compliance with the spirit of the IAL policy
- Conducting open scientific discussion of those evidence-based approaches
- Sharing resources to facilitate inclusion across the lifespan.

Greetings from the National Institutes of Health

Francis Collins, MD, PhD, Director, NIH; Michael Lauer, MD, NIH Deputy Director of Extramural Research; Richard Hodes, MD, Director, NIA; Diana Bianchi, MD, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); Janine Clayton, MD, Director, Office of Research on Women's Health (ORWH); and Eliseo Perez-Stable, MD, Director, National Institute on Minority Health and Health Disparities (NIMHD)

Members of NIH leadership offered greetings to IAL-II Workshop participants and remarked on the value and purpose of the Workshop. When new policies are established, it is vital to check in on how implementation of those policies is proceeding, what obstacles may have been encountered, and any further actions that might be needed to carry out the full intent of those policies. IAL-II is an opportunity for that implementation checkup.

NIH clinical research is intended to advance the health, well-being, and quality of life of Americans and citizens of the world, who themselves are diverse. Only by including diversity across age and other dimensions of demographics can that goal be achieved. NIH has gotten better at addressing the challenge of inclusion across the lifespan and is moving toward ensuring that clinical research study participants are

representative of the populations affected by a particular health concern. For example, in the 1980s, many clinical trials included primarily white men, but, today, more than half of the participants in NIH clinical trials are women. There has been progress, but we can do better; hence, the importance of the IAL-II Workshop.

COVID-19 provides a dramatic lesson about the importance of inclusiveness across the lifespan. Ignoring the variation in what happens after exposure to this virus—depending on many different parameters such as age, gender, socioeconomic status, race, and ethnicity—would leave a significant gap in our understanding of what actions to take. Because COVID-19 particularly afflicts older adults, a vaccine’s protective effect on older adults is highly important. Likewise, the disease seems to be more severe for those with chronic illnesses as well as certain populations who are not in a good position to follow our best public health measures (e.g., sheltering at home, social distancing). In the early days of the pandemic, infected children seemed to do fairly well; however, we are now aware of a new condition called multisystem inflammatory syndrome in children (MIS-C), a postinfectious vasculopathy that desperately needs to be understood. To ensure that clinical trials collect the evidence of greatest utility, all communities must take part so that they can benefit equally from those medical advances. As vaccine trials against COVID-19 are under way, participants in those trials must be representative of these different groups, particularly those who have experienced the most significant harms from this virus.

Implementation of the IAL Policy in Peer Review: Center for Scientific Review Perspectives

Noni Byrnes, PhD, Director, Center for Scientific Review (CSR), NIH

Dr. Byrnes provided an overview of reasons an IAL policy was necessary—arbitrary age limits for enrollment based on convenience in recruitment or ease of study design; exclusion criteria that disproportionately impact older people (e.g., multiple morbidities) or children; and failure to recruit subjects at either end of the age range even though these populations sometimes are in greater need of interventions. These factors led to gaps in the evidence base and a lack of substantive clinical guidelines for children and older adults. From the research perspective, there is a scarcity of easily accessible, disaggregated information to improve understanding of differential outcomes across different ages.

The December 2017 Notice of NIH Inclusion Policy Change (NOT-OD-18-116) mandated that participants of all ages be included in research involving human subjects, unless there is a scientific or ethical reason for exclusion of any age category.¹¹ The revision broadened applicability of the policy to individuals of all ages, including children (age <18) and older adults (age ≥ 65); clarified potentially acceptable reasons for excluding participants based on age; and included a requirement to provide data on participant age at enrollment in progress reports.

From the grant review perspective, IAL policy implementation includes reviewer training, instructions to reviewers and review panel chairs, and postreview labeling of applications. (CSR alone uses 18,000 reviewers and conducts 1,600 panel meetings a year.)

Individual reviewers independently assess whether the age range of the subjects is justified in the context of the proposed scientific question and rate inclusion plans as “acceptable” or “unacceptable” based on

¹¹ National Institutes of Health. Revision: NIH policy and guidelines on the inclusion of individuals across the lifespan as participants in research involving human subjects. Retrieved from <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>.

the Approach (rigor of experimental design), additional review criteria, and preliminary overall impact sections. Critique templates include evaluation of inclusion plans. Scientific Review Officers (SROs) examine individual reviewers' critiques prior to the meeting to ensure that inclusion plans are addressed.

During the review meeting, the panel as a whole assesses IAL with regard to age-appropriate inclusion or exclusion of individuals in the research project *before final scoring*. After the meeting, SROs flag discussed applications as "acceptable" or "unacceptable."

Acceptable scientific exclusions are as follows:

- The condition does not occur/topic not relevant to excluded group (e.g., Alzheimer's disease in children).
- Knowledge is already available in the excluded group. For example, a study of a drug previously approved for adults that is now being studied in children does not need to include adults.
- A separate study in the excluded age group is warranted and preferable.
- Age differences should be taken into account when feasible.
- Collection/analysis of data on pre-enrolled participants AND age-inclusive data are not available.

Acceptable ethical exclusions are as follows:

- Laws/regulations bar the inclusion of individuals in the age group.
- The risk to the excluded group is unacceptable and, therefore, their inclusion is unethical.

Unacceptable reasons for exclusion include cost, convenience, lack of explanation for the chosen age range, and concerns about noisy data.

Following review, comments are provided in the individual reviewer critiques in the summary statements to applicants whose IAL plans were flagged as unacceptable and whose applications were not scored or not discussed. If the application was scored or discussed, the summary statement is flagged as unacceptable, annotated to indicate why it is unacceptable, and coded as "U" in the NIH system. Any application coded as "U" is barred from funding until the reasons for the flag are resolved, regardless of score/percentile. Resolution occurs during interactions between the applicant and program staff.

Since the IAL policy was implemented, about 3 percent of 46,794 applications proposing human subjects research have been rated unacceptable due to IAL policy. In general, reviewers comment on IAL and appropriately distinguish between acceptable and unacceptable with regard to the IAL policy. Assessments of inclusion plans are reflected in the scores; applications with unacceptable codes for children/older adults score worse. In the first year, the most common reason an application was flagged as "unacceptable" was the lack of any explanation for the age group chosen. This is not surprising because it takes time for the community to understand requirements of a new policy.

IAL resources related to the grant application process include Frequently Asked Questions (<https://grants.nih.gov/faqs#/inclusion-across-the-lifespan.htm>), the NIH Office of Extramural Research Inclusion Across the Lifespan Compliance Page at <https://grants.nih.gov/policy/inclusion/lifespan.htm>, and Guidance for Peer Reviewers at https://grants.nih.gov/grants/peer/guidelines_general/Review_Human_Subjects_Inclusion.pdf.

Key Points:

- From the grant review perspective, IAL policy implementation includes reviewer training, instructions to reviewers and review panel chairs, and postreview labeling of applications.
- Postreview feedback in the form of summary statements provides useful information to applicants about compliance with the IAL policy.
- Most of the applications coded as unacceptable lack a rationale for the age group proposed for the study.

Implementation of the IAL Policy: National Library of Medicine Perspectives

Patricia Brennan, RN, PhD, Director, National Library of Medicine (NLM), NIH

Dr. Brennan's presentation focused on how NLM fosters inclusion across the lifespan in NIH-funded research; specifically, how the NIH repository, [ClinicalTrials.gov](https://clinicaltrials.gov), serves to acquire information about age across the lifespan as well as how that information is encoded and used in the repository's operation.

The Office of the National Coordinator of Health Information Technology has adopted United States Core Data for Interoperability, a standardized set of health data classes and constituent data elements for nationwide, interoperable health information exchange that establishes a way to identify 27 parameters that must be present in all clinical records (e.g., allergies, clinical note observations, patient demographics). In addition, the FHIR standard (i.e., fast healthcare interoperability resource) provides a way to codify messages and make them accessible in an electronic exchange (e.g., between care facilities).

Common Data Elements (CDEs) offer systematic ways to label phenomena of interest in a particular research project. In effect, a series of subject matter experts have come together to describe a preferred way to measure a specific phenomenon of interest. For example, CDEs for persons involved in a COVID study include infectious disease testing outcomes, morbidity, diagnosis, and psychosocial impact.

CDEs for age are of particular relevance to the IAL policy; specifically, in clinical trials. Age can be time-since-birth or categorical descriptions (e.g., birth to 6 months, up to 18 years). It is important to understand how age is captured at the point of enrollment in a study, which may be different from how that study reports age in the [ClinicalTrials.gov](https://clinicaltrials.gov) repository.

When a trial is registered in [ClinicalTrials.gov](https://clinicaltrials.gov), a unique study record documents key protocol details as well as key recruitment information such as eligibility criteria, which must include age limits of potential participants. At trial completion, results are summarized, including baseline characteristics (age is required), primary and secondary outcome measures, adverse events, and the protocol and statistical analysis plan. Age reporting options include age, continuous; age, categorical (up to 18 years old, over 18 and up to 65 years, 65 years or older); and age, customized. Choosing the age, continuous or age, customized options makes it more difficult to understand the study in terms of inclusion across the lifespan and comparison across studies. Of the 43,510 study records with results posted as of June 22, 2020, 72 percent use age, continuous; 35 percent use age, categorical; and 10 percent use age customized.

The age-related [ClinicalTrials.gov](https://clinicaltrials.gov) CDEs support insights into research and public accountability and accommodate selected special issues. Age-related CDEs also are used to match patients to trials based on eligibility criteria.

NLM supports having age categories that are reflective of the clinical phenomenon of interest (e.g., to address the heterogeneity of health status within the population over age 65). However, study results are not required to be reported by age. It is important to be careful not to mislead the public by suggesting that one could compare across ages when the study was not sufficiently powered for age.

Dr. Brennan noted that, under NIH policy and U.S. Food and Drug Administration (FDA) regulations, financial and operational sanctions can be imposed if a clinical trial does not complete a final report within one year of the point where the last participant completed. The Office of Extramural Research developed a policy interpretation that allows results to be reported even before they have been verified in order to meet the one-year reporting deadline.

Key Points:

- The ClinicalTrials.gov repository supports research insights and public accountability and assists with matching patients to trials.
- Two of the age options available during study registration on ClinicalTrials.gov—age, continuous and age, customized—make it more difficult to understand study performance in terms of inclusion across the lifespan and reduce comparability across studies.

Panel Discussions with Q&A

Topic Area 1: Inclusion/Exclusion Criteria

The study population defined by the eligibility criteria should be representative of the population of people with the condition being studied. Inclusion and exclusion criteria should be objective and written in clear, concise language, and investigators should provide a scientific justification for each criterion. The co-chairs discussed this topic with specific considerations for the pediatric and older adult perspectives.

Inclusion of Pediatric Populations in Clinical Trials

Florence Bourgeois, MD, MPH, Harvard Medical School

Historically, children have been largely underrepresented in clinical trials, which leads to pediatric clinical care that is not always evidence based. Currently, 52 percent of drugs do not have pediatric prescribing guidelines. Physicians widely extrapolate findings from adult studies and use products in children without age-specific research on dosing, safety, or efficacy.

Barriers to the inclusion of children in clinical trials—many of which are well justified—center on ethical, legal, and financial considerations and incentives from the sponsors' perspective. In the United States, research must involve no more than minimal risk to the child in order for the child to be enrolled; if the risk is greater than minimal, at least one of three specific criteria must be met: the research must present potential for direct benefit to the child, the research must be likely to yield generalizable knowledge about the participant's condition, or it must present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. In essence, the acceptable risk is much lower for pediatric populations than it is for adults. Financial considerations include higher cost to recruit and enroll children and more limited prospects for profit, given the smaller market for many conditions compared with those in adults.

COVID-19 presents an interesting use case for looking at how these factors relate to inclusion of children in clinical trials. Starting in March 2020, many organizations quickly designed and launched large global clinical trials. Many were multicenter. Some were funded by government sources such as the National Institute of Allergy and Infectious Diseases, the World Health Organization, or specific sponsors looking at different interventions. As of August 27, 2020, out of 1,761 interventional studies, only 164 were open to children. Even in the race to develop therapies for COVID-19, generating high-quality evidence to guide treatment of children is necessary and feasible, and it could be done efficiently.

The NIH IAL policy requires applications to describe plans for including individuals across the lifespan with a rationale for selecting specific age ranges if certain populations are excluded. Application of the policy to enrollment of children and the potential to increase pediatric enrollment raises two considerations: (1) the justification for the pediatric inclusion or exclusion must be scientifically and ethically appropriate and well described; and (2) the proposed enrollment for pediatric patients must be feasible and scientifically meaningful. Extending the age of eligibility down to include children may not be sufficient. For many interventional studies, including children in an adult study may not be sufficient to account for their unique enrollment requirements nor scientifically meaningful; in such cases, separate pediatric studies may be appropriate.

Successful implementation of the IAL policy starts with meeting application requirements. Applications must provide detailed descriptions of the inclusion/exclusion rationale in the context of the study question; the number of children that need to be enrolled across pediatric age subgroups; and sufficient information to assess whether the proposed inclusion is scientifically meaningful. At the preaward stage, it is important to ensure review panels have appropriate pediatric expertise to evaluate the proposed inclusion and exclusion plan—whether inclusion of children is justifiable and scientifically meaningful and whether the proposed enrollment plan for the specific pediatric age groups is rigorous and feasible.

Practices around public reporting and transparency also provide an opportunity to maximize the impact of the IAL policy. NIH must report at an aggregate level on the inclusion of relevant age categories in its triennial report. Evidence-based improvements to IAL policy implementation would be facilitated by providing study-level data on age-based inclusion and exclusion in a timely fashion via NIH RePORTER or ClinicalTrials.gov. This would enable the scientific community to perform more frequent analyses for the success and impact of the NIH policy and support identification of opportunities and, perhaps, consistent barriers to inclusion.

Key Points:

- Barriers to the inclusion of children in clinical trials center on ethical, legal, and financial considerations and incentives from the sponsors' perspective.
- Justification for the pediatric inclusion or exclusion from a study must be scientifically and ethically appropriate and well described; the proposed enrollment for pediatric patients must be feasible and scientifically meaningful.
- Successful implementation of the IAL policy starts with meeting application requirements and continues through the preaward and public reporting and transparency stages.

Inclusion of Older Adults in Clinical Research

Cynthia Boyd, MD, Johns Hopkins Bloomberg School of Public Health

Dr. Boyd presented on the inclusion of older adults in clinical research, both observational research and clinical trials, while recognizing that most special populations are present as we age. A number of studies have demonstrated that this is a common scenario.

When considering how research is applied in older populations, a fundamental question is whether the research participants are representative of the population that has the condition or conditions of interest. In general, the affected population is often older and has more chronic conditions than the clinical study population. In general, the affected population is often older and has more chronic conditions than the clinical study population. Over the past decade, the number of trials with explicit age exclusions has decreased, which has led to an increased trial enrollment of older patients; however, this is still well below the levels of older patients actually affected by the clinical situation being studied. Over this same period, the number of trials that exclude people with specific comorbidities or coexisting conditions may increase; for example, the number of heart failure trials that exclude people with specific and very common comorbidities to heart failure increased from 1985 to 1999; again, this has a fundamental effect on representativeness and applicability to the research.

The 5-T Framework for Recruiting Older Adults (Target population, Team, Tools, Time, and Tips to accommodate)¹² aims to increase inclusion of older adults in clinical research by providing guidance to researchers who do not specifically study aging. Guidance for each of the 5Ts is outlined below.

- **Target population:** Understand the prevalence of the study condition in older adults and avoid exclusions that limit study generalizability. For example, an analysis of the National Health and Nutrition Examination Survey found that having multiple chronic conditions is common among women aged 65 or older.¹³ Although this problem is particularly relevant to older populations, as people age with chronic diseases and develop other coexisting conditions, there can be a very high prevalence of common conditions that affect whether a recommended treatment applies. Thinking about who has the condition and what comorbidities they also may have is fundamental to designing trials and studies that inform their care.
- **Team:** Engage geriatrician researchers and aging experts and connect with caregivers and community resources to ensure that the full breadth of people involved in their care and well-being are involved.
- **Tools:** Choose appropriate measures of function, physical performance, and patient-reported outcomes, and balance data collection needs with participant burden.
- **Time:** Consider participant and study time. Anticipate longer study visits for some participants. Recognize that it may be necessary to accommodate comorbidities during long study visits (e.g., snacks for diabetics). Recognize that it may take longer to schedule follow-up visits for participants who depend on others for transportation.

¹² Bowling C.B., Whitson H.E., & Johnson T.M. 2nd. (2019). The 5Ts: Preliminary development of a framework to support inclusion of older adults in research. *Journal of the American Geriatric Society*, 67(2), 342-346. doi: 10.1111/jgs.15785. Epub 2019 Jan 29.

¹³ Boyd C.M., Leff B., Wolff J.L., Yu Q., Zhou J., Rand C., & Weiss C.O. (2011). Informing clinical practice guideline development and implementation: prevalence of coexisting conditions among adults with coronary heart disease. *Journal of the American Geriatric Society*, 59(5), 797-805. doi: 10.1111/j.1532-5415.2011.03391.x.

- Tips to accommodate: It may be necessary to budget for door-to-door transportation. Use high-contrast print materials with larger font sizes. Plan for a higher attrition rate, which has implications for sample size and power calculations.

The 5T Framework is built upon the Geriatric 5Ms: Mind, Mobility, Medications, Multicomplexity, and Matters most to me.¹⁴ When moving beyond the clinical setting, the 5Ms have important implications for study designs that maximize inclusion of older adults.

- Mind: Consider cognition, which may include simplifying study processes, including caregivers and proxies, and not excluding people with cognitive changes unless necessary.
- Mobility: Ensure access. Home visits may be necessary for follow-up.
- Medications: Think about how to include the caregiver proxy responsible for medications. Be sure to collect information about nonstudy medications and, when appropriate, discontinue or reduce the dosage of those that may be potentially harmful. Be prepared for adverse events.
- Multicomplexity: Limit exclusions to maximize representativeness. Account for competing risks and be prepared to address trade-offs that balance the goals for multiple conditions.
- Matters most to me: Include outcomes that are important and meaningful to patients and stakeholders, including family members.

These principles must form the foundation for design of clinical studies that are inclusive of older adults, including those who fall under the special populations.

Key Points:

- Successful implementation of the NIH policy requires special considerations during planning of the study, at the application stage, during preaward review, and at the level of reporting and public disclosure.
- Inclusion of older adults must be meaningful and allow conclusions to be drawn about this diverse population.
- Inclusion of older adults requires thoughtful and deliberate approaches to common conditions and syndromes.

Inclusion of Minorities in Clinical Research and Addressing Health Disparities

Lucile L. Adams-Campbell, PhD, Georgetown University

Social determinants of health—economic stability, neighborhood and physical environment, education, food, community and social context, healthcare system—play a major role in health outcomes, including mortality, morbidity, life expectancy, healthcare expenditures, health status, and functional limitations.¹⁵ Social determinants of health are central to understanding the causes of health disparities.

¹⁴ Bowling C.B., Whitson H.E., & Johnson T.M. 2nd. (2019). The 5Ts: Preliminary development of a framework to support inclusion of older adults in research. *Journal of the American Geriatric Society*, 67(2), 342-346. doi: 10.1111/jgs.15785. Epub 2019 Jan 29.

¹⁵ Alliance for Strong Families and Communities. (2020). Social Determinants of Health issue brief. Retrieved from <https://alliance1.org/web/resources/pubs/social-determinants-health-issue-brief.aspx>

There is a widespread myth—likely an implicit bias—that people with poor social determinants of health do not participate in clinical research due to a lack of interest. They are interested; when they have cancer and are surviving cancer, they would love to have state-of-the-art treatment.

Barriers to participation include employment loss during treatment and related legal issues. Georgetown University’s medical-legal partnership enhances the institution’s ability to recruit and engage people in trials. A study of African American participation in clinical trials at Howard University Hospital and Cancer Center found that study design exclusion and inclusion criteria rendered the majority of the study population ineligible; among African Americans, comorbidities were a major issue.¹⁶

Dispelling clinical trial myths about minorities requires action. Traditional, cookie-cutter exclusion criteria must be re-examined; criteria from 40 or 50 years ago may no longer be relevant. Cultural sensitivity is critical to the big picture; team members must be able to relate to and talk to the participants. Patient-provider communication must be enhanced to ensure patient understanding. Diversity among principal investigators and staff must be increased to include minorities and other underrepresented groups.

Key Points:

- Social determinants of health are central to understanding the causes of health disparities.
- Approaches to dispelling or reducing clinical trial myths about minorities include rethinking cookie-cutter exclusion criteria, building cultural sensitivity, and being intentional about increasing diversity among members of the clinical trial team.

