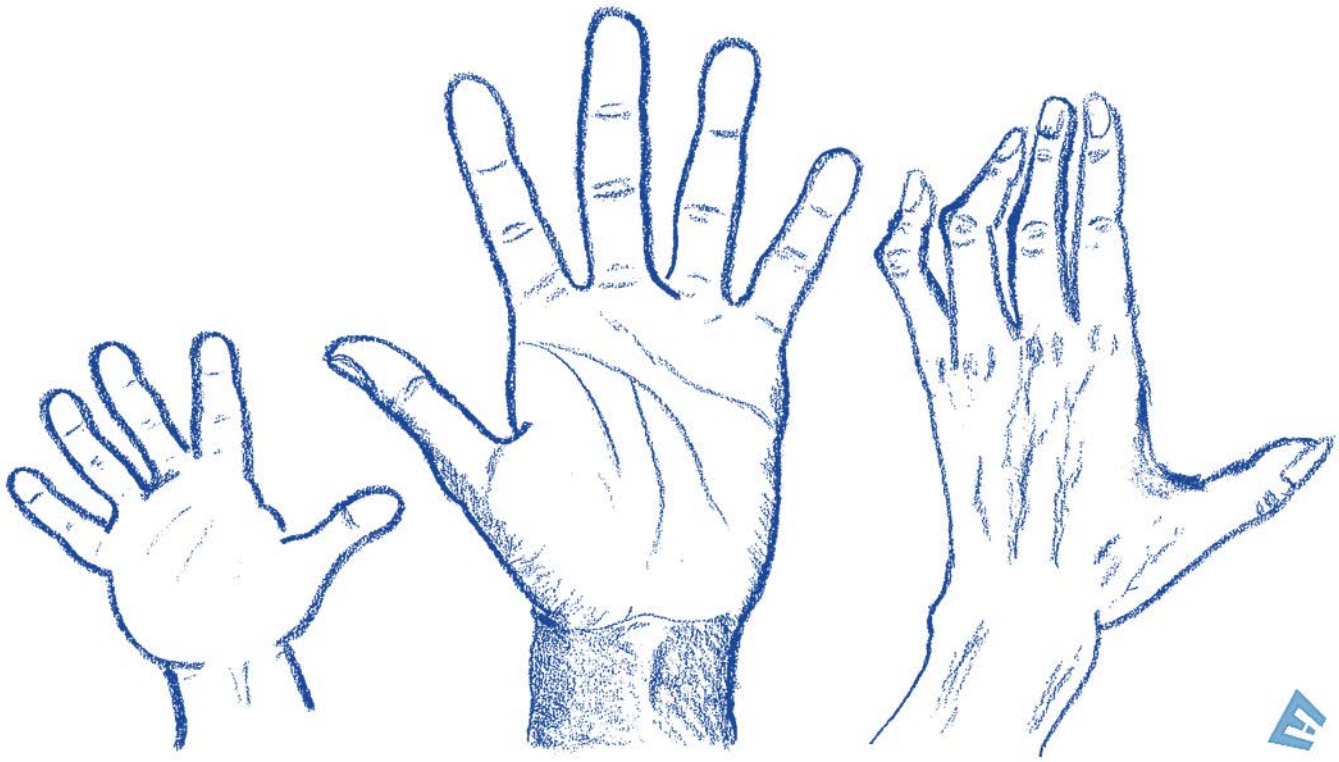
National Institutes of Health
Turning Discovery Into Health

Inclusion Across the Lifespan



June 1–2, 2017 Workshop Summary

TABLE OF CONTENTS

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 Request for Information. Prevailing themes of the workshop are highlighted within the summary and do not necessarily represent the views of the National Institutes of Health, the U.S. Department of Health and Human Services, or the U.S. government.

EXECUTIVE SUMMARY

Clinical research, including clinical trials, plays a critical role in providing the evidence-based information needed to deliver the highest quality care to people of all ages. To generate the best evidence possible and to ensure that all communities benefit equally from advances in treatment, management, or prevention of disease, it is important for clinical research and trials to include participants who adequately represent those with the disease or condition under study. However, this is often not the case. Investigators often exclude children (individuals under age 18) or older adults (individuals ages 65 and older) either explicitly, by limiting the age range of eligible participants in their exclusion criteria, or implicitly, by excluding those with co-morbid conditions or polypharmacy use, both of which are common in older populations. As a result, many interventions are inadequately tested in the very old and the very young.