Inclusion of Pregnant and Lactating Women in Clinical Research

George Saade, MD, University of Texas Medical Branch

When thinking about the inclusion of pregnant and lactating women (hereafter referred to as pregnant women) in clinical research, the picture is very similar to that of children, although this population may be lagging slightly behind inclusion of children in research. Reasons for including pregnant women in research include the high number of pregnancies in the United States (4 million per year) and worldwide (more than 100 million). Pregnancy outcomes are worsening, with complicated pregnancies and maternal morbidity and mortality on the rise. All of this is happening during a period in a woman’s life for which there is limited evidence on which to base treatment and interventions. Physiological changes that occur during pregnancy affect pharmacokinetics (PK), which means that findings from nonpregnant women cannot be extrapolated to pregnant women.

In general terms, exclusion of pregnant women from clinical research overemphasizes the risk to the fetus and underemphasizes the risk of lack of evidence. Options for pregnant women are to take a medication with unknown safety efficacy or not take that medication; neither is a good option. Reluctance to include pregnant women in clinical trials due to concerns about the fetus paradoxically increases risk to the fetus from use of drugs in clinical practices.

¹⁶ Adams-Campbell, L.L., Ahaghotu, C., Gaskins, M., Dawkins, F.W., Smoot, D., Polk, O.D., Gooding, R., & DeWitty, R.L. (2004). Enrollment of African Americans onto clinical treatment trials: Study design barriers. *Journal of Clinical Oncology*, 22(4), 730-734.

A paternalistic attitude (what used to be called *vulnerability of pregnant women*) is another issue that limits inclusion of pregnant women in clinical research. This designation has been removed from the [Final Rule on the Federal Policy for the Protection of Human Subjects](#) (Common Rule) but remains in the minds of researchers, regulators, and others.¹⁷ Additional barriers to inclusion include regulatory hurdles such as providing evidence of safety in pregnancy to obtain an Investigational New Drug application from FDA and limited Institutional Review Board (IRB) expertise with pregnancy.

Approval of inclusion of pregnant women in an interventional study requires that there be no more than minimal risk, but what is minimal risk when every pregnancy has some risk? The lack of good clinical research models for pregnancy, particularly pregnancy complications, makes risk assessment particularly difficult. For inclusion of children in clinical research, when the risk is greater than minimal, inclusion is possible if specific criteria are met; that is, the research must be likely to yield generalizable knowledge about the participant's condition. However, this exception is not available for inclusion of pregnant women. Perhaps this exception might be allowed in the future.

Because of a perceived lack of return on investment and litigation disincentives, industry support for phase III clinical trials in pregnant women is lukewarm. NIH primarily supports discovery, preclinical, and/or translational research, and then industry spends millions of dollars to obtain FDA approval in order to implement promising treatment into clinical practice.

To overcome these barriers to inclusion of pregnant women in clinical research, there is a strong need to incentivize industry through new laws similar to the [Best Pharmaceuticals for Children Act](#). The burden of research in pregnancy can be reduced by improving the composition of the IRB or using a centralized IRB with strong expertise in research and pregnancy. Revising regulations to include measures of minimal risk and possibly add the generalizable knowledge option when minimal risk is exceeded also would reduce burden. Furthermore, research that is more cost-effective that allows for easier inclusion of pregnant women during clinical care should be promoted; for example, comparative effectiveness, group-randomized, or cluster-randomized trials.

Finally, risk and benefit can be reframed; that is, focus on the benefit of research in pregnancy rather than on the risks. The risks of inclusion should be balanced with the risk of exclusion. Expectations for risk assessment need to be realistic; if safety data are required before inclusion of pregnant women but there are no good preclinical models, the cycle cannot be broken.

To improve pregnancy outcomes, it not only is acceptable to include pregnant women in research and clinical trials; it is also imperative.

Key Points:

- Barriers to inclusion of pregnant women in clinical trials are similar to those for inclusion of children.
- Pregnancy outcomes are worsening.
- Barriers to inclusion of pregnant women include an overemphasis on risk and underemphasis on risk of exclusion, paternalistic attitudes, regulatory burden, IRBs with limited expertise in pregnancy, inability to measure minimal risk and lack of preclinical research models, and lack of interest from industry.

¹⁷ Final Rule on the Federal Policy for the Protection of Human Subjects (Common Rule) regulations. (2017 Jan 19). Retrieved from <https://www.govinfo.gov/content/pkg/FR-2017-01-19/pdf/2017-01058.pdf>.

- Approaches to reducing barriers to inclusion of women in clinical trials include incentivizing industry; improving IRB composition or using a centralized IRB with strong, relevant expertise; revising regulations to include measures of minimal risk and allowing exceptions for generalizable knowledge when minimal risk is exceeded; and promoting cost-effective trials such as comparative effectiveness and group- or cluster-randomized trials.
- Inclusion of pregnant women in clinical research can be increased by focusing on benefits rather than risk and balancing risks of inclusion with risks of exclusion.

Inclusion of Sexual Minority Youth in Clinical Research

Celia Fisher, PhD, Fordham University

According to Dr. Fisher, sexual minority adolescent males (adolescent males who have sex with males ([AMSM]) account for 81 percent of new teen HIV infections. Although state mature minor laws permit youth under 18 to have independent access to HIV services and Office for Human Research Protections (OHRP) and FDA regulations for research consider mature minors to be adults, IRBs have been reluctant to waive guardian permission for mature minors based in part on concerns regarding youth capacity to self-consent. This has become a critical barrier to HIV research recruitment, as AMSM have refused participation due to fears that guardian permission will “out” them, leading to family rejection. As a result, studies are underpowered and include only those youth with supportive family relationships (a nonrepresentative sample).

Nonetheless, in 2018, FDA approved pre-exposure prophylaxis (PrEP) for adolescents, a daily pill found effective for reducing HIV acquisition in adults. This is troublesome because medications for adolescents based on extrapolations of data from adult studies do not address developmental challenges for medication uptake and adherence in this age group.

Adherence problems with PrEP pills led to current randomized controlled trials (RCTs) with adult men who have sex with men (MSM) comparing efficacy and safety of oral PrEP to a longer-lasting injectable form (Cabotegravir). Once approved, these trials will be conducted with AMSM, underscoring the urgency to evaluate process data on mature minors’ capacity to consent to ensure these studies include adequate samples.

To inform these trials, consent capacity for an oral versus injectable PrEP RCT was assessed, comparing adolescents aged 14–17 years to older MSM whose legal right to self-consent is unchallenged. After participants view a video and a consent form, they answer open-ended and yes/no questions. Across ages, the majority demonstrate understanding of the following consent competencies: procedures, side effects, random assignment, confidentiality, etc.; they demonstrate consequential reasoning ability by indicating they are unlikely to consent if they anticipate negative consequences. However, regardless of age, some have indicated only partial understanding of inclusion criteria, prandomization safety testing, and study purpose, and they have not included comparison of risks and benefits of their participation in reasoning.¹⁸

¹⁸ Fisher, C.B., Arbeit, M.R., Dumont, M.S., Macapagal, K., & Mustanski, B. (2016). Self-consent for HIV prevention research involving sexual and gender minority youth: Reducing barriers through evidence-based ethics. *Journal of Empirical Research on Human Research Ethics*, 11(1), 3-14. doi: 10.1177/1556264616633963. Epub 2016 Mar 7.

Key Points:

- Permitting self-consent of mature minors is essential toward reducing barriers to recruitment and adequately powering HIV trials involving MSM, as well as including adequate sampling of other adolescent populations in health research.
- Additional data on consent capacity of mature minors can address IRB concerns and inform procedures with potential to reduce consent vulnerabilities.
- Guidance is needed for compliance with new Common Rule requirements for identifying key consent information.
- Medications for adolescents based on extrapolation of data from adult studies fail to address developmental challenges related to adherence and medication uptake in this age group.

Inclusion of Older Adults in Cancer Research

William Dale, MD, PhD, City of Hope

Cancer is associated with aging. In many ways, older adults are typical cancer patients, which makes it especially ironic that they are less represented in most of the trials that guide therapies for cancer care. Notably, the age distributions for phase II and III NCI Cooperative Group Trials have changed minimally since 2001.

Older adults with comorbidities, functional impairments, and cognitive impairments are excluded from participation in clinical research. Older adults who are included tend to be aging all-stars; they are healthier and have fewer comorbidities. For this reason, findings from completed trials that included these all-stars are surprisingly similar to those for younger adults. This reflects a failure to design trials that allow for enrollment of vulnerable patients of all kinds.

The American Society of Clinical Oncology (ASCO) clinical practice guideline for older patients with cancer recommends appropriate implementation of validated and standardized clinical assessment tools and decision-making models that have sufficient evidence from a number of people to be used for any and all patients, both in practice and in trials, to identify vulnerabilities.¹⁹ Second, essential geriatric assessment (GA) domains must be included in all of the areas that are most important (e.g., functional

¹⁹ Boyd, C.M., Burhenn, P.S., Canin, B., Cohen, H.J., Holmes, H.M., Hopkins, J.O., Janelins, M.C., Khorana, A.A., Klepin, H.D., Lichtman, S.M., Mustian, K.M., Tew, W.P., & Hurria, A. (2018). Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. *Journal of Clinical Oncology*, 36(22), 2326-2347. doi: 10.1200/JCO.2018.78.8687.

losses, cognitive impairments, social losses, emotional concerns, falls). Omitting these domains will fail to identify those elements that are most importantly associated with outcomes. Third, noncancer prognostication of life expectancy should be conducted independent of the patient's cancer diagnosis, as clinicians run the risk of overtreating cancer in vulnerable patients and exacerbating other conditions that would shorten their lives. Fourth, GA-guided, targeted interventions should be implemented. At a recent ASCO meeting, four RCTs were presented showing how such interventions can lead to substantial decreases in chemotherapy toxicity and hospitalizations as well as increased quality of life. Some have argued that these assessments are too difficult to include in research studies and even clinical practice. To the contrary, a number of studies have shown that they are no more difficult to do than a number of standard procedures (e.g., imaging studies, biopsies), and most can be performed by nonphysician staff to obtain essential information needed to make important decisions.

Key Points:

- Older adults with cancer continue to be underrepresented in cancer clinical trials, which reduces applicability of study findings for this vulnerable population.
- The ASCO Guideline for Geriatric Oncology recommends the use of clinical assessment tools and decision-making models.
- Recent trials of GA-guided, targeted interventions have shown that such interventions can lead to substantial decreases in hospitalizations and chemotherapy toxicity and improved quality of life in older adults with cancer.

Discussion

- Short-term approaches to increase enrollment of pregnant women in clinical trials include a centralized IRB for research in pregnancy and the addition of a generalizable knowledge criterion to the Common Rule (similar to the one for research in children). Long-term, we need to support and promote more research on how to determine risks in pregnancy; we lack good methods and good preclinical models. Developing these models will require investment at NIH or outside NIH. The Human Placenta Project is a start, but we need more.
- Patient navigation is a useful approach to addressing barriers; navigators identify problems and find and use resources to address them. Navigators are involved in clinical trial recruitment because they anticipate problems and address them early and follow patients to increase patient adherence.
- Appropriate timing of the clinical competence to consent assessment becomes an equity issue because normative healthy adults and adolescents who are 18–19 years old and considered legal adults are not assessed for competence. It is possible to have a consent advocate available if the individual or an IRB thinks the child might need some kind of assistance. NIH, FDA, and OHRP need to have open discussion with IRBs and perhaps apply greater pressure on them to follow the regulations that define mature minors as adults.
- A number of validated tools can be used as a package to perform a comprehensive GA, and these are listed in the ASCO Guideline. The GA provides extensive information that identifies areas to target during the trial and other conditions to target when providing comprehensive

care. Substantial benefits are gained from a small investment of time to include them, and these tools need to be incorporated into the trial design from the start. According to a soon-to-be-published survey on the use of GAs in clinical practice and clinical trials, 20 to 25 percent of responders used some version of a GA; about 10 percent reported using the complete version.

- Perceived barriers to using the GA fall into two categories: (1) people who do not include the GA in the study design because they are unaware of it or do not recognize its value; and (2) others who are aware of the value of a GA but lack resources or have time barriers. There is need to educate researchers about the value of GAs and the ease with which they can be included in studies.
- Preliminary studies on child health needs are required to inform selection of inclusion/exclusion criteria. The same should be done for research in pregnant women. Studies have shown that clinical research often is not well aligned with these needs in pediatric populations. Additional guidance on the greatest areas of need could help encourage additional research in specific areas where there are gaps.

Topic Area 2: Study Design and Metrics

The study design and metrics of a clinical trial should be constructed in a way to be more inclusive across all ages, using input from the entire study population. These presentations examine challenges faced by investigators when designing studies and approaches to study design that can increase the heterogeneity of today's populations, approaches to enhance our ability to apply findings of trials to special populations like children, and approaches to selecting outcomes that really matter to older patients and their caregivers.

Study Design and Metrics

Jerry Gurwitz, MD, University of Massachusetts Medical School

At the August 14th Presidential Health Briefings, the question was raised as to how vaccine distribution will be prioritized once available.²⁰ The response was that those who are most vulnerable (e.g., older adults and those in nursing homes and retirement centers) should be the early recipients. This response aligns closely with recommendations included in the draft report on equitable allocation of COVID-19 vaccine released this week by the National Academies.²¹

When looking at the median age of phase I and phase II trial participants—which range from 33 to 43 in the cited studies—it is clear that these participants are not representative of those who many feel

²⁰ Remarks by President Trump in Press Briefing. (2020 Aug 14). Retrieved from <https://www.whitehouse.gov/briefings-statements/remarks-president-trump-press-briefing-august-14-2020/>.

²¹ National Academies of Science, Engineering, and Medicine. (2020 Sep 1). News release: National Academies release draft framework for equitable allocation of a COVID-19 vaccine, seek public comment. Retrieved from <https://www.nationalacademies.org/news/2020/09/national-academies-release-draft-framework-for-equitable-allocation-of-a-covid-19-vaccine-see-public-comment>.

should be prioritized for receiving vaccines.^{22,23,24,25} Many would argue that this is acceptable, as this is not the nature, or purpose, of early-stage trials. According to a recent *Lancet* commentary, “Phase 3 trials should be rapid, pragmatic, and large enough to address efficacy in subgroups of interest (older adults, those with comorbidities who are often excluded from clinical trials, or ethnic or racial groups more severely affected by COVID-19).”²⁶

However, Phase III eligibility criteria exclude pregnant women and children and have a strong preference for the inclusion of healthy adults—not the population identified for early vaccine distribution. For example, the inclusion criteria for current COVID-19 vaccine trials require “Healthy adults or adults with pre-existing medical conditions who are in stable condition. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment.”²⁷

Key Points:

- Older adults and vulnerable patients likely will be prioritized for early vaccination.
- These vulnerable populations are unlikely to be represented in vaccine trials.
- Approaches to study design are important to consider in light of this discrepancy.

²² Jackson, L.A., Anderson, E.J., Roupheal, N.G., Roberts, P.C., Makhene, M., Coler, R.N., McCullough, M.P., Chappell, J.D., Denison, M.R., Stevens, L.J., Pruijssers, A.J., McDermott, A., Flach, B., Doria-Rose, N.A., Corbett, K.S., Morabito, K.M., O'Dell, S., Schmidt, S.D., Swanson, P.A. 2nd, Padilla, M., Mascola, J.R., Neuzil, K.M., Bennett, H., Sun, W., Peters, E., Makowski, M., Albert, J., Cross, K., Buchanan, W., Pikaart-Tautges, R., Ledgerwood, J.E., Graham, B.S., Beigel, J.H., mRNA-1273 Study Group. (2020 Jul 14). An mRNA vaccine against SARS-CoV-2—Preliminary Report. *New England Journal of Medicine*, NEJMoa2022483. doi: 10.1056/NEJMoa2022483. Epub ahead of print.

²³ Zhu, F.C., Guan, X.H., Li, Y.H., Huang, J.Y., Jiang, T., Hou, L.H., Li, J.X., Yang, B.F., Wang, L., Wang, W.J., Wu, S.P., Wang, Z., Wu, X.H., Xu, J.J., Zhang, Z., Jia, S.Y., Wang, B.S., Hu, Y., Liu, J.J., Zhang, J., Qian, X.A., Li, Q., Pan, H.X., Jiang, H.D., Deng, P., Gou, J.B., Wang, X.W., Wang, X.H., & Chen, W. (2020). Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: A randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*, 396(10249), 479-488. doi: 10.1016/S0140-6736(20)31605-6. Epub 2020 Jul 20.

²⁴ Xia, S., Duan, K., Zhang, Y., Zhao, D., Zhang, H., Xie, Z., Li, X., Peng, C., Zhang, Y., Zhang, W., Yang, Y., Chen, W., Gao, X., You, W., Wang, X., Wang, Z., Shi, Z., Wang, Y., Yang, X., Zhang, L., Huang, L., Wang, Q., Lu, J., Yang, Y., Guo, J., Zhou, W., Wan, X., Wu, C., Wang, W., Huang, S., Du, J., Meng, Z., Pan, A., Yuan, Z., Shen, S., Guo, W., & Yang, X. (2020). Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: Interim analysis of 2 randomized clinical trials. *Journal of the American Medical Association*, 324(10), 1-10. doi: 10.1001/jama.2020.15543. Epub ahead of print.

²⁵ Folegatti, P.M., Ewer, K.J., Aley, P.K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E.A., Dold, C., Faust, S.N., Finn, A., Flaxman, A.L., Hallis, B., Heath, P., Jenkin, D., Lazarus, R., Makinson, R., Minassian, A.M., Pollock, K.M., Ramasamy, M., Robinson, H., Snape, M., Tarrant, R., Voysey, M., Green, C., Douglas, A.D., Hill, A.V.S., Lambe, T., Gilbert, S.C., Pollard, A.J., Oxford COVID Vaccine Trial Group. (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: A preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet*, 396(10249), 467-478. doi: 10.1016/S0140-6736(20)31604-4.

²⁶ Bar-Zeev, N., & Moss, W.J. (2020). Encouraging results from phase 1/2 COVID-19 vaccine trials. *Lancet*. Retrieved from [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31611-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31611-1/fulltext).

²⁷ National Library of Medicine. (2020). A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19: Inclusion criteria. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT04470427>

Heterogeneity in the STRIDE Fall Injury Prevention Trial

Peter Peduzzi, PhD, Yale School of Public Health

The STRIDE Fall Injury Prevention Trial is a large-scale pragmatic trial conducted between 2015 and 2020 to determine effectiveness of an evidence-based, patient-centered multifactorial fall injury prevention strategy.^{28,29,30,31,32,33} The goal of a pragmatic trial is to yield generalizable findings. In order to do this, it is necessary to include a heterogeneous population from multiple, diverse sites and geographic settings.

One hundred sixty-two clinical practices were assessed for eligibility. Of those, 86 practices—across 10 health systems—were selected based on study eligibility criteria, including: sufficient number of eligible patients, access to community exercise programs, access to electronic health records, and availability of practice characteristics (size, location, and ethnicity).

Despite efforts to obtain a heterogeneous study population, respondents (N=5,451) were overwhelmingly urban (91%), white (81%), and English-speaking (93%). As such, trial participants were more educated

²⁸ Bhasin, S., Gill, T.M., Reuben, D.B., Latham, N.K., Ganz, D.A., Greene, E.J., Dziura, J., Basaria, S., Gurwitz, J.H., Dykes, P.C., McMahon, S., Storer, T.W., Duncan, P.W., Ganz, D.A., Basaria, S., Miller, M.E., Trivison, T.G., Greene, E.J., Dziura, J., Esserman, D., Allore, H., Carnie, M.B., Fagan, M., Hanson, C., Baker, D., Greenspan, S.L., Alexander, N., Ko, F., Siu, A.L., Volpi, E., Wu, A.W., Rich, J., Waring, S.C., Wallace, R., Casteel, C., Magaziner, J., Charpentier, P., Lu, C., Araujo, K., Rajeevan, H., Margolis, S., Eder, R., McGloin, J.M., Skokos, E., Wiggins, J., Garber, L., Clauser, S.B., Correa-De-Araujo, R., Peduzzi, P., for the STRIDE Trial Investigators. (2020). A randomized trial of a multifactorial strategy to prevent injury from falls. *New England Journal of Medicine*, 383, 129-140. Doi: 10.1056/NEJMoa2002183.

²⁹ Gill, T.M., McGloin, J.M., Shelton, A., Bianco, L.M., Skokos, E.A., Latham, N.K., Ganz, D.A., Nyquist, L.V., Wallace, R.B., Carnie, M.B., Dykes, P.C., Goehring, L.A., Doyle, M., Charpentier, P.A., Greene, E.J., & Araujo, K.L. (2020). Optimizing retention in a pragmatic trial of community-living older persons: The STRIDE Study. *Journal of the American Geriatric Society*, 68, 1240-1247. doi: 10.1111/jgs.16356.

³⁰ Ganz, D.A., Siu, A.L., Magaziner, J., Latham, N.K., Trivison, T.G., Lorenze, N.P., Lu, C., Wang, R., Greene, E.J., Stowe, C.L., Harvin, L.N., Araujo, K.L.B., Gurwitz, J.H., Agrawal, Y., Correa-De-Araujo, R., Peduzzi, P., Gill, T.M., STRIDE Investigators. (2019). Protocol for serious fall injury adjudication in the Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE) Study. *Injury Epidemiology*, 6(14), 1-8. doi: 10.1186/s40621-019-0190-2.

³¹ Bhasin, S., Gill, T.M., Reuben, D.B., Latham, N.K., Gurwitz, J.H., Dykes, P., McMahon, S., Storer, T.W., Duncan, P.W., Ganz, D.A., Basaria, S., Miller, M.E., Trivison, T.G., Greene, E.J., Dziura, J., Esserman, D., Allore, H., Carnie, M.B., Fagan, M., Hanson, C., Baker, D., Greenspan, S.L., Alexander, N., Ko, F., Siu, A.L., Volpi, E., Wu, A.W., Rich, J., Waring, S.C., Wallace, R., Casteel, C., Magaziner, J., Charpentier, P., Lu, C., Araujo, K., Rajeevan, H., Margolis, S., Eder, R., McGloin, J.M., Skokos, E., Wiggins, J., Garber, L., Clauser, S.B., Correa-De-Araujo, R., & Peduzzi, P. (2018). Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE): A cluster-randomized pragmatic trial of a multifactorial fall injury prevention strategy: Design and methods. *Journals of Gerontology Series A Biological Sciences and Medical Sciences*, 73(8), 1053-1061. doi: 10.1093/gerona/glx190.

³² Gill, T.M., McGloin, J.M., Latham, N.K., Charpentier, P.A., Araujo, K.L., Skokos, E.A., Lu, C., Shelton, A., Bhasin, S., Bianco, L.M., Carnie, M.B., Covinsky, K.E., Dykes, P., Esserman, D.A., Ganz, D.A., Gurwitz, J.H., Hanson, C., Nyquist, L.V., Reuben, D.B., Wallace, R.B., & Greene, E.J. (2018). Screening, recruitment, and baseline characteristics for the Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE) study. *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, 73(11), 1495-1501. doi: 10.1093/gerona/gly076.

³³ Reuben, D.B., Gazarian, P., Alexander, N., Araujo, K., Baker, D., Bean, J.F., Boulton, C., Charpentier, P., Duncan, P., Latham, N., Leipzig, R.M., Quintiliani, L.M., Storer, T., & McMahon, S. (2017). The Strategies to Reduce Injuries and Develop Confidence in Elders intervention: Falls risk factor assessment and management, patient engagement, and nurse co-management. *Journal of the American Geriatric Society*, 65(12), 2733-2739. doi: 10.1111/jgs.15121.

than the general population and less representative of racial/ethnic groups, other than white, and of persons with substantial cognitive impairment, leaving STRIDE—and other similar trials—with the challenge of how to enhance representativeness and generalizability.^{34,35,36,37,38,39}

Key Points:

- Study eligibility requirements often limit trial diversity.
- Sample homogeneity presents a challenge in obtaining generalizable findings.

Strategies for Inclusion of Underrepresented Populations in Pragmatic Trials: The Diabetes Telephone Study Example

Alyce S. Adams, PhD, Kaiser Permanente Northern California

Dr. Adams addressed the inclusion of underrepresented populations in pragmatic trials; specifically, through the example of the Diabetes Telephone Study, a behavioral intervention funded by the Patient-Centered Outcomes Research Institute (PCORI), with additional funding from the Aging Initiative and

³⁴ Bhasin, S., Gill, T.M., Reuben, D.B., Latham, N.K., Ganz, D.A., Greene, E.J., Dziura, J., Basaria, S., Gurwitz, J.H., Dykes, P.C., McMahon, S., Storer, T.W., Duncan, P.W., Ganz, D.A., Basaria, S., Miller, M.E., Trivison, T.G., Greene, E.J., Dziura, J., Esserman, D., Allore, H., Carnie, M.B., Fagan, M., Hanson, C., Baker, D., Greenspan, S.L., Alexander, N., Ko, F., Siu, A.L., Volpi, E., Wu, A.W., Rich, J., Waring, S.C., Wallace, R., Casteel, C., Magaziner, J., Charpentier, P., Lu, C., Araujo, K., Rajeevan, H., Margolis, S., Eder, R., McGloin, J.M., Skokos, E., Wiggins, J., Garber, L., Clauser, S.B., Correa-De-Araujo, R., Peduzzi, P., for the STRIDE Trial Investigators. (2020). A randomized trial of a multifactorial strategy to prevent injury from falls. *New England Journal of Medicine*, 383, 129-140. Doi: 10.1056/NEJMoa2002183.

³⁵ Gill, T.M., McGloin, J.M., Shelton, A., Bianco, L.M., Skokos, E.A., Latham, N.K., Ganz, D.A., Nyquist, L.V., Wallace, R.B., Carnie, M.B., Dykes, P.C., Goehring, L.A., Doyle, M., Charpentier, P.A., Greene, E.J., & Araujo, K.L. (2020). Optimizing retention in a pragmatic trial of community-living older persons: The STRIDE Study. *Journal of the American Geriatric Society*, 68, 1240-1247. doi: 10.1111/jgs.16356.

³⁶ Ganz, D.A., Siu, A.L., Magaziner, J., Latham, N.K., Trivison, T.G., Lorenze, N.P., Lu, C., Wang, R., Greene, E.J., Stowe, C.L., Harvin, L.N., Araujo, K.L.B., Gurwitz, J.H., Agrawal, Y., Correa-De-Araujo, R., Peduzzi, P., Gill, T.M., STRIDE Investigators. (2019). Protocol for serious fall injury adjudication in the Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE) Study. *Injury Epidemiology*, 6(14), 1-8. doi: 10.1186/s40621-019-0190-2.

³⁷ Bhasin, S., Gill, T.M., Reuben, D.B., Latham, N.K., Gurwitz, J.H., Dykes, P., McMahon, S., Storer, T.W., Duncan, P.W., Ganz, D.A., Basaria, S., Miller, M.E., Trivison, T.G., Greene, E.J., Dziura, J., Esserman, D., Allore, H., Carnie, M.B., Fagan, M., Hanson, C., Baker, D., Greenspan, S.L., Alexander, N., Ko, F., Siu, A.L., Volpi, E., Wu, A.W., Rich, J., Waring, S.C., Wallace, R., Casteel, C., Magaziner, J., Charpentier, P., Lu, C., Araujo, K., Rajeevan, H., Margolis, S., Eder, R., McGloin, J.M., Skokos, E., Wiggins, J., Garber, L., Clauser, S.B., Correa-De-Araujo, R., & Peduzzi, P. (2018). Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE): A cluster-randomized pragmatic trial of a multifactorial fall injury prevention strategy: Design and methods. *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, 73(8), 1053-1061. doi: 10.1093/gerona/glx190.

³⁸ Gill, T.M., McGloin, J.M., Latham, N.K., Charpentier, P.A., Araujo, K.L., Skokos, E.A., Lu, C., Shelton, A., Bhasin, S., Bianco, L.M., Carnie, M.B., Covinsky, K.E., Dykes, P., Esserman, D.A., Ganz, D.A., Gurwitz, J.H., Hanson, C., Nyquist, L.V., Reuben, D.B., Wallace, R.B., & Greene, E.J. (2018). Screening, recruitment, and baseline characteristics for the Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE) study. *Journals of Gerontology Series A Biological Sciences and Medical Sciences*, 73(11), 1495-1501. doi: 10.1093/gerona/gly076.

³⁹ Reuben, D.B., Gazarian, P., Alexander, N., Araujo, K., Baker, D., Bean, J.F., Boulton, C., Charpentier, P., Duncan, P., Latham, N., Leipzig, R.M., Quintiliani, L.M., Storer, T., & McMahon, S. (2017). The Strategies to Reduce Injuries and Develop Confidence in Elders intervention: Falls risk factor assessment and management, patient engagement, and nurse co-management. *Journal of the American Geriatric Society*, 65(12), 2733-2739. doi: 10.1111/jgs.15121.

the National Institute of Diabetes and Digestive and Kidney Diseases Center for Diabetes Kidney Research at the Division of Research.

This study presented issues relating to older adults of color in clinical trials, including things like awareness, opportunity, acceptance, and retention—specifically, whether or not these populations even have the information about the existence of clinical trials and whether or not they have the capacity to understand the materials related to those trials because of language or physical barriers.⁴⁰

It is important to also consider retention—it is not enough for patients to enroll; they need to stay, and this often is related to the patient’s perception of the value of continuing to participate in the trial.

The Diabetes Telephone Study was a pragmatic trial of a five-minute automated symptom and side effect monitoring call with provider feedback/alert via the electronic health record. The Study enrolled 1,252 Kaiser Permanente Northern California members; specifically, those who had been newly treated for diabetes peripheral neuropathy symptoms. The striking thing about the Study was that it had a participation rate of 83 percent and a 93 percent retention rate. Participants also tended to be older, and the Study included 43 percent nonwhite participants.⁴¹

This was accomplished by focusing on stakeholder engagement. An effort was made to reach groups who may not otherwise have been aware of the trial. The trial was designed with limited exclusion criteria—people with multiple chronic conditions and people with disabilities and minor cognitive impairment were included. Both patients and clinicians were involved in the intervention design, which likely facilitated acceptance. Finally, in terms of retention, attempts were made to minimize the burden of research participation as much as possible.⁴²

A high level of altruism was observed among these patients, which has direct implications for the COVID trials under discussion.

Many of the same barriers to recruitment and retention of underrepresented groups will be present in trials without deliberate, intentional planning. There are many barriers to recruitment and retention of underrepresented groups, including lack of actionable information and lack of opportunity mediated by provider and health system factors, mistrust, costs, and fear of harm.^{43,44} Active, iterative, and ongoing

⁴⁰ Ford, J.G., Howerton, M.W., Lai, G.Y., Gary, T.L., Bolen, S., Gibbons, M.C., Tilburt, J., Baffi, C., Tanpitukpongse, T.P., Wilson, R.F., Powe, N.R., & Bass, E.B. (2008). Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. *Cancer, 112*(2), 228-242. doi: 10.1002/ncr.23157.

⁴¹ Adams A.S., Bayliss E.A., Schmittdiel J.A., Altschuler A., Dyer W., Neugebauer R., Jaffe M., Young J.D., Kim E., Grant R.W., Diabetes Telephone Study Team. (2016). The Diabetes Telephone Study: Design and challenges of a pragmatic cluster randomized trial to improve diabetic peripheral neuropathy treatment. *Clinical Trials, 13*(3), 286-293, doi:10.1177/1740774516631530.

⁴² Adams A.S., Bayliss E.A., Schmittdiel J.A., Altschuler A., Dyer W., Neugebauer R., Jaffe M., Young J.D., Kim E., Grant R.W., Diabetes Telephone Study Team. (2016). The Diabetes Telephone Study: Design and challenges of a pragmatic cluster randomized trial to improve diabetic peripheral neuropathy treatment. *Clinical Trials, 13*(3), 286-293, doi:10.1177/1740774516631530.

⁴³ Jaklevic, M.C. (2020). Researchers strive to recruit hard-hit minorities into COVID-19 vaccine trials. *Journal of the American Medical Association, 324*(9), 826-828. doi: 10.1001/jama.2020.

⁴⁴ Chastain, D.B., Osa, S.P., Henao-Martinez, A.F., Franco-Paredes, C., Chastain, J.S., & Young, H.N. (2020). Racial disproportionality in COVID clinical trials. *New England Journal of Medicine, 383*, e59. doi: 10.1056/NEJMp2021971.

engagement of stakeholders within and outside the health system (e.g., trusted community leaders) can spread awareness and address mistrust, particularly in communities of color.^{45,46}

Key Points:

- It is necessary to address factors related to awareness, opportunity, and acceptance in order to improve retention.
- There are many barriers to recruitment and retention of underrepresented groups in trials, including lack of actionable information and lack of opportunity mediated by provider and health system factors, mistrust, costs, and fear of harm.
- Active, iterative, and ongoing engagement of stakeholders within and outside the health system (e.g., trusted community leaders) can spread awareness and address mistrust, particularly in communities of color.

Extrapolation and Drug Development

Danny Benjamin, MD, PhD, Duke Clinical Research Institute

Extrapolation often is used in drug development to avoid ethical concerns related to repeating unnecessary studies. However, avoiding studies when they are needed is also unethical. There are three clinical phases: dosing, safety, and efficacy. Though there are many informal definitions of extrapolation, there is also a regulatory definition that is in use by FDA, the European Medicines Agency, etc.

It is important to remember that dosing is much more complex than just mg/kg. Approximately one-third of small molecules have a “PK surprise” in children.⁴⁷ These cannot be solved by models, animal studies, or older human PK data. Most surprises occur in children under the age of 2 years, with only about 2 percent occurring in adolescents. One of the lessons learned is that extrapolation should never be used for dosing; dosage studies always should be done.

In the first 10 years of the pediatric exclusivity program, there were some very unpredictable central nervous system findings in the 100–200 molecules for which exclusivity was granted. Therefore, the second lesson learned is to never extrapolate safety.

Although safety surprises are much less frequent than PK and dosing surprises, in order to ascertain whether the molecule is safe in a particular patient population, it is necessary to do the trial. In response to this issue, FDA has developed a pediatric study decision tree to guide decisions related to conducting PK, safety, and efficacy studies.⁴⁸

Many clinicians view extrapolation as a means of last resort to provide patient care. However, with: (1) a common understanding and definition, (2) a formal assessment of when it should (and should not) be

⁴⁵ Jaklevic, M.C. (2020). Researchers strive to recruit hard-hit minorities into COVID-19 vaccine trials. *Journal of the American Medical Association*, 324(9), 826-828. doi: 10.1001/jama.2020.

⁴⁶ Chastain, D.B., Osae, S.P., Henao-Martinez, A.F., Franco-Paredes, C., Chastain, J.S., & Young, H.N. (2020). Racial disproportionality in COVID clinical trials. *New England Journal of Medicine*, 383, e59. doi: 10.1056/NEJMp2021971.

⁴⁷ Benjamin, D.K. Jr., Smith, P.B., Murphy, M.D., Roberts, R., Mathis, L., Avant, D., Califf, R.M., & Li, J.S. (2006). Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *Journal of the American Medical Association*, 296, 1266-1273.

⁴⁸ U.S. Food and Drug Administration. (2018). Pediatric science and research activities. Retrieved from <https://www.fda.gov/science-research/pediatrics/pediatric-science-and-research-activities>.

used, and (3) efforts focused on questions that can and should be answered, extrapolation can be a powerful tool that benefits public health.

Via the formal process of extrapolation in pediatrics, we have learned that it sometimes can be used for efficacy (most typically in partial extrapolation), it should not be used for safety, and it should not be used for dosing.

A potential power of using extrapolation is that it allows us to focus our efforts on feasible studies that improve the human condition.

For the price of one randomized, pivotal study, we can conduct multiple randomized pharmacokinetics-pharmacodynamics studies that fully describe dosing, provide important safety information, and give proof of concept of efficacy.

Key Points:

- Extrapolation can be a powerful tool that benefits public health.
- While it sometimes can be used for efficacy, extrapolation should not be used for safety or dosing.
- A potential power of using extrapolation is that it allows us to focus our efforts on feasible studies that improve the human condition.

Design Considerations in Geriatric Oncology: Selecting Outcomes That Matter to Older Patients and Caregivers

Supriya Mohile, MD, University of Rochester

Our goal is to help design clinical research to improve our data on safety and efficacy in older adults, particularly those that are underrepresented and those with comorbidities and medical problems that don't facilitate accrual. Treatments are often available only to the fittest, healthiest, younger patients, and the data are only applicable to those patients, yet we use the treatments in clinical practice for older adults all the time, despite the fact that they often are harmed due to limited therapeutic benefit. Clinical trials would benefit from working with actual stakeholders.

There are certain standards within clinical trial design and oncology that are accepted by our structure—outcomes, survival, progression-free survival, response rates, grade 3–5 toxicity, and treatment, as measured by clinicians and not necessarily patients—and, in fact, are often at odds with patient concerns. Aging-related concerns in geriatric oncology treatment include those related to function, physical performance, comorbidity, cognition, psychological status, nutrition, and social support.⁴⁹

We conducted a PCORI-funded study that showed that when GA information is provided to oncologists in clinical care, providers not only are more likely to talk about outcomes that are important to older adults and their caregivers, but it also leads to improved patient and caregiver satisfaction.

In the GA intervention trial, patients were randomized to receive either GA intervention or usual care. In the GA intervention arm, the oncology physician was provided with a GA summary and GA-guided recommendations for each enrolled participant prior to starting new chemotherapy/agents with similar prevalence of toxicity. The geriatric assessment presented data related to physical performance, comorbidity/polypharmacy, cognition, nutrition, psychological status, social support, and function. This

⁴⁹ Mohile, S.G. 2014 Cancer Forum

type of assessment can help predict toxicity and mortality, guide decisions and care management, foster communication, and improve clinical outcomes.^{50,51,52,53}

Endpoints included clinician-rated grade 3–5 toxicity, survival at six months, treatment decisions, functional and physical decline, and patient-reported toxicities.⁵⁴ Significant differences were found related to physical performance, cognition, and social support.

The tolerability of a medical product is the degree to which symptomatic and nonsymptomatic adverse events associated with the product's administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy.⁵⁵ A complete understanding of tolerability should include direct measurement from patients on how they are feeling and functioning while on treatment.⁵⁶

Key Points:

- Current clinical trial design/oncology standards do not always reflect patient concerns.
- Providing geriatric assessment information to oncologists in clinical care results in providers being more likely to address outcomes important to older adults as well as improved patient and caregiver satisfaction.
- Clinical trials would benefit from working with actual stakeholders.
- A complete understanding of tolerability should include direct measurement from patients on how they are feeling and functioning while on treatment.

⁵⁰ Soto-Perez-de-Celis, E., Li, D., Yuan, Y., Lau, Y.M., & Hurria, A. (2018). Functional versus chronological age: Geriatric assessments to guide decision making in older patients with cancer. *Lancet Oncology*, *19*(6), e305-e316. doi: 10.1016/S1470-2045(18)30348-6.

⁵¹ Hurria, A., Mohile, S., Gajra, A., Klepin, H., Muss, H., Chapman, A., Feng, T., Smith, D., Sun, C.L., De Glas, N., Cohen, H.J., Katheria, V., Doan, C., Zavala, L., Levi, A., Akiba, C., & Tew, W.P. (2016). Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *Journal of Clinical Oncology*, *34*(20), 2366-2371. doi: 10.1200/JCO.2015.65.4327.

⁵² Mohile, S.G., Dale, W., Somerfield, M.R., Schonberg, M.A., Boyd, C.M., Burhenn, P.S., Canin, B., Cohen, H.J., Holmes, H.M., Hopkins, J.O., Janelins, M.C., Khorana, A.A., Klepin, H.D., Lichtman, S.M., Mustian, K.M., Tew, W.P., & Hurria, A. (2018). Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. *Journal of Clinical Oncology*, *36*(22), 2326-2347. doi: 10.1200/JCO.2018.78.8687.

⁵³ Mohile, S.G., Epstein, R.M., Hurria, A., Heckler, C.E., Canin, B., Culakova, E., Duberstein, P., Gilmore, N., Xu, H., Plumb, S., Wells, M., Lowenstein, L.M., Flannery, M.A., Janelins, M., Magnuson, A., Poh Loh, K., Kleckner, A.S., Mustian, K.M., Hopkins, J.O., Liu, J.J., Geer, J., Gorawara-Bhat, R., Morrow, G.R., & Dale, W. (2020). Communication with older patients with cancer using geriatric assessment: A cluster-randomized clinical trial from the National Cancer Institute Community Oncology Research Program. *Journal of the American Medical Association Oncology*, *6*(2), 196-204. Epub 2019 Nov 7. doi: 10.1001/jamaoncol.2019.4728.

⁵⁴ Mohile, S.G., Epstein, R.M., Hurria, A., Heckler, C.E., Canin, B., Culakova, E., Duberstein, P., Gilmore, N., Xu, H., Plumb, S., Wells, M., Lowenstein, L.M., Flannery, M.A., Janelins, M., Magnuson, A., Poh Loh, K., Kleckner, A.S., Mustian, K.M., Hopkins, J.O., Liu, J.J., Geer, J., Gorawara-Bhat, R., Morrow, G.R., & Dale, W. (2020). Communication with older patients with cancer using geriatric assessment: A cluster-randomized clinical trial from the National Cancer Institute Community Oncology Research Program. *Journal of the American Medical Association Oncology*, *6*(2), 196-204. Epub 2019 Nov 7. doi: 10.1001/jamaoncol.2019.4728.

⁵⁵ Friends of Cancer Research. (2020). Broadening the definition of tolerability in cancer clinical trials to capture the patient experience. Retrieved from <https://friendsofcancerresearch.org/tolerability>.

⁵⁶ Ibid.