Over the past 30 years, the National Institutes of Health (NIH), a major funder of clinical research and clinical trials, has instituted policies to ensure that participants in NIH-supported clinical research are representative of affected patient populations. Beginning in the 1980s and early 1990s, policies and legislation required the inclusion of women and minorities. NIH issued a policy requiring the inclusion of children in 1998 and in 2015 revised the definition of children from under 21 to under 18. Most recently, the *21st Century Cures Act*—signed into law in December 2016—requires NIH to collect data on the inclusion of participants in clinical trials by age.[1] It also called for NIH to convene a workshop focused on the inclusion of pediatric and older adult populations in clinical research, including clinical trials.[2]

On June 1–2, 2017, investigators, experts, and clinicians participated both in person and via webcast in the "Inclusion Across the Lifespan" Workshop to discuss the challenges and barriers to including children and older adults in clinical research as well as to identify strategies that would produce more age-inclusive clinical trials. In his opening remarks at the workshop, NIH Director Francis S. Collins, M.D., Ph.D., called it "an opportunity to look at our current approach to inclusion and see what we can do to be as inclusive as possible." The workshop participants were charged with considering inclusion on a broad spectrum, across government research funding agencies (GRFs), regulatory agencies, publishers, and the scientific community.

The workshop consisted of four discrete workgroups:

- Study Population
- Study Design and Metrics
- Ethical Challenges and the Enrollment of Vulnerable Populations
- Data Collection and Reporting to Support Age-Specific and Subgroup Analyses

Each workgroup met to discuss current issues and challenges in facilitating inclusion within clinical research and to develop strategies for overcoming these issues. Additionally, the NIH issued a Request for Information (RFI) on Inclusion in Clinical Research Across the Lifespan (NOT-OD-17-059) to augment information gathered during the workshop. The RFI was published on April 26, 2017 and was open for comment through June 30, 2017.

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[1] U.S. Congress. *H.R. 34: 21st Century Cures Act.* 2016. Retrieved from https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf

[2] Lockett, Jaron. "Let's talk about inclusion of all ages in research." Inside NIA Blog. April 26, 2017.

Challenges and Barriers to Inclusion

As part of their efforts, each of the four workgroups examined the challenges and barriers that can prevent inclusion of children and older adults in clinical research.

Study Population

The Study Population workgroup identified four main challenge areas:

1. **Inclusion/Exclusion Criteria:** Including older and younger populations in clinical research raises a number of challenges for the investigator, such as balancing the need for a representative study population against potential risks to participants who may be uniquely vulnerable. Additionally, including children and cognitively impaired older adults may add to the administrative burden and, if limited numbers are recruited, may affect the ability to implement traditional study designs.
2. **Recruitment, Enrollment, and Retention:** Investigators may lack experience working with the very old or very young, and children and older adults (particularly if cognitively impaired or otherwise disabled) may encounter practical barriers to participation (e.g., inability to drive to an appointment). Obtaining legal consent may also be an issue in these populations.
3. **Data Analysis and Study Interpretation:** Detailed information on the number of older adults and children in clinical trials is not easily accessible, which limits interpretation of trial outcomes for different age groups.
4. **Government Requirements:** Many, if not most, GRFs do not require inclusion of older adults and generally do not monitor age distribution of participants in clinical trials. Guidance is limited, and the policies that do exist have not been evaluated for effectiveness.

Ethical Challenges and the Enrollment of Vulnerable Populations

Currently, some rules to protect vulnerable populations may contribute to their underrepresentation in research, even though these groups stand to benefit from participation and may have great impact on furthering scientific understanding. To mitigate this disconnect, a culture shift is needed whereby *protection from research* is replaced by *protection through research*. The members of this workgroup indicated that the ultimate assessment of an individual's vulnerability should be based on his or her cognitive ability as well as capacity to make autonomous decisions and provide informed consent. This vulnerability may necessitate additional safeguards or may justify exclusion if there are safety concerns.