Discussion

- We need to uproot the structure of how we do clinical trials and how we think through the research questions and design and metrics. Experts in recruiting patients that reflect the target population should have a seat at the table. For example, when designing a trial for older adults, people with aging expertise should be involved in the design and approval processes.
- We should be working with patients and their families during the design process; we should not be isolated from what matters to them.
- Considerations should include structure and incentives, how treatments are paid for, and why the structure enables perpetuation of this inequity over time. Until policies change, the same things will continue to happen.
- Despite all efforts, we failed to enroll a more heterogeneous population to a large pragmatic trial. When investigators and sites are encouraged to recruit more and more, it is easy to lose focus on the actual represented population. Strategies for recruiting heterogeneous populations need to be in place before the trial starts; once operations are up and running, it already may be too late.
- Perhaps some of the methods from implementation science could be used to look at barriers, but unless this is addressed in the beginning, it is much more difficult to recruit a heterogeneous population.
- Complexity sometimes is the impediment in a trial. Consider the concept of large-sample trials that have been advocated in the United Kingdom, where the populations are very heterogeneous and studies are designed to inform public health questions and implement therapies or interventions that could be readily adopted in practice. Pragmatic trials need to move toward simplicity; most are more explanatory and pragmatic.
- In order to encourage participation, it is imperative that research questions reflect the concerns of the target population. Researchers should be able to ask themselves, “Are we asking questions that are important to the community we want to recruit?” If they can’t answer that question, they are too distant from the population they are trying to affect. Having those individuals on the team is important.
- A single individual cannot serve as a proxy for an entire group of people. It is important to get input from stakeholders in the community. Establishing these types of relationships creates a resource that can be utilized to revise recruitment strategies when barriers are encountered.
- The fact that children are excluded from current COVID-19 phase III trials presents issues related to both safety and dosing. Because extrapolation should not be used for safety or dosing, complete exclusion should be considered unethical. If there are molecules or vaccines with some indication of efficacy and safety—for example, partway through these phase III trials—that is when the moral imperative to expand to children arises.
- The lack of planning as it relates to children and COVID-19 has major societal repercussions. COVID-19 likely will be the defining event for this generation. The long-term impact—as it relates to disparities, health, mental health, physical health—will be directly associated with the ability to get children safely back to face-to-face instruction. At present, children are being ignored in the pandemic response.
- There is no geriatric equivalent of the pediatric decision tree in use by geriatricians. This represents a different approach to safety and efficacy than what geriatricians currently use.

- In the cancer world, there is almost no information on the impact of polypharmacy on cancer treatment, therapeutic safety, and efficacy. This gap in knowledge is a source of concern for clinicians who care for older adults who are trying to make treatment decisions. Although some new studies are starting to look at this impact, very few data are available at present.

Topic Area 3: Recruitment, Enrollment, and Retention

Ensuring appropriate representation of children and older adults in clinical trials goes beyond the inclusion criteria—additional consideration is needed to design effective methods to identify, enroll, and retain children and older adults in clinical studies and trials. Presenters examined pediatric and geriatric recruitment and retention considerations with emphasis on special populations—racial and ethnic minorities, women, sex and gender minorities, rural/isolated populations, and others who may experience barriers to recruitment and retention—and provided concrete, evidence-based approaches that may be useful for Workshop attendees.

Recruitment, Enrollment, and Retention of Diverse Populations: A Geriatric Perspective

Steven Wallace, PhD, University of California, Los Angeles

The 2017 IAL-I Workshop identified recruitment, enrollment, and retention challenges across the lifespan and proposed relevant solutions.⁵⁷ Identified recruitment and retention challenges included study structure and protocols that limit participant ability to join, lack of stratification of enrollment participants, consent issues, a lack of experienced investigators, a lack of innovative enrollment techniques and new communication tools, and attrition during follow-up periods. Potential solutions included involvement of stakeholders, particularly the affected populations, in planning for study representativeness; engagement of experts, community representatives, and clinicians to help identify, recruit, and retain populations; provision of resources and increased support to assist with recruitment of children and older adults; and study designs that take into account ease of participation and accommodate participants with impaired function or disabilities. Other recommendations included using innovative methods to target recruitment efforts; providing detailed guidance to IRBs related to assessing appropriateness of nonfamilial consent; and using a universal assessment for participant capacity to provide consent (i.e., define unique abilities of adolescents to provide consent and develop a more robust assent process for individuals who lack the cognitive function to provide consent).

The great diversity within older adult and youth populations should be viewed from an intersectional perspective. Demographic characteristics of age, race, ethnicity, and gender intertwine with health status and other factors that create special needs for recruiting and retaining these populations.

Characteristics of older adults that influence their recruitment and retention include employment status (more likely to be retired than actively working) and being more likely to have seen a physician in the past year and to report functional limitations or be disabled in some way. Older adults are less likely to have a cell phone (and when they do, it is less likely to be a smartphone) and less likely to use the

⁵⁷ National Institutes of Health. (2018). Inclusion Across the Lifespan. June 1-2, 2017 workshop summary. Retrieved from <https://report.nih.gov/UploadDocs/NIH%20Inclusion%20Across%20the%20Lifespan%20Workshop%20Summary%20Report.pdf>.

Internet—disadvantages for communications that are reinforced in rural areas and low-income households.

The older population is not a uniform population; thus, recruiting individuals who are 65+ years of age does not mean the diversity of that population will be represented. There is great variation of race and ethnicity among individuals age 65+ years. Older adults of color are more likely to live in multigenerational households and have lower education and income levels (about 40% are below 200% of the federal poverty line), and older Latinx and Asian adults are more likely to have limited English proficiency (LEP). To the extent that education and income levels and LEP have an impact on recruitment, enrollment, and retention of older Americans, these will present much bigger challenges for older adults of color. For example, even older adults who seem fluent in English as their second language may feel more comfortable discussing health issues in their native languages.

Recruitment and retention of diverse communities across the lifespan is not a new concern. This has been the target of cores in the [Resource Centers for Minority Aging Research \(RCMAR\)](#) program since its establishment in 1998. A special supplement of *The Gerontologist* in 2011 featured papers on the science of recruitment and retention, specifically among ethnically diverse older adults.⁵⁸ Key ideas from that source included the importance of understanding cultural distinctions across groups (e.g., values, beliefs) as well as sources and dynamics of community cohesion and its collective history. This understanding is instrumental for outreach to different groups within communities and necessitates sensitivity to their sociopolitical conditions. In addition, it is important to maintain connections with research participants even after study completion so as to build and preserve trust and engagement within those communities.

In 2019, NIA sponsored a Gerontological Society of America (GSA) preconference,⁵⁹ Strategies for Successful Recruitment and Retention of Minority Elders (see presentations available at <https://rcmar.org/events/2019preconferenceworkshop/>), and selected papers will be published in a special issue of *Ethnicity and Disease* this fall. Presentations touched on sensitive areas such as brain donation, interventions for Alzheimer's disease, and behavioral trials; recommendation included registries, community and family engagement, and showing how the research benefits the community.

Although the 5-T Framework for Recruiting Older Adults is specific for older adults, many of the dimensions translate across older and younger populations.⁶⁰ In brief, the Framework includes the following guidance: consider the target population in advance and avoid exclusions that will limit generalizability of the study to any particular population; include relevant expertise on the team as well as members of the population; recognize that visits may take longer for participants with disabilities and budget accordingly; follow tips for accommodating specific comorbidities and age-related impairments that may require additional protocols to make the trial more attractive and easier for participants; and incorporate appropriate tools that take age and cultural responsiveness into account.

⁵⁸ Wallace, S.P., Chadiha, L.A., Crowther, M., Napoles, A.M., & Sood, J.R. (Eds.). (2011). The science of recruitment and retention among ethnically diverse older adults. *Gerontologist*, 51(Suppl 1). <https://doi.org/10.1093/geront/gnr045>.

⁵⁹ Resource Centers for Minority Aging Research. (2019). 2019 GSA preconference: Strategies for successful recruitment and retention of minority elders: An NIA priority area. Retrieved from <https://rcmar.org/events/2019preconferenceworkshop/>.

⁶⁰ Bowling C.B., Whitson H.E., & Johnson T.M. 2nd. (2019). The 5Ts: Preliminary development of a framework to support inclusion of older adults in research. *Journal of the American Geriatric Society*, 67(2), 342-346. doi: 10.1111/jgs.15785. Epub 2019 Jan 29.

Key Points:

- View the great diversity within older adult and youth populations from an intersectional perspective that recognizes how other demographic characteristics (race, ethnicity, gender) intertwine with health status and other factors that create special needs for recruiting and retaining these populations.
- The older population is not a uniform population; thus, recruiting individuals who are 65+ years of age does not mean the diversity of that population will be represented.
- Resources on recruitment, enrollment, and retention of older adults in clinical research include the RCMAR program, a special 2011 supplement of *The Gerontologist*, and the 2019 GSA preconference, Strategies for Successful Recruitment and Retention of Minority Elders.

Optimizing Recruitment and Retention in Underrepresented Populations

Michelle S. Hamstra, MS, Cincinnati Children's Hospital Medical Center

Dr. Hamstra summarized a research participant's experience as a subject in an immunotherapy clinical trial. An educated white female residing in a major metropolitan area with good health insurance, she had easy access to top medical care and a vast web of social support. As a journalist, she is comfortable asking questions and pressing for answers. Despite all of these advantages, she struggled. She felt overwhelmed when handed a 27-page consent document. Now a cancer survivor, she is an advocate for more accessible and collaborative clinical research where study participants have a voice. This is an important message. Regardless of background and resources, everyone deserves excellent care. Investigators must take steps, big and small, to minimize and eliminate barriers that stand in the way of equal access and care.

Diverse clinical research populations include young and old racial and ethnic minorities, sex and gender minorities, people with disabilities and comorbidities, rural and isolated populations, and language-minority individuals. Diversity is more than age, race, and ethnicity. Some have difficulty trusting the healthcare system; lack reliable transportation; live far away from the study location; may not read, speak, or understand English; may be uninsured; and may be undocumented. Many are busy living their lives, working, attending school, and caring for children and other family members.

The persistent lack of diversity in clinical trials means that many therapies never are tested on the very patients they are intended to serve. To address that challenge, study populations must better reflect patient populations so that the data being generated will be as generalizable as possible. The more practical, evidence-based advice is shared, the closer we will come to achieving the goal of truly representative research.

Overcoming barriers to inclusion of underrepresented populations begins with recognizing the importance of trust, communication, and fostering of relationships that facilitate inclusion and participation. Successful, inclusive participation should be an intentional goal. Strategies include establishing a robust, representative team; identifying potential barriers; budgeting wisely; drafting, implementing, and evaluating an inclusive plan; and minding the 5Ts.

Time must be taken to cultivate a diverse, representative team and network of collaborators who can help create an environment that supports participation. Diversity within the team will foster diversity within the study population. A representative team provides perspectives from various stakeholders—not only the scientific community but also statisticians, data managers, and the coordinators who are boots on the

ground and establishing relationships with participants as well as their parents and caregivers. The broader the team, the more representative the perspectives, and the better the design and execution. Input should be sought from experts in the field, providers, patients, and their caregivers. It is important to talk with people who have various perspectives to understand what particular barriers a trial might face and work to address those barriers while developing the protocol rather than waiting for them to appear during the trial when they will hinder implementation.

The family unit to which pediatric and geriatric participants belong must be considered; specifically, the caregivers who accompany these participants. Participation needs to be feasible from their perspective; the plan should take into account time away from work as well as other caregiving responsibilities. These factors should be considered when compensating for time and effort.

Unintended consequences of participation must be anticipated. Will standard-of-care costs be reimbursed to patients enrolled in a clinical study? Will compensation be taxed? Will compensation potentially disqualify a participant for Medicaid or another benefit? Will a participant be asked to provide a Social Security number or a tax I.D. in order to receive compensation? What if the participant does not have one? Conscientiousness and understanding in resolving these uncertainties are important because these factors will influence participant decisions about participation.

Special considerations about the intended participant populations include intentionally accommodating special needs throughout the lifetime of the study, determining how to reach participants and communicate with them, and adjusting the number of visits required. In the current COVID-19 situation, thought must be given to what study activities can be done remotely. Investigators must be innovative in their approaches to study encounters and mindful of ways to make research more accessible; for example, accommodating families by scheduling visits outside of normal business hours or doing home visits.

The plan should account for the time required to develop a well-thought-out protocol and navigate the complicated review and contracting process; find and reach the patient population; and develop relationships with participants, caregivers, and local providers. Roles and responsibilities of team members should be carefully defined, taking into account timing of examinations, assessments, and visits; where these will be done; and workload of team members.

Finally, investigators need to consider the tools necessary to execute the study, including the study budget—effort, procedural costs, plus costs to foster participation (e.g., reimbursement compensation and incentives). There may be resources that can supplement the budget in terms of communication, patient-facing materials, and advertising (e.g., social media, patient advocacy groups). Forums can be established to share tools and resources with other investigators so they can avoid reinventing the wheel. For example, Dr. Hamstra has shared guidance she developed for study chairs to use during protocol development; this guidance encompasses recruitment, enrollment, adherence, and retention, and overlaps with the 5-T model.

Goal-setting should include study benchmarks. This is particularly important for demonstrating effectiveness in intervention studies. For multicenter studies, the plan should be flexible enough to accommodate local variability. During study implementation, it is important to stop at regular intervals and evaluate progress, refine, and revise. The plan also should include dissemination of results. Showing participants a return on their investment may be one of the few advantages or benefits that can be offered to potential participants. In the case of a health study, results can demonstrate how participants' data can help advance care for others.

Key Points:

- Diversity is more than age, race, and ethnicity.
- The persistent lack of diversity in clinical trials means that many therapies never are tested on the very patients they are intended to serve. To address that challenge, study populations must better reflect patient populations so that the data being generated will be as generalizable as possible.
- The more practical, evidence-based advice is shared, the closer we will come to achieving the goal of truly representative research.
- Time must be taken to cultivate a diverse, representative team and network of collaborators who can help create an environment that supports participation. Diversity within the team will foster diversity within the study population. A representative team provides perspectives from various stakeholders. The broader the team, the more representative the perspectives and the better the design and execution.
- Showing them a return on their investment may be one of the few advantages or benefits that can be offered to potential participants. In the case of a health study, results can demonstrate how participants' data can help advance care for others.

Optimizing Recruitment and Retention: Lessons from Pediatric Trials

Michelle S. Hamstra, MS, Cincinnati Children's Hospital Medical Center

Dr. Hamstra shared her experiences with recruitment and retention of pediatric patients for several clinical trials. One of the keys to success is starting with a good team that includes the perspectives of various stakeholders (e.g., scientific team, trial coordinators, parents and caregivers, healthcare providers, patient advocacy groups). When developing the protocol, the team should identify barriers faced by the target population and consider ways to address them. The budget should include funds for study procedures and infrastructure to accommodate the needs of participants. An inclusive recruitment and retention plan should be carefully drafted and implemented and evaluated at regular intervals. Iterative improvements often are needed to effectively reach target populations. Many elements of the 5T Framework that was developed for geriatric populations are relevant to working with pediatric populations as well.

The Marfan Trial was an RCT comparing atenolol v. losartan in 608 children and young adults with Marfan Syndrome (MFS) in 21 centers across the United States, Canada, and Europe.^{61,62,63} Barriers

⁶¹ National Library of Medicine. (2015). Comparison of Two Medications Aimed at Slowing Aortic Root Enlargement in Individuals with Marfan Syndrome—Pediatric Heart Network. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT00429364>.

⁶² Lacro, R.V., Dietz, H.C., Sleeper, L.A., Yetman, A.T., Bradley, T.J., Colan, S.D., Pearson, G.D., Selamet Tierney, E.S., Levine, J.C., Atz, A.M., Benson, D.W., Braverman, A.C., Chen, S., De Backer, J., Gelb, B.D., Grossfeld, P.D., Klein, G.L., Lai, W.W., Liou, A., Loeys, B.L., Markham, L.W., Olson, A.K., Paridon, S.M., Pemberton, V.L., Pierpont, M.E., Pyeritz, R.E., Radojewski, E., Roman, M.J., Sharkey, A.M., Stylianou, M.P., Wechsler, S.B., Young, L.T., Mahony, L., Pediatric Heart Network Investigators. (2014). Atenolol versus losartan in children and young adults with Marfan's syndrome. *New England Journal of Medicine*, 371(22), 2061-2071. doi: 10.1056/NEJMoa1404731.

⁶³ Hamstra, M.S., Pemberton, V.L., Dagaincourt, N., Hollenbeck-Pringle, D., Trachtenberg, F.L., Cnota, J.F., Atz, A.M., Cappella, E., De Nobele, S., Grima, J., King, M., Korsin, R., Lambert, L.M., MacNeal, M.K., Markham, L.W., MacCarrick, G., Sylvester, D.M., Walter, P., Xu, M., Lacro, R.V., Pediatric Heart Network Investigators. (2020). Recruitment, retention, and adherence in a clinical trial: The Pediatric Heart Network's Marfan Trial experience. *clinical trials*, 1740774520945988. doi: 10.1177/1740774520945988. Epub ahead of print.

included the fact that MFS is a rare disease, restrictive eligibility criteria, a diverse age range (6 months to 24 years), a complex study and medication regimen, and a three-year commitment from participants. The wide age range of participants required the study team to be nimble in its approaches to enrolling a 6-month-old versus a 22-year-old living on a college campus and/or trying to become established in the real world.

At the beginning of the study, there was a general feeling that losartan was a miracle drug, so investigators needed to explain why the study was needed as a step toward a larger RCT. In the end, both drugs were relatively equivalent and the number of reported adverse events was relatively comparable.

Although Marfan exceeded its enrollment target, it took more time and resources than expected. Retention of trial participants was excellent, with 88 percent achieving the primary outcome measure. After the study ended, investigators looked at overall recruitment, retention, and adherence to measures and looked for predictors of adherence across site, age, race, and medical history. Sites were surveyed about strategies and resources they had used, and differences in success were observed across sites and age groups. One of the biggest keys to study success was sharing of lessons via monthly teleconferences attended by site team members; National Heart, Lung, and Blood Institute staff; and others. For example, sites that were more successful at assessing adherence to the study medication described strategies they used—providing a small incentive (\$5 per returned bottle) and/or prepaid mailers.

Young adults and African American participants had lower adherence. To foster adherence, it is important to employ multiple strategies; invest in resources; minimize staff turnover to maintain rapport with participants; maximize collaboration with providers, family members, and other sites; and use patient advocacy resources. There is power in partnering with patient advocacy groups. The Marfan Foundation provided immeasurable support in terms of promotion, including an annual conference to which investigators were invited and where they were able to conduct screenings. Success requires time, effort, and money. The Marfan Foundation provided financial support and dedicated staff who assisted with participant travel from remote locations. Reaching more potential participants outside of one site's catchment area required creativity and fostering of relationships with outside physicians. Differences in age and race required different strategies (i.e., materials for youngest and oldest patients, flexible study visit scheduling).

The FUEL (Fontan Udenafil Exercise Longitudinal) trial was a phase III RCT that compared a six-month treatment regimen of udenafil with placebo in adolescents with Fontan physiology.^{64,65} The enrollment goal of 400 adolescents was reached with financial support from an industry partner and assistance from a patient advocacy group. The patient advocacy group provided input on the study design, stressing the importance of including travel funds to help patients get to the medical sites. Based on input from the advocacy group, some visits were converted to virtual visits or home visits from a nurse. Building on the lessons on adherence from the Marfan trial, participants were provided with iPods, which were used for medication reminders and communication. A robust compensation plan also was developed. One of the

⁶⁴ NCT0274115 and NCT03013751

⁶⁵ Goldberg, D.J., Zak, V., Goldstein, B.H., McCrindle, B.W., Menon, S.C., Schumacher, K.R., Payne, R.M., Rhodes, J., McHugh, K.E., Penny, D.J., Trachtenberg, F., Hamstra, M.S., Richmond, M.E., Frommelt, P.C., Files, M.D., Yeager, J.L., Pemberton, V.L., Stylianou, M.P., Pearson, G.D., Paridon, S.M., Pediatric Heart Network Investigators. (2018). Design and rationale of the Fontan Udenafil Exercise Longitudinal (FUEL) trial. *American Heart Journal*, 201, 1-8. doi: 10.1016/j.ahj.2018.03.015. Epub 2018 Apr 3.

key successes of the trial was a WebEx meeting held to share study results with patients and families. Lessons from FUEL were applied to the extension study FUEL OLE (Open Label Extension).

The DO IT! (Dyslipidemia of Obesity Intervention in Teens) Trial is a randomized, double-blind, placebo-controlled trial to determine whether treatment of chronic dyslipidemia of obesity in adolescents with pitavastatin will improve vascular measures of early atherosclerosis with acceptable safety.⁶⁶ The enrollment goal is 354 10- to 18-year-old subjects. The study launched in the summer of 2018. As of August 2020, 148 patients had been consented and 91 had been randomized, highlighting the challenges of recruitment to this study. The trial protocol includes nine in-person visits with blood draws, medication, and a two-year commitment, which are significant requirements for a patient population that feels well. The initial plan included compensation incentives and partnerships with care providers and families. Multiple protocol amendments have been made to try to enhance recruitment, including extending the duration of recruitment, streamlining measurements, making eligibility criteria more inclusive, and eliminating two in-person visits. The challenges with this trial highlight the need to have the right tools, the right team, and the right resources.

Overcoming barriers to trial recruitment takes creativity, innovation, and going the extra mile. In the end, it is worth it to ensure trials generate meaningful results that will improve patient outcomes.

Key Points:

- Strategies to improve recruitment and retention include establishing a robust and representative team, identifying potential barriers, budgeting for recruitment and retention activities, creating an intentionally inclusive plan, and periodically evaluating the plan and making adjustments to improve it.
- Working with partners—including industry and advocacy organizations—can help with recruitment and retention.
- Collaborative learning among trial sites can promote recruitment, retention, and adherence.

Lifespan Lessons

Raegan Durant, MD, MPH, University of Alabama at Birmingham

Dr. Durant presented lifespan lessons and lessons learned from enrollment of pediatric populations, particularly in the context of oncology trials and their application in older adult populations.

The pediatric cancer world is one bright spot in the enrollment of pediatric populations.^{67,68} Roughly 27–86 percent of children with cancer are enrolled in clinical trials. This is in stark contrast to enrollment of adult cancer populations where an estimated 1.5 to 4 percent of adults with cancer are enrolled in trials. The percentage of adults 65 or older with cancer is about twice as large as the percentage of those patients enrolled in trials; with each increasing increment of cutoff (i.e., 65+, 75+), the proportion of the U.S.

⁶⁶ National Library of Medicine. (2020). Dyslipidemia of Obesity Intervention in Teens (DO-IT). Retrieved from <https://clinicaltrials.gov/ct2/show/NCT02956590>.

⁶⁷ Faulk, K.E., Anderson-Mellies, A., Cockburn, M., & Green, A.L. (2020). Assessment of enrollment characteristics for Children’s Oncology Group (COG) upfront therapeutic clinical trials 2004-2015. *PLOS One*, 15(4), e0230824. <https://doi.org/10.1371/journal.pone.0230824>.

⁶⁸ Talarico, L., Chen, G., & Pazdur, R. (2004). Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *Journal of Clinical Oncology*, 22(22), 4626-4631. doi: 10.1200/JCO.2004.02.175.

cancer population diminishes, but the proportion of cancer patients enrolled in trials in each age group is significantly smaller; less than one-third of persons age 75+ with cancer are enrolled in trials.

The Children's Oncology Group (COG) is a national coordinated network of trials conducted at about 200 institutions.⁶⁹ Approximately 19 percent of cancer patients aged 0–19 are enrolled in a COG trial (27% aged 0–9, 12.8% aged 10–19), with equal distribution by gender. Racial/ethnic distribution is largely proportionate to representation among U.S. pediatric cancer cases. Socioeconomic factors also are equally distributed across age groups.

Some characteristics influencing enrollment in cancer clinical trials are similar for children and older adults. For example, older adults among the Medicare-eligible population and younger children have lower rates of uninsurance, and recruitment involves engagement of others (i.e., parents of children, caregivers of dependent older adults). Sources of care differ between the two age groups—more than 90 percent of pediatric cancer patients younger than 15 years in the United States are treated at National Cancer Institute (NCI)-sponsored institutions, and most older adult cancer patients receive care from community oncologists. Many tumor types are far more prevalent in children (e.g., neuroblastoma); some tumor types are more prevalent in older adults, but not exclusively.

Trial access can be expanded to older adults in two ways: (1) increase access to NCI-designated cancer centers and other research-intense sites of care and (2) expand research opportunities to community-based cancer centers and community-based primary care or geriatrics practices. The latter can be accomplished by expanding recruitment to the community-based centers and conducting the research activities at more research-intense, often academic, sites. Examinations, lab-only studies, or basic imaging studies could be done in the community where research participants receive care, which usually is more geographically accessible to them.

Studies should consider employing a family-based recruitment approach that engages caregivers. Clinical trials for individuals at opposite ends of the lifespan often require active involvement of the participant's family (parent, spouse, child) as a proxy respondent and/or caregiver rather than the participant. This is of particular importance from the standpoint of the consent process, as well as communication and transportation that will have an impact on retention and adherence.

Payment and coverage considerations should be clarified so as to optimize enrollment in a largely insured population. It is important to address any concerns participants may have about possible financial penalties. Medicare will cover standard care, even when provided in the context of a trial.

Key Points:

- Roughly 27–86 percent of children with cancer are enrolled in clinical trials. In stark contrast, an estimated 1.5 to 4 percent of adults with cancer are enrolled in trials.
- Characteristics influencing enrollment in cancer clinical trials that are similar for children and older adults include lower rates of uninsurance as well as the involvement of others (parents, caregivers) in recruitment, decision making, transportation, and adherence.

⁶⁹ Faulk, K.E., Anderson-Mellies, A., Cockburn, M., & Green, A.L. (2020). Assessment of enrollment characteristics for Children's Oncology Group (COG) upfront therapeutic clinical trials 2004-2015. *PLOS One*, 15(4), e0230824. <https://doi.org/10.1371/journal.pone.0230824>.

- Trial access can be expanded to older adults by increasing access to NCI-designated cancer centers and other research-intensive sites of care and by expanding research opportunities to community-based cancer centers and primary care or geriatrics practices.
- Payment and coverage considerations should be clarified to address participant concerns.

Compare and Contrast

Mark Supiano, MD, University of Utah School of Medicine

Dr. Supiano described similarities and differences in clinical trial populations at opposite ends of the lifespan. Because measures of function and cognition supersede chronological age, reporting participant age is not sufficient. Rather, the ability to identify these important phenotypes of individuals at opposite ends of the lifespan is critical.

Children and older adults are potentially vulnerable individuals, requiring trial design to weigh participant burden. Children and some older adults need a proxy respondent and/or caregiver, which is relevant to consent and/or assent, communication, transportation, etc. Study visits may require more time and special accommodations; for example, site accessibility is an important factor, and in-home assessments or, in the era of COVID, virtual visits should be considered. For clinical trials recruiting populations at opposite ends of the lifespan, it is important to take higher attrition rates into account for design and budget. Furthermore, outcome measures that matter to participants should be included.

Dr. Supiano provided two examples of clinical trials in which he has been involved: the Systolic Blood Pressure Intervention Trial (SPRINT)^{70,71,72,73} and Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults (PREVENTABLE).^{74,75}

SPRINT demonstrated that a diverse and particularly older population can be recruited, randomized, and assessed for follow-up, including cognitive function over more than five years, with very successful retention and adherence outcomes. The trial exceeded its recruitment goal with 9,361 participants (101% of goal) and met subgroup recruitment goals—28 percent of participants were 75+ years of age, of whom

⁷⁰ National Library of Medicine. (2018). Systolic Blood Pressure Intervention Trial (SPRINT). ClinicalTrials.gov Identifier: NCT01206062.

⁷¹ Ambrosius, W.T., Sink, K.M., Foy, C.G., Berlowitz, D.R., Cheung, A.K., Cushman, W.C., Fine, L.J., Goff, D.C. Jr, Johnson, K.C., Killen, A.A., Lewis, C.E., Oparil, S., Reboussin, D.M., Rocco, M.V., Snyder, J.K., Williamson, J.D., Wright, J.T. Jr, Whelton, P.K., SPRINT Study Research Group. (2014). The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: The Systolic Blood Pressure Intervention Trial (SPRINT). *Clinical Trials*, 11(5), 532-546. doi: 10.1177/1740774514537404. Epub 2014 Jun 5.

⁷² Ramsey, T.M., Snyder, J.K., Lovato, L.C., Roumie, C.L., Glasser, S.P., Cosgrove, N.M., Olney, C.M., Tang, R.H., Johnson, K.C., Still, C.H., Gren, L.H., Childs, J.C., Crago, O.L., Summerson, J.H., Walsh, S.M., Perdue, L.H., Bankowski, D.M., Goff, D.C., & SPRINT Study Research Group. (2016). Recruitment strategies and challenges in a large intervention trial: Systolic Blood Pressure Intervention Trial. *Clinical Trials (London, England)*, 13(3), 319-330. <https://doi.org/10.1177/1740774516631735>.

⁷³ SPRINT Research Group, Wright, J.T. Jr, Williamson, J.D., Whelton, P.K., Snyder, J.K., Sink, K.M., Rocco, M.V., Reboussin, D.M., Rahman, M., Oparil, S., Lewis, C.E., Kimmel, P.L., Johnson, K.C., Goff, D.C. Jr, Fine, L.J., Cutler, J.A., Cushman, W.C., Cheung, A.K., & Ambrosius, W.T. (2015). A randomized trial of intensive versus standard blood-pressure control. *New England Journal of Medicine*, 373(22), 2103-2116. doi: 10.1056/NEJMoa1511939. Epub 2015 Nov 9.

⁷⁴ National Library of Medicine. (2020). Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults (PREVENTABLE). ClinicalTrials.gov Identifier: NCT04262206.

⁷⁵ NIA U19AG065188 : <https://www.nih.gov/news-events/news-releases/could-taking-statins-prevent-dementia-disability>

26 percent were Black or Hispanic. One-third of the 75+ age group met criteria for being frail and had average Montreal Cognitive Assessment scores of 22/30. The cardiovascular and mortality outcomes were segregated by frailty and gait speed. Cognitive impairment outcomes were included in the trial design from the beginning. Mild cognitive impairment and dementia were reported in the SPRINT MIND (Memory and Cognition in Decreased Hypertension) sub study.

Mass mailings targeted by age and zip code achieved the greatest yield for recruitment purposes.

SPRINT limitations to generalizability are due to exclusion of people with baseline dementia or who resided in nursing homes at the time of randomization.

Recruitment into the PREVENTABLE trial began on September 1, 2020, with a recruitment goal of 20,000 participants age 75 years and older who do not have an indication to receive a statin medication. Of great importance to geriatricians is that the primary outcome of this trial is relevant to geriatrics—the primary composite of death, dementia, and persistent disability. The trial will use a computable electronic medical records (EMR) phenotype. Ten “preventer” advisors (i.e., potential participants age 75 and older) have been engaged in PREVENTABLE from the outset of the application, providing critically important input to the steering committee. In light of COVID, the trial design includes a single in-person visit at the time of randomization; this may be modified to allow for virtual enrollment, electronic consenting, and follow-up visits conducted via a combination of in-home assessments and a telephone cognitive battery. This is expected to facilitate recruitment as well as retention.

Key Points:

- Measures of function and cognition supersede chronological age; the ability to identify these important phenotypes of individuals at opposite ends of the lifespan is critical.
- Considerations for design of pediatric and geriatric studies include potential vulnerability of these populations, the need for proxy respondents and caregivers, and increased time and accommodations required for study visits.

Evaluation of Inclusion of Older Adults in Clinical Trials

Wendy Kohrt, PhD, University of Colorado Anschutz Medical Campus

Dr. Kohrt described the work that University of Colorado Anschutz Medical Campus (UCAMC) investigators are doing to help nongerontologists conduct studies including older adults in compliance with the NIH IAL policy. She outlined some of the guidelines UCAMC researchers have put into place for their studies involving older adult populations.

Until a policy requiring the use of a central clinical trial management system was added in 2019, Dr. Kohrt and her colleagues lacked the tools and data needed to assess the success of enrollment of older adults in clinical research at UCAMC. Now, a central database provides the means for tracking a number of metrics about the number of individuals being enrolled in protocols and enables cross-institution queries. A three-step process is used to evaluate how well the institution is doing in terms of including older adults in clinical trials: (1) identify clinical trials that intend to enroll adults aged 65+ years; (2) if the trial does not intend to enroll older adults, determine whether that exclusion is appropriate; and (3) if the trial intends to enroll older adults, confirm whether older adults actually are enrolled. An evaluation of clinical trials conducted in 2019 found that nearly two-thirds of new protocols did not plan to enroll adults aged 65+. Out of 679 new protocols that indicated intent to enroll adults aged 65+, only 498 had enrolled a participant over the age of 50. (Note: Data are not available for the 65+ age group. It is possible that

enrollment has not begun in some of the protocols due to the impact of COVID-19.) These statistics will serve as a benchmark for future evaluations.

Dr. Kohrt outlined strategies to help investigators improve inclusion of older adults in clinical trials. She plans to reach out to units, divisions, and departments that appear to be avoiding inclusion of older adults in their research when their inclusion would be appropriate. Those who express interest will receive direct assistance, including workshops led by geriatric medicine faculty. Workshops will focus on the importance of including older adults in clinical trials, development of appropriate eligibility criteria, and strategies for recruitment and retention of older adults in clinical trials.

In addition, a UCAMC evaluation specialist is helping to develop innovative plans for enhancing recruitment and retention of older adults. Two approaches are being considered: training older adults as research specialists to recruit other older adults and using traveling Research Roadshows to foster recruitment of older, underrepresented minorities in geographically and culturally diverse communities.

Key Points:

- A centralized clinical trial management system at UCAMC enables institution-wide evaluation of inclusion of a specific population in trials.
- Strategies to help investigators improve inclusion of older adults in clinical trials include training that focuses on the importance of inclusion, development of eligibility criteria, and development of strategies to recruit and retain older adults in clinical trials.
- Innovative approaches to enhance recruitment and retention of older adults include traveling roadshows to reach geographically and culturally diverse communities and training of older adults as research specialists to help recruit other older adults.

Optimizing Recruitment Across the Continuum

Consuelo H. Wilkins, MD, MSCI, Vanderbilt University Medical Center

Vanderbilt's Recruitment Innovation Center (RIC) focuses on improving and enhancing recruitment and retention across every stage of the recruitment continuum. In the past four years, the RIC has provided consultations on 220 clinical trials, providing insights and resources for studies that include populations from children in a pediatric intensive care unit all the way to groups like those in the PREVENTABLE study (i.e., individuals aged 75+).

The work of the RIC is framed around a comprehensive recruitment and retention plan that includes how to increase awareness, create opportunities, engage individuals toward acceptance, obtain consent, enroll participants, retain participants, and return results. The RIC emphasizes minority recruitment. Although focusing on individuals, culturally tailoring materials, and using preferred language are important, it is critical to provide instruction, training, and coaching to the research teams. For this reason, the RIC has created a mass online course entitled "Faster Together: Enhancing Minority Recruitment in Trials" that is available free on [Coursera](#). The eight course modules cover critical pieces such as recognizing that people from specific groups have good reason to distrust research and how to talk through those concerns.

Dr. Wilkins outlined RIC consultations on 25 COVID-19 studies. There are nuances around engaging individuals in a study when no treatment has been proven effective, as well as the kinds of information that potential participants need in light of the volume of disinformation being disseminated. Many studies were unprepared for the fact that many individuals diagnosed with COVID or at increased risk for

COVID have limited English proficiency; study teams were not ready to make their recruitment materials, consent forms, and other communications available in multiple languages. One lesson learned is that it is best to start with the materials in the native language from the beginning rather than translating materials from English into other languages.

Key Points:

- The RIC at Vanderbilt provides insights, consultation, and resources to clinical trials, including development of comprehensive recruitment and retention plans that address every stage of the recruitment continuum: awareness, opportunity, acceptance, consent, enrollment, retention, and return of results.
- The Vanderbilt RIC offers a free eight-module course on enhancing minority recruitment in trials via Coursera.
- Consultations with COVID-19 studies have identified critical information needs for potential participants in light of the volume of disinformation being disseminated during the pandemic.
- Many COVID-19 study teams are unprepared to address language needs of individuals with limited English proficiency who have been diagnosed with COVID or are at increased risk of COVID infection.

Discussion

- In the previous session, Dr. Dale described some of the tools that are part of the routine geriatric assessment. For the PREVENTABLE trial, baseline assessments will include the Modified Telephone Interview for Cognitive Status, a Short Physical Performance Battery and Activities of Daily Living screen, and Patient-Reported Outcomes Measurement Information System ([PROMIS[®]](#)) physical function (PROMIS-PF).
- The NIA-sponsored [Research Centers Collaborative Network](#) is planning a workshop on tools for clinical trials enrolling older adults. The workshop will be held in February 2021.

Topic Area 4: Data Analysis and Study Interpretation

Appropriate data analysis and interpretation are critical to the synthesis of trial evidence and its application in treating patients. This includes careful consideration of certain subpopulations in the analysis, including children and older adults. The study of specific subpopulations must be considered throughout the process, beginning with study design and extending to data analysis, interpretation, and dissemination. With increases in inclusion of children and older adults in clinical studies, it is critical to develop data analysis plans that ensure appropriate, relevant, and meaningful study conclusions.

Age Is not Synonymous With Size

Valentina Shakhnovich, MD, Children's Mercy, Kansas City

Most analyses of pediatric clinical trial data group children based on chronological age. However, this approach fails to account for the tremendous amount of variability in organ maturation and physiology within a given age bin. For example, preterm infants exhibit substantially higher concentrations of acetaminophen than full-term infants when treated with a suppository due to differences in permeability

of the neonatal gastrointestinal tract.^{76,77} Physiological maturity also varies considerably in and around adolescence. One option is to use maturity ratings instead of age to bin pediatric patients. For example, Tanner staging is a measure of sexual maturity. However, it is important to realize that not all organs mature at the same rate (e.g., sexual organ maturity does not correlate with brain maturity).

Age also is not synonymous with size. Failure to account for size may lead to erroneous interpretation of data. For example, clearance of the drug infliximab appears to vary significantly by age, but age-related differences disappear when data are adjusted for the size of the patient. The effects of size are particularly important in the 21st century when 1 in 5 children is affected by obesity. Obese children cannot be excluded from clinical trials. Steps need to be taken to determine how to analyze and interpret pharmacologic data from children of a representative range of sizes. Trials that include children of different ages also may need to take into account differences in formulation and diet. Younger children cannot take pills, so may receive a different formulation than older children (e.g., liquid). Different formulations have different pharmacokinetic features. Observed differences between age groups could be due to either age or formulation. Infants and younger children also consume more liquids and semisolid foods than do older children, which affects gastric emptying and, consequently, drug metabolism. Children, particularly younger children, also are more likely to take medications with apple juice rather than water, which can affect drug absorption.^{78,79}

Age- and size-appropriate equipment must be used when evaluating children. For example, blood pressure cuffs must be appropriately sized for the patient. Different sizes may be needed for two patients of the same age if they are different sizes. Researchers also must be knowledgeable of age-appropriate outcome measures, such as differences in vital signs and laboratory values for adults versus children and older children versus younger children.

New technologies may facilitate research on pediatric populations when clinical trials are not possible. EMRs allow collection of data from a large and diverse pediatric population, which may lead to more generalizable findings. Challenges of working with EMR data include the need for bioinformatics expertise and interpretation of data organized based on the complicated International Classification of Diseases-10 criteria, which is designed for billing, not patient care. Physiologically based modeling tools and simulations also may be able to predict the pharmacokinetic and pharmacodynamic features of a drug in different populations. Algorithms could take into account differences in gut permeability, size, etc. These tools may not replace clinical trials but could inform trial design.

⁷⁶ Beck, D.H., Schenk, M.R., Hagemann, K., Doepfmer, U.R., & Cox, W.J. (2000). The pharmacokinetics and analgesic efficacy of larger dose rectal acetaminophen (40 mg/kg) in adults: a double-blinded, randomized study. *Anesthesia & Analgesia*, 90(2), 431-436. doi: 10.1097/0000539-200002000-00035.

⁷⁷ Van Lingen, R.A., Deinum J.T., Quak, J.M.E., Kuizenga, A.J., van Dam, J.G., Anand, K.J., Tibboel, D., & Okken, A. (1999). Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates. *ArcHIVes of Disease in Childhood Fetal & Neonatal Education*, 80, F59-F63. doi: 10.1136/fn.80.1.f59.

⁷⁸ Luo, J., Imai, H., Ohyama, T., Hashimoto, S., Hasunuma, T., Inoue, Y., Kotegawa, T., Ohashi, K., & Uemura, N. (2016). The pharmacokinetic exposure to fexofenadine is volume-dependently reduced in healthy subjects following oral administration with apple juice. *Clinical and Translational Science*, 9(4), 201-206. doi: 10.1111/cts.12400. Epub 2016 May 19.

⁷⁹ Murdoch, D.J., Krewski, D., & Wargo, J. (1992). Cancer risk assessment with intermittent exposure. *Risk Analysis*, 12(4), 569-577. doi: 10.1111/j.1539-6924.1992.tb00713.x.

Key Points:

- There is substantial heterogeneity within traditional pediatric age bins. Trials that include pediatric patients must account for differences in age as well as differences in maturity, size, diet, and formulation within age groups.
- Age-appropriate equipment and measures must be used for pediatric research participants.
- Modeling/simulations and analyses of EMR data may complement data on pediatric patients from clinical trials. EMRs can capture large heterogeneous populations, which may lead to more generalizable results. Modeling and simulations may help hone hypotheses and inform design of clinical trials or other studies.