Study Design and Metrics

The Study Design and Metrics workgroup identified the challenges that investigators face when designing studies and how these challenges can impact clinical trials. For example, age may not be considered a variable in study design, data analysis, or reporting. Additionally, researchers are not required to report exact ages of participants, and guidelines for inclusion of older adults do not exist. Larger sample sizes mean higher study costs, and the restrictions of inclusion and exclusion criteria can create a disincentive for including populations. For these reasons, many investigators are reluctant to include the very old or the very young in their studies.

Data Collection and Reporting to Support Age-Specific and Subgroup Analyses

Clinical trial researchers do not typically report information on population prevalence by age or other demographics, nor do they consistently report adequate information on those participating in trials with

respect to outcomes by age. Part of this issue stems from a lack of standard reporting guidelines for journal editors, as well as a lack of a central data repository to facilitate meta-analyses.

Strategies for Supporting Inclusion Across the Life Span

The workgroups also generated a number of potential strategies to enhance inclusion of younger and older populations in clinical research and provide additional age-specific data in publications. Some of these suggestions were directed at NIH and other GRFs, others were targeted at investigators and the scientific community, and still others were intended more broadly. Overall, these strategies fell into five general categories:

1. Participant Recruitment and Consent
2. Study Design
3. Application and Review Process
4. Data Collection, Analysis, and Reporting
5. Training and Education

Participant Recruitment and Consent

- Involve stakeholders, including affected populations, in planning for study representativeness.
- Engage experts, community representatives, and clinicians to help identify, recruit, and retain populations needed for a study.
- Provide resources and increased support to assist with recruitment of children and older adults.
- Adapt studies to accommodate participants with impaired function or disabilities.
- Define the unique abilities of adolescents to provide consent.
- Design studies for ease of participants.
- Use innovative methods to target recruitment efforts.
- Use a universal assessment to assess a participant's capacity to provide consent.
- Develop a more robust assent process for individuals without the cognitive function needed to provide consent.
- Provide more detailed guidance for Institutional Review Boards (IRBs) related to assessing appropriateness of non-familial consent.

Study Design

- Address challenges in balancing the inclusion of a representative sample of the population with the need to minimize known risks and ethical considerations of study participants.
- Recognize that the study protocol or structure may make it difficult for certain populations to participate.
- Address the issue that complete information on the population prevalence of the disease or condition by age or other demographic variables is not always presented in the grant application.
- Ensure that inclusion of pediatric and older adult populations yields scientific value.
- Consider alternative study designs to allow for greater inclusion.

Application and Review Process

- Consider inclusion in grant application structures.

- Integrate inclusion into existing Significance and Approach scored review criteria.
- Consider inclusion of peer reviewers with expertise in the proposed study populations in review panels, as this may inform assessment of proposed inclusion/exclusion criteria and study design, methods, and data analysis.

Data Collection, Analysis, and Reporting

- Consider standardizing demographic data collection and reporting guidelines across the scientific community to enhance the availability of age information and facilitate analyses.
- Investigate requiring reporting by age and monitoring inclusion of children and older persons in clinical trials.
- Pursue standardization of age groupings for results reporting to allow more meaningful interpretation of results.
- Adjust age-range reporting in published reports of clinical trials to add clarity to clinical research data.
- Consider automatic data collection to increase efficiency.
- Include age-related outcomes or comprehensive information about the age of study participants in clinical trial publications, as appropriate.
- Increase data availability and transparency to allow for secondary and meta-analyses.

Training and Education

- Implement widespread changes to language used to define vulnerable and underrepresented groups to avoid alienation.
- Develop checklists, guidance, and training for investigators, reviewers, and IRB members to increase awareness and understanding of policies on inclusion and exclusion.
- Include appropriate expertise for the populations being studied to facilitate recruitment and retention of study participants.

RECURRENT THEMES

Several common themes were identified by both the workshop workgroups and in the responses to the RFI.[3] The following is a synthesis of these recurrent themes; a more detailed discussion of the input of each workgroup is included in the sections that follow.