Data Analysis and Study Interpretation: Geriatric Perspective

Heather Allore, PhD, Yale School of Medicine and Yale School of Public Health

Age encompasses stages of development, maturity, and decline in biological systems. Health can vary widely at the same age. The study of age groups or risk strata must be considered, starting with study design and extending to data analysis, interpretation, and dissemination. One way to study the lifespan is using life course analysis, which examines health over time and involves consideration of how trajectories evolve and factors related to that evolution. Life course analyses integrate biological and social processes,⁸⁰ which is consistent with the World Health Organization definition of health as “a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity.”⁸¹ One life course analysis looked at the role of the relationship between early-life educational quality and late-life literacy in racial disparities in cognition.

Data harmonization and big data initiatives may address limitations of single studies and trial sampling. Several data harmonization efforts facilitate comparisons across studies (e.g., COMET [Core Outcome Measures in Effectiveness Trials]).⁸² Analyzing large datasets of harmonized data or health system records presents significant challenges. The [Big Data to Knowledge](#) (BD2K) program supports the research and development of innovative and transformative approaches and tools to maximize and accelerate the utility of big data and data science in biomedical research.⁸³ BD2K has trained more than 30,000 individuals in biomedical data science; created more than 250 educational resources; and developed more than 200 software, tools, and methods to help tackle data challenges.

Health and risk factors vary by racial/ethnic background and are influenced by social determinants of health. For example, the proportion of adults with a disability differs among ethnic groups; 3 in 10 American Indian/Alaska Native adults have a disability compared with 1 in 10 Asian adults. There also are differences in smoking rates and obesity by race/ethnicity. The neighborhood disadvantage Area Deprivation Index (ADI) is a set of 17 education, employment, housing-quality, and poverty measures

⁸⁰ Kuh, D.J.L., Ben-Shlomo, Y., Lynch, J., Hallqvist, J., & Power, C. (2003). Life course epidemiology. *Journal of Epidemiology and Community Health*, 57(10), 778-783.

⁸¹ World Health Organization. (1946). Preamble to the Constitution of the World Health Organization as adopted by the international health conference, New York, 19-22 June 1946. Geneva, CH: WHO.

⁸² Gliklich, R.E., Leavy, M.B., & Dreyer, N.A. (Eds). (2019). *Tools and technologies for registry interoperability, registries for evaluating patient outcomes: A user's guide* (3rd ed.), Addendum 2. Rockville, MD: Agency for Healthcare Research and Quality.

⁸³ National Institutes of Health. (2020). Big data to knowledge. Retrieved from <https://commonfund.nih.gov/bd2k>.

drawn from the American Community Survey.⁸⁴ The ADI can provide information at the census-block level (i.e., neighborhood of ~1,500 people). It has been validated and is available through the Neighborhood Atlas platform.⁸⁵

When analyzing data, treatment effects from highly selective trials should not be extended to populations not included in the trial. There is a difference between the sample average treatment effect and the population average treatment effect. Selection of trial subjects may be a source of bias that precludes extending the results of a trial to a broader population. Studies with multiple follow-up visits, long duration, or high-risk groups may have higher rates of attrition or noncompliance, resulting in missing data. This can be problematic for analysis and interpretation.

Approaches that can be used for studies across the lifespan and/or of multiple populations include meta-analyses, stratification, and subgroup analyses. Meta-analyses include systematic, critical assessments of literature and data sources that form the body of evidence leading to the ability to generalize. Reporting guidelines for journals differ, making meta-analyses for age groups or other factors difficult. Stratification may be based on risk of an outcome and should be preplanned and aligned with the design and analysis. Risk strata may capture factors such as comorbidity or sociodemographics. Secondary and subgroup analyses can be useful but face inflation of type I error due to multiple comparisons; the significance threshold should be adjusted for these analyses. For pragmatic, dissemination, and implementation trials, papers should discuss the degree to which results are generalizable to typical participants and/or typical providers, institutions, communities, and settings of care.

Key Points:

- Age encompasses stages of development, maturity, and decline in biological systems. Health can vary widely at the same age.
- Life course analysis may capture exposures throughout the lifespan.
- Data harmonization and big data initiatives may address limitations of single studies and trial sampling.
- Health and risk factors vary by racial/ethnic background and are influenced by social determinants of health. Tools such as the ADI can help incorporate these factors into research.
- Selection of trial subjects may be a source of bias that precludes extending trial results to the broader population.
- When reporting research results, there should be discussion of the degree to which results are generalizable to typical participants and/or typical providers, institutions, communities, and settings of care.

Journal Editor Perspective on Trial Design and Reporting

Robert Golub, MD, Deputy Editor, Journal of the American Medical Association

Journals and journal editors are the link between researchers and consumers of research (i.e., other researchers, clinicians, patients). Journals and editors do four things when reviewing and publishing a

⁸⁴ Kind, A.J.H., & Buckingham, W.R. (2018). Making neighborhood-disadvantage metrics accessible—The Neighborhood Atlas. *New England Journal of Medicine*, 378(26), 2456-2458. doi: 10.1056/NEJMp1802313.

⁸⁵ University of Wisconsin, School of Medicine and Public Health, Department of Medicine. (2020). About the Neighborhood Atlas®. Retrieved from <https://www.neighborhoodatlas.medicine.wisc.edu/>.

manuscript: (1) judge the validity of the study and the likelihood that the results are meaningful, (2) assess the priority of the research for the journal, (3) optimize presentation to ensure information is clear and precise, and (4) provide guidance to help readers accurately interpret information.

There are limitations to what journals and peer reviewers can do to influence reporting of trial results. Journal articles must describe the trial protocol and statistical analysis plan with complete fidelity. If flaws in the study design or analysis plan are identified during peer review, there are limitations on what the journal can ask the research team to do to address these. This is particularly true for randomized controlled trials. There is more leeway in requesting analytical updates for observation, cohort, and case-control studies that do not have formal protocols.

The need to deal with heterogeneity in treatment effect has been discussed during peer review. Journals report the mean study effect in the study population, despite the fact that the mean effect likely describes a very small percentage of participants in the study. A heterogeneous study population is needed to tease out heterogeneity in treatment effect. Subgroup analyses need to be built into the study design and analytical plan to ensure that results will be meaningful. Investigators must ensure they have enough patients to do multivariable risk analyses and adequately test for interactions. Post hoc analyses are not as robust as preplanned analyses. Results can be misleading if analyses are not done appropriately. The SPRINT trial presented by Dr. Supiano is a good example of a trial for which preplanning allowed conduct of high-quality substudies with well-defined subgroups, well-defined endpoints, and adequate sample size.

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement provides guidelines for clinical trial protocols. These guidelines are available on the EQUATOR (Enhancing the QUALity and Transparency Of health Research) Network, a repository of reporting guidelines for health research. Researchers should refer to the SPIRIT guidelines as they design their studies.

It is absolutely critical that journal articles include complete and accurate methods. Many authors provide incomplete methods because they are worried about word count; however, this prevents the ability of reviewers to judge the validity of the study. Detailed methods can be provided in online supplemental materials if needed. Problems arise when reviewers find unexplained discrepancies between protocols or statistical plans and results. Misinterpretation of statistical findings is another common problem encountered by reviewers (e.g., inappropriate interpretation of post hoc analyses). It also is challenging for reviewers and editors to interpret patient-reported outcomes that have not been well characterized or validated.

Key Points:

- Journals judge the validity of studies, assess the priority of the research for the journal, optimize presentation of information, and help ensure readers accurately interpret information.
- Journal editors and peer reviewers cannot address shortcomings in trial design, particularly for randomized controlled trials. There are limitations to the types of modifications journals can request.
- Subgroup analyses need to be built into study designs and analytical plans to ensure that results will be meaningful. Researchers should refer to the SPIRIT guidelines as they design their studies.
- Journal articles must include complete and accurate methods. This helps reviewers evaluate studies and ensures appropriate interpretation of results.

Functional Measurements and Statistical Methods

Karen Bandeen-Roche, PhD, Johns Hopkins Bloomberg School of Public Health

As other speakers have noted, age is not synonymous with maturation in children or decline in older adults, which makes measurement of function extremely important. Examples of measures of function include frailty or resilience. Age also is not synonymous with human subjects' vulnerability. While vulnerability at the extreme ends of the age span must be considered, there is a danger of unintended ageism. The ethics of including a full range of individuals must be considered alongside vulnerability. There should be more rigorous definitions of unacceptable risk that are based on factors other than age. "Tokenism" also should be avoided, and care should be taken when extrapolating treatment effects. Increasing synergy between pediatric and geriatric researchers will help address some of these problems. The Clinical and Translational Science Awards Integration Across the Lifespan group helps bring together these researchers.

Statistical methods can help address some deficits in design or inclusion. Methods that may be helpful for addressing population imbalances include causal inference techniques and inverse probability weighting. Transportability is a technique that is being explored as a way to balance the benefits of randomization with generalizability and observational studies. "Foot-in-the-door" surveys can be used to capture key outcomes from some key individuals to help address imbalances through sensitivity analysis. Statistical harmonization methods aim to improve the comparability of assessments of underlying targets through analytic adjustments; anchors are needed to apply these methods. Covariate adjustments, effect modification, and adaptive designs may be used to account for heterogeneity.

Inclusion often is viewed as a challenge that makes clinical studies more complicated; however, it provides opportunities to increase power and generalizability of findings.

Key Points:

- Measures of function (e.g., frailty, resilience) may help account for heterogeneity within chronological age groups.
- Age is not synonymous with vulnerability. Assessment of risk and vulnerability should be based on factors other than age.
- Statistical methods can help address some deficits in study design or inclusion. Harmonization can be used to allow comparison of assessments of an underlying target across studies.
- Inclusion often is viewed as a challenge, but it provides opportunities to increase power and generalizability of findings.

Promoting Inclusiveness and Standards for Limitations

Jay Magaziner, PhD, MSHyg, University of Maryland School of Medicine

NIH has made substantial progress over the past 30 years with respect to inclusion, through requirements, review processes, monitoring, and reporting. This has helped change the culture of inclusion in research, and this will bleed into other sectors as a result. However, more must be done to help policymakers, clinicians, and others appreciate the value of inclusiveness.

Additional standards are needed to facilitate interpretation of results and reporting of the limitations of research. Protocols should be developed for recording the generalizability or applicability of findings (i.e., identifying who will benefit from a treatment). Including older people in research studies is important, but

it is not enough. It is critical to consider variability within age groups and other groups. Factors to consider include comorbidities, early-life exposures and experiences, and cohort membership. Thought must be given to how different groups of older people may respond differently to a treatment. Outcomes must be measured in a way that will provide meaningful results. Researchers have a challenge and responsibility to identify ways of reporting study limitations in ways that will help policymakers, clinicians, and other scientists use results of studies in meaningful ways.

Key Points:

- NIH has promoted a culture of inclusivity. More must be done to convince policymakers, clinicians, and some researchers of the importance of inclusivity.
- Standards are needed for capturing and reporting the limitations of research, including populations to which results are applicable.

Discussion

- Using EMRs for research might be one way to capture variability within the population. Large sample sizes and availability of multiple measures are potential benefits of EMR-based research. However, there are several challenges. Data not collected for research purposes may contain biases. It often is difficult to capture phenotype information from EMRs. Interdisciplinary teams that include biostatisticians, data scientists, epidemiologists, and other subject matter experts in aging and medicine could help address some of these challenges.
- There are groups, including the Health Care Systems Research Network, that are working on these challenges in areas like cancer and mental health. These groups do rigorous data coordination and cleaning to create virtual data warehouses across healthcare systems, and researchers can apply to use these data. This has been a successful model for some large pragmatic trials and other types of trials.

Wrap-Up and Final Comments

James A. Griffin, PhD, NICHD, NIH

- Inclusion of diverse underrepresented populations is challenging, but through the application of the scientific method, progress is being made toward advancing understanding of how to address and accommodate these challenges.
- The challenges and issues relevant to inclusion of individuals at both ends of the life spectrum are similar. Therefore, innovative methods to increase inclusion must work for populations across the entire lifespan.
- Findings from adult population studies cannot be generalized to children; this is why the inclusion policy emphasizes inclusion of children in NIH-funded studies.
- Special attention must be paid to populations that are sometimes, with the best of intentions, excluded from research, such as pregnant and lactating women (see Task Force on Research Specific to Pregnant Women and Lactating Women reports and recommendations on this topic).⁸⁶

⁸⁶ Task Force on Research Specific to Pregnant and Lactating Women. (2018). Report to Secretary, Health and Human Services, Congress. Retrieved from https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf.

- There are limitations and dangers of overgeneralization and extrapolation of findings from highly selective clinical trials to populations that were not included. Estimated sample average treatment effect is not the same as the population average treatment effect. There is potential for having similar findings in geriatric studies or studies of other special populations that traditionally have been excluded from research.
- There is a critical need to carefully plan and intentionally include populations. One approach is through active engagement of community stakeholders, members of the affected populations, and healthcare providers. Examples of studies that have used or are using this approach include the [Diabetes Telephone Study](#),⁸⁷ the SPRINT trial,⁸⁸ and the [PREVENTABLE](#) trial that started recently.
- Chronological age is not equivalent to health or functional status in older adults just as age is not equivalent to organ maturation or stage or body size in children. Health, physical, and cognitive status among older adults of the same age vary greatly. Capturing this variability is an important challenge that will require ongoing work.
- Large-sample pragmatic trials have the potential for maximizing diversity and inclusivity in study samples. Pragmatic trials embedded in clinical practice settings have few exclusion criteria and use simple study protocols that enable inclusion of large numbers of diverse participants and performance of valid subgroup analyses.
- Important tips and tools for accommodating older adults are based on the 5-T Framework for Recruiting Older Adults and the Geriatric 5M framework (see Appendix III, presentations by Drs. Cynthia Boyd and Stephen Wallace).⁸⁹ The innovative program described by Dr. Kohrt (see Appendix III, Dr. Wendy Kohrt's presentation) highlights the need for aging research training for nongeriatrician specialists who conduct research that includes older adults and should be disseminated to the broad research community.
- Examples of resources that support the inclusion of the traditionally underrepresented populations in clinical research include the Recruitment Innovation Center at Vanderbilt University (see Appendix III, Dr. Consuela Wilkins' presentation summary) and the geriatric assessment tools described by Dr. Dale (see Appendix III, Dr. William Dale's presentation summary) that are applicable to other areas of research involving older individuals.

⁸⁷ Adams, A.S., Bayliss, E.A., Schmittdiel, J.A., Altschuler, A., Dyer, W., Neugebauer, R., Jaffe, M., Young, J.D., Kim, E., Grant, R.W., Diabetes Telephone Study Team. (2016). The Diabetes Telephone Study: Design and challenges of a pragmatic cluster randomized trial to improve diabetic peripheral neuropathy treatment. *Clinical Trials*, 13(3), 286-293, doi:10.1177/1740774516631530.

⁸⁸ Ramsey, T.M., Snyder, J.K., Lovato, L.C., Roumie, C.L., Glasser, S.P., Cosgrove, N.M., Olney, C.M., Tang, R.H., Johnson, K.C., Still, C.H., Gren, L.H., Childs, J.C., Crago, O.L., Summerson, J.H., Walsh, S.M., Perdue, L.H., Bankowski, D.M., Goff, D.C., & SPRINT Study Research Group. (2016). Recruitment strategies and challenges in a large intervention trial: Systolic Blood Pressure Intervention Trial. *Clinical Trials (London, England)*, 13(3), 319-330. <https://doi.org/10.1177/1740774516631735>.

⁸⁹ Bowling C.B., Whitson H.E., & Johnson T.M. 2nd. (2019). The 5Ts: Preliminary development of a framework to support inclusion of older adults in research. *Journal of the American Geriatric Society*, 67(2), 342-346. doi: 10.1111/jgs.15785. Epub 2019 Jan 29.

Dawn Corbett, MPH, NIH Office of Extramural Research

When NIH announced the IAL policy in December 2017, the expectation was that NIH-funded clinical research would be inclusive, that exclusions would be justified, and that researchers would provide data on participant age at enrollment. Today, it is clear that implementing this policy is more complex than it sounds. Saying that diverse age groups will be enrolled is one thing; actually accomplishing that is quite another.

Today's discussions included a number of considerations—how to obtain informed consent, the impact of social determinants on ability to participate in studies, participant burden, strategies to involve family and community, communication with participants, limitations of chronological age categories, appropriate study designs such as adaptive and pragmatic trials, and how to evaluate recruitment. Successful examples described today highlight the need to involve the entire scientific community in solving these issues so that inclusion across the lifespan can be achieved. In addition to academia, physicians, and scientific organizations, participants themselves should be involved in design and implementation.

Appendix IV. Background Documents

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Appendix V. Responses to Request for Information

The purpose of the RFI on Inclusion Across the Lifespan II Workshop (NOT-OD-20-044) was to solicit input concerning a planned follow-up NIH workshop on implementation of the new Inclusion Across the Lifespan policy regarding the recruitment and retention of pediatric, geriatric, and other underrepresented participants in clinical studies.

In the RFI, NIH expressed interest in receiving input on the following 11 topics:

- Challenges and barriers to enrollment of individuals of all ages in clinical research studies
- Challenges and barriers to collection and reporting of participant-level data, including age at enrollment
- Implementation strategies that address potential ethical challenges when including individuals under 18 years of age, frail or cognitively impaired older adults, and other vulnerable populations in clinical trials or clinical studies
- Strategies and special considerations for including other underrepresented populations in clinical study designs that were not specifically addressed in the first workshop (e.g., sex/gender minorities, racial/ethnic minorities, people with disabilities, rural/isolated populations, language minority individuals, pregnant and lactating women, people with comorbidities, and others who are not well represented in clinical research)
- Development, implementation, and dissemination of scientifically appropriate and ethical inclusion and exclusion criteria for clinical trials or clinical studies
- The effect of developmental/aging stages on responses to biomedical and behavioral interventions, and strategies to tailor study planning and implementation to life stages
- How to overcome barriers to inclusion in clinical studies related to comorbidities, impairments, and disabilities
- Practice- or evidence-based strategies and necessary adaptations in recruitment/retention methods, modified safety monitoring, and how to use life stage-specific and patient-oriented outcomes in clinical trials or clinical studies
- Opportunities for education and outreach to clinical researchers, community physicians, and their patients about the importance of participation in research
- Strategies to disseminate and support the adoption of proven implementation techniques and strategies that overcome barriers and maximize the inclusion of a broad range of ages, sexes/genders, races/ethnicities, and other underrepresented participants in clinical trials or clinical studies
- Any other issues or concerns that NIH should consider regarding the implementation of optimal study designs that ensure the inclusion of participants across a broad range of ages and underrepresented groups.

The RFI was released on December 10, 2019, with a response date of February 15, 2020. NIH received over 40 responses from individuals and associations. Common themes and key points are organized into three main topic areas: inclusion and exclusion criteria; study design and metrics; and recruitment enrollment retention.

RFI Topic 1: Inclusion/Exclusion Criteria

Implementation strategies that address potential ethical challenges when including individuals under 18 years of age, frail or cognitively impaired older adults, and other vulnerable populations in clinical trials or clinical studies

- Research is needed to address the relationship between vulnerable pediatric patients and their families, disease course, growth and development, and the environment - exploring such factors as exposure to trauma, poverty, geography, language, family health history, and chronic stressors might enable earlier intervention and better treatment adherence - these same factors also impact levels of patient engagement when it comes to study participation.
- The UCSF Pepper Center Vulnerable Aging Resource Core, led by Drs. Rebecca Sudore and Brie Williams, offers a wealth of helpful resources on recruiting and retaining vulnerable older adults and securing informed consent, particularly when study participants may live with cognitive impairments.
- Because review panels will play a vital role in implementing Inclusion Across the Lifespan recommendations, there should be an emphasis on how to ensure there is appropriate expertise on such panels so that review panels can assess research designs and enrollment/retention plans.
- At the pre-award stage, rigorously review the inclusion rationale in each application or proposal prior to consideration by scientific review groups to ensure peer reviewers are able to appropriately assess plans for pediatric inclusion.
- At the pre-award stage, ensure the peer review process has appropriate pediatric expertise to evaluate pediatric inclusion plans in grant applications.
- Implement a process to make the inclusion data it collects public at the individual study-level to allow for routine analysis of the data beyond statutorily required triennial NIH inclusion reports.
- Provide transparency into the number of awards seeking age-based exclusions and the specific grounds on which exclusions are being sought so the pediatric research community can understand barriers that may be preventing children from participating in research and develop solutions to overcome such barriers.

Strategies and special considerations for including other underrepresented populations in clinical study designs that were not specifically addressed in the first workshop (e.g., sex/gender minorities, racial/ethnic minorities, people with disabilities, rural/isolated populations, language minority individuals, pregnant and lactating women, people with comorbidities, and others who are not well represented in clinical research)

Underrepresented Minority Populations

- Burden of participation may be different—caregivers within underrepresented minority populations more often can't take time off work, don't have transportation, and have limited access to phone, computer, or Wi-Fi resources to provide patient-reported outcomes.
- There is a lack of availability of translators and support for the extra time needed to consent non-English-speaking patients.
- Cultural differences affect trust related to participation in research.
- Provision of consent forms in Spanish, or free or minimal cost translation services to enable translation of consents/questionnaires into language appropriate for underrepresented minorities.
- Translation of study materials including standardized survey questions to non-English languages at an appropriate health literacy level can be time consuming and costly and deter investigators from including non-English-speaking populations in their studies. A publicly available repository of

translated and validated versions of survey questions could be one helpful strategy to encourage and support research including non-English-speaking individuals.

- Recruiting, training, and retaining research staff with specific language skills or insider knowledge may require additional time and resources; additional funding allowances should be considered.
- Centers that care for underrepresented populations often have fewer resources available to support participation in studies. The clinician caring for the patient may also serve as the study coordinator, and sometimes as the laboratory technician. There should be focused effort on
 - (1) fitting trial consent and data collection within the normal workflow as much as possible and
 - (2) providing off-site support to troubleshoot study-related issues and to help with data entry—especially if the data captured is not able to be readily retrieved from the electronic medical record.
- Consulting with such physicians very early in the design of the study and including site visit(s) during the course of a study (e.g., by a central/off-site coordinator) would help make studies of rare diseases more often successful.
- It must be an NIH priority to encourage and fund clinical studies that reflect the actual US population and the patients we care for; otherwise, clinical studies that do not include ages across the lifespan, individuals from racial/ethnic minority groups, language minority groups, etc., could exacerbate health disparities and fail to promote health equity.
- Community-engaged research including community-participatory research methods is an effective strategy to include underrepresented populations in clinical research. This approach can help develop efficacious interventions that can be implemented in real world settings and increase the capacity of community-based organizations to conduct relevant health-related research to improve the health of their communities.
- There is also a need for mechanisms of funding to support the planning and development of academic-community partnerships based on trust, equity, and inclusion so that together, academic and community investigators can propose, develop and implement clinical studies most pertinent and high impact for underrepresented populations.
- Encouraging research, training, and interdisciplinary collaborations in human centered design/design thinking approaches could also be a valuable strategy to support inclusion across the lifespan and ensure that the voices of multi-level stakeholders are at the forefront in the co-creation of new knowledge and solutions to health and healthcare problems.

Rural Populations—Expand IDeA Program Eligibility?

NICHHD, via the NIH IDeA [Institutional Development Award] program, instigated programs to include pediatric patients in rural areas in clinical trials; West Texas was specifically excluded from that NICHHD CTS program as we are not allowed to participate in the NIH IDEA program.

The short answer to the questions you pose, at least for the rural and underserved area of West Texas is that what is needed are funds from the NIH, and the ability to participate in funding programs from the NIH, such as the IDEA program and related NICHHD efforts, that are designed to enable rural participation in clinical trials. Virtually zero dollars are expended by the NIH to put in infrastructure for research into West Texas. Given the population here is greater than several IDEA states COMBINED (especially for pediatric patients), this is a failure on the part of the NIH to address a major underserved population, in spite of the NIH having programs designed to address underserved rural populations. *In short, West Texas has fallen through a huge gap in the NIH's attempt to address getting clinical studies to underserved rural patients, especially when it comes to pediatric patients.*

Sex and Gender Minorities

- Consider how sex and gender identity can be clearly reported in a way that includes SGM [sex and gender minority] populations.

Veterans

The participants rapidly identified a critical gap in clinical knowledge, namely, a thorough understanding of HPV [human papillomavirus]-related oropharyngeal squamous cell carcinoma (OPSCC) epidemiology within the veteran population. They identified utilization of both the Million Veteran Program and cross-institutional collaborations as critical elements in the first steps to leveraging existing Veterans Health Administration (VHA) database resources towards better understanding disease incidence and prevalence in the modern era.

To address the HPV-positive OPSCC cohort, the participants have proposed formation of an active, multi-disciplinary working group to vet and coordinate multi-institutional clinical trials within the VHA to target OPSCC in particular and head and neck cancer more broadly. With respect to the latter patient cohort, the participants identified the VHA as a uniquely positioned healthcare delivery system to conduct the first multi-institutional prospective OPSCC survivorship registry study designed to understand the oncologic, functional, and quality-of-life outcomes associated with HPV-positive OPSCC smokers.

Persons with Disabilities

I am writing to ask for a broader consideration of increasing the inclusion of study participants—across the lifespan—with disabilities. This includes those with vision, hearing, mobility, and cognitive impairments, learning disabilities, and other conditions that affect daily life. People with these disabilities often are excluded from research—either directly or indirectly—and this leads to an underrepresentation of people with all types of disabilities across research studies.

Further, for people with disabilities, collecting current measures can be difficult or impossible (consider a participant who is blind or visually impaired in a study that is assessing cognitive functioning with visual tests). And without advances in adaptive testing or considering how to harmonize alternative testing approaches, these individuals cannot contribute to research.

To overcome these challenges, I believe, we need more researchers with disabilities themselves. “Champions of change” are often required to ensure that select populations are included. Without including people with disabilities as researchers themselves, the voice of disability is not often heard, or not heard from the nuanced and unique perspective of the lived experience.

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People with sensory impairments, including visual or hearing impairment, are often excluded from research studies, planning, testing, or analyses. Exclusion criteria often limit the inclusion of those with sensory impairments from many major studies, and there are little to no standardized accommodation approaches to administering testing (i.e., how to administer cognitive testing batteries to those with VI [visual impairment]). This results in biased outcomes for many analyses, as those with sensory impairments are not included. From a social justice perspective, this all acts to perpetuate the marginalization of these groups. We recommend that the workshop explore ways that individuals with sensory impairments are engaged throughout the research process.

NIH has considered appropriate scientific review and monitoring processes, as well as necessary age-specific expertise, to promote inclusion or define appropriate exclusion for younger and older

populations. We would ask that the same considerations be given for populations with sensory impairments to ensure that study design and implementation have taken into account the specific needs of individuals with sensory loss.

Disabilities are one of the four groups called out by the NIH as a “protected category.” Grant submissions must currently justify inclusion of women, minorities, and considerations for gender/sex differences. The September 2020 Workshop includes a discussion and policy development that promotes justification for the inclusion or exclusion of individuals with disabilities—including sensory impairment—in research studies.

Pregnant and Lactating Women

- Promote and support comparative effectiveness research in pregnancy. This will allow clinical trials to be embedded within clinical care. Pregnancy is an ideal condition for such trials given that many of the management and intervention strategies in clinical practice have not been adequately tested.
- Encourage and support non-traditional clinical trial designs such as cluster randomization, preferably on a national level.
- Maintain research infrastructures that have been successful in enrolling pregnant women in clinical trials, specifically the NICHD-funded Maternal Fetal Medicine Network. The impact of this Network on clinical practice has been immense. Continued efficiency of this Network is essential to enroll pregnant women in large clinical trials and longitudinal cohorts.
- Encourage and educate Institutional Review Boards (IRBs) to remove unnecessary burden for research involving pregnant women. Use of central IRBs with expertise in pregnancy research will improve this burden but does not eliminate it since local IRBs will continue to have some sway.
- Engage with the FDA in streamlining the conduct of research in pregnant women.
- Encourage the use of innovative interventions and technologies.
- Study coordinators or research assistants with substantial experience carrying out research in a culturally and ethically sensitive manner.
- Use of bilingual and bicultural research staff adept at working with pregnant women.
- Education and outreach to community members and healthcare providers regarding the importance of prenatal research.
- Involve patients in selecting a number of “patient-reported outcomes” to be included in clinical trials.
- Align the content of maternal and pediatric consents so that prenatal research only requires the consent of the pregnant person.
- Implement the Common Rule. Its latest iteration declassified pregnant women as a vulnerable population; thus, pregnant women should be included in research where appropriate without additional barriers or concerns. IRBs can facilitate and ensure that researchers are protecting women through research rather than from research.
- Leverage existing infrastructures, like the Maternal-Fetal Medicine Units (MFMU) network, to share best practices for inclusion of pregnant populations in clinical research involving therapeutics and devices.
- As you consider various populations in clinical research across the lifespan as well as life course, I think you will want to think about child-bearing women 18-40. Special considerations have to be account for with including this population of women into clinical trials. Therefore, I can imagine a specific segment that addresses this population.

- There is growing consensus that clinical trials of new drugs should include pregnant women earlier in the drug development process. Such research requires careful and specific planning for inclusion of pregnant women. For example, the reproductive-toxicity animal studies needed to ensure there is not a safety signal for use of a drug in pregnancy are generally not completed until phase III efficacy trials are near completion; earlier completion of these studies, prior to initiation of phase III trials, is needed to allow initiation of initial pharmacokinetic studies of the drug in pregnancy.
- Pharmacokinetic studies in pregnant women could be conducted for promising new drugs once initial phase II early human studies indicating acceptable safety, dosing, and preliminary efficacy in non-pregnant individuals are available (preferably studies including non-pregnant women and not limited to men). Initial pharmacokinetic studies of new drugs in pregnancy could be conducted in parallel to an ongoing phase III efficacy trials in non-pregnant individual or could be embedded into the phase III clinical trial design. Once the drug is shown to have adequate drug levels and preliminary safety data in pregnancy from pharmacokinetic studies, pregnant women could then be enrolled directly into a phase III trial. The purpose of enrollment of pregnant women is not to separately evaluate efficacy of the drug in pregnancy but to allow the availability of additional safety data in pregnancy at the time the drug is approved for adults. Interim pregnancy-related analyses could be conducted with early stopping rules for the pregnancy subgroup for safety.

Cognitively Impaired, Intellectually Disabled, and Neurodiverse Individuals

- The IDD [Intellectual and Developmental Disabilities] population is underrepresented in research. There is a newly formed section on Adults with IDD in the AAN [American Academy of Neurology].
- I would like to propose that neurodiversity be formally incorporated into the NIH guidelines on inclusion across the lifespan.
- Our research has shown that there is urgent need to understand how neurodiversity intersects with the aging process and I am proposing that the NIH consider mandating developmental history [screening] so as to immediately address the omission of developmental differences as a form of diversity inclusion. All told, a better accounting of developmental history across all human subjects research will facilitate novel disease prevention strategies and inform research on these developmental differences themselves.

Development, implementation, and dissemination of scientifically appropriate and ethical inclusion and exclusion criteria for clinical trials or clinical studies

IAL-II workshop participants can advance the needs of the research community by paying special attention to capacity in persons with cognitive impairment. Discussions should focus on devising strategies that:

- Do not limit opportunities to participate in research based on cognition.
- Promote appropriate protections and privacy for people with impairments.
- Definition of healthy older population: What is the standard definition of “the older population” we need to be studying? This segment of the population may span upwards of 40 years and is extremely heterogeneous (e.g., there are 65-year-olds managing 3-4 chronic diseases with mobility issues and 95-year-olds living disease-free and independently).
- Healthy older adults versus not healthy older adults to target in order to get them healthy. Researchers want to evaluate people at risk for a condition or people who have it. Are we studying too healthy people? Screening is key.

- Exclusion Criteria: Strict exclusion criteria results in targeting the healthiest of the healthy. This both makes it difficult to recruit, and also study results may not be generalizable to the overall population who are managing multiple chronic conditions.
- Consideration is to target the translation/link to animal models—appropriate aging animal model(s)—to generalize to studying the older population.

How to overcome barriers to inclusion in clinical studies related to comorbidities, impairments, and disabilities

Overcoming barriers related to comorbidities, impairments, and disability means (1) understanding how these conditions impact older study participants and researchers by extension and (2) ensuring proven strategies for maximizing age inclusivity can be shared and adopted as widely as possible. Ultimately, enrollment plans should use evidence-based strategies for recruitment and retention of older populations when applicable, so the health status of the research population mirrors that of persons living with the condition under study.

IAL-II workshop participants should take note of work by Dr. Lona Mody and colleagues, who offer a compelling outline of common health concerns and their effects on recruitment and retention strategies for older adults.

Careful consideration of exclusion criteria is key. We tend to study very healthy older adults, but most older people have at least two comorbidities. This causes a problem then with how generalizable are results to the general public. Be careful to consider study inclusion/exclusion (I/E) criteria as older adults typically have multiple comorbidities, disorders, and diseases, and are on multiple medications. I/E criteria should only be based on the safe conduct of the study. For example, if a potential participant is stable with HTN, why does the study have to exclude [that individual] if your study does not pertain to HTN or would [not] affect their condition?

Strategies to disseminate and support the adoption of proven implementation techniques and strategies that overcome barriers and maximize the inclusion of a broad range of ages, sexes/genders, races/ethnicities, and other underrepresented participants in clinical trials or clinical studies

- Need to incentivize/ support site investigators to take the extra time to recruit challenging patients/families (e.g., language barrier, education status, physical disabilities, etc.)
- To support the dissemination of proven implementation techniques, IAL-II discussions should emphasize a broad approach to supporting inclusivity based on age and other characteristics that impact and are impacted by age. These include sex/gender, race/ethnicity, socioeconomics, and sociocultural background, all of which can contribute to participant underrepresentation. The AGS [American Geriatrics Society] also recommends further exploration of accurate disease demographics to ensure our understanding of study populations *and* health conditions can support inclusivity in tandem.

Any other issues or concerns that NIH should consider regarding the implementation of optimal study designs that ensure the inclusion of participants across a broad range of ages and underrepresented groups

- Need to focus on transition from pediatric to adult care and study strategies to improve the process.

- Need to identify targeted medications beyond “re-purposing” those used for adult-onset disease, and related to this, need to study strategies to increase adherence with goal to exposure to glucocorticoids and adverse effects in children.
- Need to establish demographically representative RCT (samples of rare disease populations—this is difficult, but necessary).
- Studies need to measure and address quality of life and psycho-social health in children and adolescents who have a visible chronic illness, as these are particularly relevant to well-being.
- Develop community-based research models.
 - o Leverage PCPs.
 - o Leverage schools.
- Develop mechanisms for use of commercial reference labs (Labcorp, Quest) for study-related sample collection.
- The AGS recommends that NIH consider participant inclusion in study design to maximize relevance and the likelihood of success when administering protocols. Studies must be designed not only for inclusion and retention but also for relevance to older participants and populations with multiple chronic conditions.
- Inclusion of staff that represent the target audience be a part of the recruitment team as well as included in the design and implementation of the research.
- Inclusion criteria may have to be modified to include more diverse adults as well as multiple age groups. It may be possible that different criteria can be utilized to accommodate recruitment of diverse individuals across the lifespan.
- Expansion of funding guidelines to include multiple age groups that may benefit from the proposed research policy.
- As NIH expands the concept of inclusion in clinical research, it will be important to consider how the policy might be applied to different types of studies. For instance, discovery-oriented research involving fundamental aspects of human physiology may require a different approach than clinical trials involving drugs or other interventions. Drug trials would clearly benefit from including study populations that are as broad and inclusive as the population that uses the drug or intervention, and we share the concern that drugs may be developed and approved through narrowly tailored clinical trials that do not reflect the demographics of the population, often older adults, that are most likely to use the drug. However, for discovery-focused fundamental research, it may be more appropriate to conduct initial studies within a defined age range and then expand the scope of research to include more heterogeneous populations. The biomedical research community would therefore benefit from the development of guidance or suggestions on approaches that are specific for different types of investigations involving human participants.
- We applaud recent policy changes and developments intended to include pediatric populations in research, but there remain significant challenges to the recruitment of children for clinical studies. In some cases, studies involving all ages face institutional barriers e.g., if a hospital that treats children does not want to be liable for studies involving adults. Even where reciprocity agreements exist that allow for more effective partnering between institutions to allow for all-age studies, other logistical barriers exist such as different EHRs [electronic health records] for adults and children, or the inability to recruit at certain sites if staff are not trained to work with heterogeneous populations.
- It will be important for NIH to consider ways to reduce liability concerns and other logistical barriers to inclusion and enable institutions to seamlessly partner on studies involving multiple age groups and populations.

- Vulnerable groups are insufficiently studied or included in studies because IRBs are afraid to acknowledge these individuals' capacity to consent to participate in research. In the past, scientists and researchers have manipulated these populations, hence the need to build in protections to ensure coercion is not occurring.
- There are successful models that allow for "vulnerable" groups to ethically be included, as participants, in research. IRBs need to make these processes more transparent, and meaningfully consider novel processes, rather than engage in knee-jerk "no" responses. Researchers have come to expect this, diminishing the amount of meaningful investigations that include these populations.

RFI Topic 2: Study Design and Metrics

The effect of developmental/aging stages on responses to biomedical and behavioral interventions, and strategies to tailor study planning and implementation to life stages

- Study designs should look for heterogeneity of treatment effects, particularly since health and care can change across the lifespan. Workshop discussions can advance implementing age inclusivity by helping researchers explore the biological plausibility of evaluating cognition and function, particularly among older study participants.
- In particular, workshop participants should consider additional measures of health status, such as gait speed, self-reported health, comorbidity burden, or frailty indices. These are critical for the scientific community to understand whether the health status of the study population mirrors the typical clinical population.
- Investigate how different types of research studies may benefit from development of guidance or suggestions on approaches that are specific for different types of clinical investigations.
- Explore new approaches to research on aging in general.
- Demographic, structural, regulatory, technical, and economic challenges all contribute to slowing drug development for children. The pediatric population crosses the age span from neonate to adolescents, requiring drug combinations, strengths, and formulations that vary by age and weight. Despite regulatory incentives and requirements for pediatric drug development plans for new drugs, studies of new drugs are delayed due to the need to evaluate the safety and dosing across the spectrum of pediatric ages and weights and the need to ensure child-friendly drug formulations for the younger children.
- Additionally, the need for different formulations at different ages can lead to a fragmented, low-volume market for pediatric drugs, discouraging drug development for children.
- There are many challenges faced in data collection and reporting in pediatrics and geriatrics:
 1. Errors in measuring birth rate in clinical areas because there are no policies or systems that manipulate data effectively
 2. Lack of patient awareness instead of revisit at clinic such as old age people [??]
 3. Inconsistent tools for data collection and compilation
 4. Inefficiency of experts that deal with pediatric data collection.

Appropriate Pediatric Age Groupings

- Establish appropriate pediatric age groupings to simplify the enrollment data available so it can be easily understood and acted upon in order to effectively understand whether studies are reaching their potential to improve child health through pediatric research.
- There is significant value in the NIH establishing a standardized set of pediatric age groupings. These groupings could then be used for tracking data across the institutes (including for reporting on

enrollment by age in the required triennial report) and in the development of a standardized tool for the analysis of the individual-level data.

- Children are not little adults, but rather they change rapidly from birth through adulthood. Each developmental stage brings with it new physiological and behavioral factors. A neonate, for instance, is profoundly different from an adolescent and, as such, both cannot be meaningfully categorized together for the purposes of evaluating the inclusion of children in research. Congress was clear in passage of the 21st Century Cures Act that data on relevant age categories must include data on “pediatric subgroups” and may not lump all children together. To effectively understand whether studies are reaching their potential to improve child health through pediatric research, the de-identified continuous data must be simplified through age groupings so it can be easily understood and acted upon.
- In 2012, Williams et al. proposed age groupings for pediatric clinical trials based on the pediatric terminology published by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The authors proposed eight groupings: preterm neonatal, term neonatal, infancy, toddler, early childhood, middle childhood, early adolescence, late adolescence. While no set of proposed age groupings could be perfect, our organizations believe these groupings are reasonable, developmentally appropriate, and strike an appropriate balance between simplicity and specificity. We propose that NIH adopt these groupings (see table) with one amendment, which would be to raise the upper age limit of late adolescence to 26 years, to better align with the current understanding of the end of the adolescent/young adult period.

TABLE: Proposed Age Groupings	
STAGE	DEFINITION
Preterm neonatal	Birth – 28 days (the period at birth when a newborn is born before the full gestational period)
Term neonatal	Birth – 28 days
Infancy	29 days – 11 months
Toddler	12 months – 23 months
Early childhood	2 – 5 years
Middle childhood	6 – 11 years
Early adolescence	12 – 17 years
Late adolescence	18 – 25 years

Standardized Tools

- NIH should develop a standardized "dashboard," tools, and reports to analyze the submitted enrollment data that would be shared with investigators and program officers for each individual study. Such a tool will be essential to empower program officers to actively address recruitment and enrollment issues in real time, so that the intent to enroll children described in an application reflects the population that is ultimately enrolled and studied. Similarly, the availability of a study-level inclusion tracking tool will give the investigator insight into the diversity of trial enrollment and therefore be appropriately attuned to gaps in enrollment that must be addressed.

Strategies and special considerations for including other underrepresented populations in clinical study designs that were not specifically addressed in the first workshop (e.g., sex/gender minorities, racial/ethnic minorities, people with disabilities, rural/isolated populations, language minority individuals, pregnant and lactating women, people with comorbidities, and others who are not well represented in clinical research)

- For HIV, global stakeholders have come together in recent years under the umbrella of the Global Accelerator for Pediatric formulations (GAP-f) to enable more focused and coordinated action to make age-appropriate optimal formulations more rapidly available to pediatric patients living with HIV. A similar global stakeholder investment might be useful to ensure studies in pregnant women as well.
- There is a need for specialized clinical, laboratory, and regulatory infrastructure to conduct vital, high quality, scientifically sound research in children and pregnant and lactating women. In order for these populations to be appropriately included in studies, structures must be established to facilitate close collaboration of pediatric and maternal networks to ensure appropriate expertise is available for the conduct of studies in these populations and to recruit appropriate researchers to work together. An example of this is the specialized, collective expertise that the HIV International Maternal Pediatric Adolescent AIDS clinical trials (IMPAACT) Network brought together, including pediatricians, adolescent specialists, and obstetricians/gynecologists, which helped to coordinate studies across children, adolescents, and pregnant and lactating women. Many of the advances in the prevention of mother-to-child transmission of HIV, early infant diagnosis, and availability of lifesaving pediatric HIV treatments are a result of the meaningful research conducted within the IMPAACT Network.
- Additionally, inter-network collaboration with adult HIV networks and HIV vaccine and prevention networks allows sharing of the essential expertise in pediatrics, adolescents, and pregnant and lactating women for studies that may involve these populations.
- I would repeat that research assistants/coordinators need to be diverse in many areas. Enrolling patients in satellite sites/community locations as supposed to large hospitals with paid parking often keep many minorities and low-income [individuals] away. Easy-to-read materials and explaining why the research is important to them is key. There are people that participate for altruistic reasons, but the larger group that we need to reach is those affected or those who can serve as healthy controls for underrepresented populations. One study my department is currently working on is a breast cancer vaccine. Explaining the goals/risk of the study is paramount, but to get the large volume of female participants one needs to understand why [it] is important that they participate.

Pregnant and Lactating Women

Historically, and increasingly in recent years, it has been difficult to recruit and retain pregnant women for research. While a variety of strategies have been employed to increase participation, women decline to participate for a variety of reasons, including an increasing number of requests to participate, time commitments, language barriers, intrusiveness of the study (i.e., biological sampling), and a perception of a lack of benefit from participation. Failure to adequately recruit and retain this population bypasses a very important population of patients—mothers and fetuses—that leaves tremendous gaps of knowledge that could have lifelong impact and compromise research integrity. We propose the following to address the difficulties in recruitment and retention of pregnant and lactating women in research:

- Promote and support comparative effectiveness research in pregnancy. This will allow clinical trials to be embedded within clinical care. Pregnancy is an ideal condition for such trials given that many of the management and intervention strategies in clinical practice have not been adequately tested.

- Encourage and support non-traditional clinical trial designs such as cluster randomization, preferably on a national level.
- Maintain research infrastructures that have been successful in enrolling pregnant women in clinical trials, specifically the NICHD-funded Maternal Fetal Medicine Network. The impact of this Network on clinical practice has been immense. Continued efficiency of this Network is essential to enroll pregnant women in large clinical trials and longitudinal cohorts.
- Encourage and educate Institutional Review Boards (IRBs) to remove unnecessary burden for research involving pregnant women. Use of central IRBs with expertise in pregnancy research will improve this burden but does not eliminate it since local IRBs will continue to have some sway.
- Engage with the FDA in streamlining the conduct of research in pregnant women.
- Encourage the use of innovative interventions and technologies.
- Study coordinators or research assistants with substantial experience carrying out research in a culturally and ethically sensitive manner.
- Use of bilingual and bicultural research staff adept at working with pregnant women.
- Education and outreach to community members and healthcare providers regarding the importance of prenatal research.
- Involving patients in selecting a number of “patient-reported outcomes” to be included in clinical trials.

Any other issues or concerns that NIH should consider regarding the implementation of optimal study designs that ensure the inclusion of participants across a broad range of ages and underrepresented groups

- It is difficult to recruit, enroll, and follow participants long enough to see your outcome of interest within a five-year grant period.
- Lack of methods for reconciliation of discordance between parent and patient-reported outcomes.

RFI Topic 3: Recruitment, Enrollment, Retention

Challenges and barriers to enrollment of individuals of all ages in clinical research studies

Pediatric Populations

- In rheumatology, nomenclature remains a major barrier to including of patients across age categories in clinical (and translational) research. This barrier is most prominent in the area of arthritis, where all patients with disease beginning before age 16 are categorized as subtypes of juvenile idiopathic arthritis whereas all patients diagnosed in adult clinics are categorized as other diseases, such as rheumatoid arthritis or ankylosing spondylitis, even for diseases where biological continuity is largely acknowledged (e.g., RF+/CCP arthritis, systemic JIA/adult-onset Still's disease, and axial spondyloarthropathy). This problem could be addressed through a systematic effort to identify biological categories, using age as one criterion but not necessarily the defining one. The FDA's October 2, 2019, "FDA/UMD CERSI polyarticular JIA Drug Development Workshop" exemplified this approach.
- Need for additional assessment tools validated in pediatric disease groups and classification subcategories as well as across the range of ages of affected individuals.
- Attention to logistics around parental consent and requirement for two parent signatures for certain studies, which adds complexity and delay to the consent process and subsequent study eligibility. Divorced parents, in particular, often do not want to consent without the other parent's permission,

even when allowed. Consider alternative methods to obtain consent from a second parent (e.g., via phone, or an app, or a secure online mechanism).

- Consideration is needed to the stage of development of the child for consent/assent issues as well as study design if therapeutic interventions are considered. Too often trials are fashioned after adult studies and do not take into account differences in drug absorption, distribution, metabolism, and excretion that may impact design and statistical considerations.
- A major barrier to enrollment is need for individual site IRBs and data share agreements. Sites differ in their IRB and consent requirements, as well as data share allowances. When working with rare diseases, multi-center collaboration is needed, but it may not be feasible for a given site's investigator to get approval for the study if they are only going to enroll a few patients, given the increasingly onerous IRB and data share agreement approval process.
- A Master IRB/data share agreement that could be used for multiple similar types of studies rather than having separate IRB applications would accelerate enrollment and support collection of data from rare patients. This would be most effective for studies with minimal risk that are often pilot or early investigation studies that generate data needed to conduct larger studies. Examples include retrospective data collection (e.g., estimation of frequency of a response) and prospective observational studies, (e.g., data registries). This would be particularly helpful for studies [that] were conducted by a common group of investigators (i.e., CARRA members) where data are to be collected under the same consent and housed in the same off-site virtual location for a series of studies.
- Legal guardianship—most people do not have papers for legal guardianship so cannot give consent for a child to be on a study.
- Parents working and cannot take time off to come to the clinic.
- Participants cannot take time off work for participation in clinical trials
- Eligibility criteria too stringent.
- Parents do not want child to miss school.
- Because of the shift to single IRB review of IMPAACT 2026 for US sites, we are now required to include any assent forms that will be used at any sites (even non-US sites) in the 2026 protocol. Preparing those assent forms will take a lot of work and time and will slow down the approval process terribly. Assent forms and parental consent forms are to be adapted to local site situations in any case, and this is generally only done after the final protocol has been disseminated to all sites. So, the 2026 team decided not to include minors due to difficulty of obtaining all possible assents from all possible sites, as part of the protocol beforehand, and this is really a pity. This requirement is not helping the enrollment of pregnant minors in any country in any study and should be looked at. Every country has its own IRB regulations on enrolling minors and there should not be a prerequisite inclusion of the forms in the protocol, but the protocol should rather include language enabling each site to make their assent and parental consent form site specific to local regulations, especially as pregnant minors are more frequently found at international sites and the single IRB is not even applicable to those sites to start with.
- With regard to pediatric enrollment, a particularly sticky issue is the large amount of expected variability due to age within the pediatric age window for many studies and trials. This variability demands equal or larger (not smaller) sample size in order to make meaningful conclusions about the pediatric age group from study data. In contrast, due to funding constraints, the difficulty of enrolling pediatric patients, and the need to carefully define pediatric endpoints, study protocols often plan to include a small number of pediatric participants. This, in turn, raises questions about the ethics of enrolling children in the study/trial at all. If there is no hope of generating knowledge about this population (no benefit), why should they be included in the study (and bear the risks of the research)?

- If the goals include testing hypotheses in pediatric populations, it is not enough to include a “token” number of children (or any other underrepresented group) in study enrollment, only to have their data subsumed by a much larger majority. Worse yet is the scenario where pediatric data are excluded from the main analysis because [they are] too different from the “adult data,” and the sample size is so small that when analyzed separately there is little hope of identifying significant findings and little confidence in anything that is seen in the data. Instead, I advocate for inclusion of robust pediatric sub-cohorts that are appropriately powered for stratified analyses. Alternately, separate pediatric studies must be pursued (with adequate funding to overcome the barriers to pediatric recruitment and ascertainment of outcomes). Otherwise, we will continue to be lacking in evidence for the youngest segments of our population.
- Our group recently conducted a large qualitative study throughout the NCORP [NCI Community Oncology Research Program], which identified a number of barriers and facilitators to enrolling adolescents and young adults (AYA) in the community setting including lack of knowledge of the disparity in AYA enrollment, resource constraints to opening trials for rare diseases (most AYA cancers meet these criteria), poor communication between pediatric oncologists and medical oncologists, and others. To date, few efforts have been made to address and overcome these barriers to enrollment. There is an urgent need to increase AYA enrollment onto cancer clinical trials.

Geriatric Populations

- 1) Individual limitations: especially related to frailty, mobility, and cognitive decline;
- 2) logistical issues: transportation, weather; and 3) lack of familiarity with research: lack of understanding what it means to participate in research.
 - Need to better address the issue of older adults’ understanding of what a clinical trial is. A barrier is this demographics’ understanding of what a trial is and the benefits of participating in a research trial. Perhaps there are pockets of certain ages and/or ethnic groups that we should be targeting for education purposes.
 - Understanding the motivation of older adults who would want to participate in research is important.
- A suggestion to improve recruitment of older adults is to better partner and collaborate with local Council on Aging organizations and assisted living facilities.
- Working with nursing home populations has its own challenges. Need to form solid collaborators within those facilities. Have found these facilities are more willing to work with a medical director or MDs versus researchers. Breaking barriers with these facilities for non-MD access.
- Very difficult to recruit rural older population into research studies, primarily due to accessibility issues.
- For older adults, assessing comfortability and confidence with technology is important. For example the comfort level of working on a computer or not. Carrying out food or not. Can they carry it, transport it, store it? Can we mail them the food, and at what cost?
- Worth thinking about telemedicine and telecommunication approaches for the older adult population.
- Geriatric syndromes (sensory impairment, cognitive impairment, etc.), multiple chronic conditions, and declining function pose challenges for older individuals as research participants. The IAL-II agenda should address related barriers and the role research registries can play in facilitating better engagement. One potential approach for overcoming barriers that result because researchers from other disciplines are unfamiliar with this population is highlighted in the *5Ts* Framework by Dr. C. Barrett Bowling and colleagues.
- An additional barrier to older adults’ participation in research studies is that the constructs being assessed are not of interest to older adults. Outcomes such as the impact of a treatment on daily function and their ability to engage in valued activities may be more relevant to an older adult than a

purely medical or psychological outcome. Obtaining stakeholder input into outcomes of importance to older adults may result in a study of greater interest and relevance to the population.

- Challenges to study participation can be numerous and related to the physical and cognitive changes often associated with aging. Travel to multiple in-person research visits may be a large barrier, particularly for older adults who no longer drive. Sitting for extended periods of time may be uncomfortable for older adults with joint pain. Hearing impairments may make communication over the phone difficult, and informed consents with small print may be difficult to read. While many older adults do not experience these changes, failure to account for them in study procedures may lead to enrollment of a healthier sample that does not represent the larger population.
- Older adults, particularly those with functional impairments, may rely on formal and/or informal caregivers to complete ADLs [activities of daily living] and IADLs [instrumental activities of daily living]. Participation in a research study may add additional burden to these caregivers, some of whom may be also caring for dependent children. Assessing the impact of study procedures on an older adult's caregiver and taking steps to minimize this burden may improve study participation. Further, greater inclusion of these caregivers in research projects is an important area of research.
- We need much better demographic information (and centralized information so there is not disagreement) to help PIs understand the value of recruiting subjects in the older age groups.
- First of all, geriatricians or any healthcare providers who care for octogenarians and nonagenarians (and centenarians) face many obstacles every day. A fundamental one is that many of the healthcare services (e.g., prescribing a medication, vaccination, or performing a procedure, etc.) that we provide to this oldest-old and frail, most vulnerable subset of older adults lack sound scientific evidence. Often times, we extrapolate data from studies in the younger population. It is critical for NIH to address this issue head-on as part of the Inclusion Across the Lifespan. One can cite many reasons for the lack of studies targeted to this oldest-old subset of older adults. Historically, there were not many octogenarians and nonagenarians even 15 or 20 years ago. Even today, with many of them around (and more to come), these individuals are not easy to recruit into clinical studies. They tend to be frail with multiple comorbid diseases and disability and less engaged (due to lack of transportation and many other reasons).

Underserved Populations

- Older adults from racial and ethnic minority groups may be hesitant to participate in research due to historical abuses by the medical and research communities. Older adults may be more likely to remember or have experience with these abuses. Legitimate concern over being “guinea pigs” may lead to refusal to enroll in studies. Further, LGBTQ+ populations may be hesitant to participate in research due to the historical role of the mental health field in pathologizing sexual orientation.
- One strategy to address enrollment challenges is to partner with a medical provider trusted by the older adult. For example, an older adult may have a longstanding relationship with his/her primary care physician. Working with the physician to present the study to the patient and initiate recruitment procedures may increase the older adult's willingness to engage with study staff. However, integration of a research project into a medical setting requires prior planning to ensure study procedures are clear to medical staff and do not disrupt the flow of clinic services.
- In my opinion, one of the major barriers to enrollment of minorities in research studies is the lack of incentives to minorities and community health activists.
- My patients will not be enrolling in studies run by unknown-to-them scientists that are not going to support their daily problems.
- Geriatric populations will be willing to enroll in studies if they are supported by their local organizations, if they have local representatives willing to spend time explaining the minutiae.

- Immigrants, especially undocumented migrants and refugees deserve special consideration in the planning process. An increasing share of US population growth is attributable to international migration, and these individuals and their descendants are present across the entire lifespan. A variety of factors, including language, socioeconomic conditions, and relations with state institutions, may make it more difficult to recruit and retain such individuals in clinical and population-based studies. I encourage the workshop agenda and discussion to consider this group and related underrepresented groups. I further encourage the NIH to seek out the most recent methodological research on reaching such groups and developing valid scientific inferences for assessing their well-being.
- Research assistants/coordinators tend to recruit those that are similar to them or those that they are familiar with. A diverse group of coordinators—age/sex/religion/race, etc.—are important to diversify the participant pool. In my capacity, there are often conversations about this topic. As a black female, I have no problem recruiting older AA people. I look at them as my mom, dad, aunts, and uncles, and I am at ease discussing things with them. Conversely, my co-worker literally said, “Bring on the 40-year-old white people and 70-year-olds!” I did not take offense to it because she loves older people. She always mentions that she feels like she is talking to her grandmother, and her parents are in their 40s. She is 25 and has a good pulse of what type of barriers there are for her age group, such as no one under 40 wants to return research information/questions, etc., via mail.

Miscellaneous Comments

- The workshop should emphasize that inclusion must be meaningful; research participants from across the lifespan should not simply be included in token ways.

Challenges and barriers to collection and reporting of participant-level data, including age at enrollment

- Consideration in study budgets of the additional time required to consent minors.
- Sensory impairment and changes in cognitive health, mobility, and stamina represent key challenges to reporting accurate data but also key opportunities for developing better solutions. IAL-II workshop participants should consider *both* as we work to implement the best research protocols possible.
- A continued goal of the workshop should also be to discuss the role of inclusive terminology and research journals in disseminating results. The AGS has identified significance in the language used when reporting results of aging research as an important avenue for ensuring policymakers and the public understand the key role research plays in improving how we all age.

Implementation strategies that address potential ethical challenges when including individuals under 18 years of age, frail or cognitively impaired older adults, and other vulnerable populations in clinical trials or clinical studies

- There are trust issues around participating in research within certain ethnic groups. Need to build the trust so that they trust you and before giving you their information.
- Where to best target/recruit and focus on building trust in those target groups.
- Understanding cultural norms and having researchers/staff that speak the language is important.
- Capacity to consent to study procedures is an important consideration when enrolling older adults. Many older adults with cognitive impairment may retain the capacity to consent to study participation, depending on the complexity of study procedures. Short screening measures to assess capacity to consent to minimal risk studies are available. (A handbook related to the assessment of older adults with diminished capacity developed by APA (American Psychological Association) and the American Bar Association is available here:

<https://www.apa.org/pi/aging/programs/assessment/capacity-psychologist-handbook.pdf>.) Ensuring that older adults have the capacity to consent to a study and developing procedures for assent with proxy consent are important to ensuring comprehensive representation of older adults in research studies.

- We need a living clinical directives program, similar to a living will but which is administered by healthcare providers (not lawyers) to increase accessibility and specifically address clinical research participation. This would involve an optional form for patients to fill out and keep on file with their primary physician which details whether or not they would be willing to participate in clinical research, and if so which types of research should they become frail or cognitively impaired in the future. The form could be updated every 5-10 years. This directive would allow the physicians and family members who must decide whether a patient should be enrolled in a clinical study to know the patient's wishes prior to their decline, alleviating some of the ethical concerns of enrolling a patient who may not be clearly capable of weighing the risks and benefits of trial participation at the time of enrollment.

Practice- or evidence-based strategies and necessary adaptations in recruitment/retention methods, modified safety monitoring, and how to use life stage-specific and patient-oriented outcomes in clinical trials or clinical studies

- Need capacity for long-term follow-up from pediatric into adult life phases, in order to capture outcomes with a lifespan perspective.
- Consider ways to facilitate the recruitment of healthy individuals at all stages, including families with healthy children and older adults.
- At the post-award stage, empower program officers and investigators to actively address recruitment and enrollment issues in real time, so that the intent to enroll children described in an application reflects the population that is ultimately enrolled and studied.
- Meeting presenters should adopt “older adult” or “older people” as the preferred terms for describing individuals aged 65 years and older as opposed to “seniors,” “the elderly,” and “the aged.”
- Presenters are encouraged to provide a specific age range (e.g., “older adults aged 75 to 84 years”) or to use specific qualifiers (e.g., “older American women 75 to 84 years of age”) when describing research or making recommendations about patient care or the health of the population.
- Given that much of gerontological and geriatrics research references disorders, diseases, or functional limitations that affect some older adults, this guidance highlights how not to talk about disabilities or disease. Authors should put the person first by avoiding descriptions of people as victims or using emotional terms that suggest helplessness (e.g., “afflicted with,” “suffering from,” “stricken with,” “maimed”).
- Avoid euphemistic descriptions such as “physically challenged” or “special.” This supports a person- and family-centered focus on the whole person and prevents defining an individual based on a disease or disability.

Opportunities for education and outreach to clinical researchers, community physicians, and their patients about the importance of participation in research

- There are many opportunities for patient and family education regarding the importance of research. Care of their own or their child’s, problems is built on the willingness of people before them to participate in research.
- Culture change required: we need to embed recruitment to studies within usual clinical care settings. Common issues including time pressure, lack of space, room turnover expectations, lack of privacy in waiting rooms, etc., all limit capacity of patients and providers to participate in research.

- Education of older adults and their key family members or informants will be important in the recruitment of older culturally diverse adults (African American, Caribbean, Latino/Hispanic) into clinical research.
- Consider opportunities to educate researchers about the enrollment of special populations to address the lack of expertise among some investigators in including younger populations in research.
- Need more professional research positions within the same population you are trying to recruit/retain. Researchers and/or highly qualified staff from the same population are key.
- Interfacing with the point populations via primary care: experience is that primary care physicians and practices are overwhelmed and do not have time to add a research component within scheduled visits.
- Our investigators have found it difficult to establish the necessary relationships with primary care clinics, and part of this difficulty is educating the physicians/practices on the importance of research. The primary care physicians/practices need to see the value in it in order to collaborate successfully. See this as very different in other countries where support is given to research.
- Idea: promote these relationships as primary care could benefit from collaborating on research projects. Research results then could benefit the healthcare system.
- Pace of recruitment vis-a-vis the length of the grant can be a challenge to partnering with primary care clinics.
- Research in a lab versus research out of the lab/in the community. Need to collaborate with the stakeholders in those communities and to build trust to work in the community versus in the lab.
- Key: give community something back, build a legacy, and leave something behind that they can carry on with once the study is done.
- Simple strategies such as the use of large print and training research staff to present information more slowly and in small chunks can increase older adults' ability to understand study information and comfort with participation. Reducing the number of in-person visits required for study participation can also reduce study burden. Strategies include co-timing study visits with medical appointments, conducting the study over the telephone, and making in-home visits to complete study procedures. Technology-based approaches such as video conferencing and online surveys can be used with older adults to overcome some of these barriers. However, do not assume older adults will have the equipment required to engage in technology-based procedures. For example, provision of tablets or Internet service may be required to ensure all older adults can participate. In addition, older adults may require targeted training and ongoing support to successfully use technology-based platforms. With these supports, older adults can utilize technology to complete study procedures.