Age Inclusivity

The workshop participants and those submitting responses to the RFI agree that GRFs should review current policies on the inclusion of pediatric and older adult populations in clinical research, including clinical trials, to determine what updates are needed to allow clinical research "to be as inclusive as possible." This includes reviewing and updating justifiable reasons for exclusion of pediatric and older adult populations in clinical research (e.g., define safeguards needed to address vulnerabilities and allow for inclusion under specified circumstances). Many workshop attendees expressed the need for the culture within the scientific community to shift to one more focused on inclusion of diverse groups of participants in clinical research and trials. By establishing inclusion as the default position, study design

[3] Request for Information (RFI) on Inclusion in Clinical Research Across the Lifespan (NOT-OD-17-059). Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-059.html

can focus on identifying ways to adopt responsible inclusion. **Rather than trying to reduce the risk to vulnerable populations from research, the scientific community should consider how these populations might benefit from greater participation in such research, including the generation of efficacy data that are applicable to them.**

Similarly, many workshop participants noted that some populations may be excluded from clinical research and trials because their participation can make conducting research more complex (e.g., physiological changes in children, comorbidities or organ decline in older adults). As a result, these populations often are viewed as being at greater risk for adverse effects and excluded from trials. However, this risk is difficult to assess, particularly when these individuals commonly have the conditions of interest and could therefore significantly benefit from new therapies. Without adequate inclusion in clinical trials, data cannot be captured regarding actual risks and benefits of interventions that are critical to informing care for these populations.

Analyses presented during the workshop demonstrated that not only are there fewer pediatric clinical trials relative to the overall increase in the number of trials registered in ClinicalTrials.gov but a discrepancy also exists between intent to include and actual inclusion of children in trials (see Appendix IV, Dr. Diana Bianchi's presentation summary). Other data demonstrated that while the prevalence of common diseases or conditions may be highest in older adult populations, those populations often are not proportionately included in trials (see Appendix IV, Dr. Florence Bourgeois' presentation summary). Currently, age is not consistently collected as part of the official inclusion record, nor is it required for human subjects reporting beyond simply "over/under the age of 18", limiting the ability to monitor the age distribution across grant portfolios.

While U.S. Department of Health and Human Services (HHS) Regulatory Requirement Protections (Subpart D) require justification for the exclusion of children in HHS-supported clinical research, similar guidelines do not exist for the exclusion of older adults. Without such guidelines for the justification of exclusion for older adults, investigators can omit them without scientifically sound justification, and reviewers are less likely to judge the proposed study population as inadequate.

Age is not a stand-alone indicator or a valid justification for exclusion. The two most clear-cut and acceptable justifications for exclusion of particular ages are that the disease or condition does not exist within the age group or that the study presents an unacceptable risk to the participant. However, exclusion based on age is appropriate when studies target a specific age group by design (e.g., a clinical trial designed to promote self-monitoring of blood glucose levels in adolescents with Type 1 diabetes).

Vulnerability

Defining what makes an individual or population vulnerable is complex. Vulnerable populations can be loosely defined as individuals at increased risk for undue influence, coercion, or exploitation. Protecting the rights and welfare of vulnerable groups—which include children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons as defined in the revised Common Rule regulations[4] scheduled to go into effect in 2018—requires additional safeguards.

Concerns regarding vulnerability identified at the workshop include the following:

[4] Common Rule regulations (2009, January 15). Retrieved from: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

- Consideration of cognitive function as well as the ability to make autonomous decisions and provide informed consent when assessing vulnerability.
- Potential negative perceptions associated with referring to an entire population as "vulnerable."
- The importance of avoiding assumptions about an individual's ability or interest to enroll in clinical studies and trials based on the investigator's assessment of an individual's or group's need for protection.

Whenever it is safe to do so, studies should be adapted to allow for inclusion of children and older adults with impaired physical or cognitive function or disabilities to ensure researchers can acquire data on, and generalize their findings to, these populations. Appropriate scientific review and monitoring processes, as well as necessary pediatric and aging expertise, are required for studies that include these populations to ensure appropriate use of inclusion/exclusion criteria.

NEXT STEPS

The *21st Century Cures Act* requires the NIH Director to review the themes identified at this workshop to determine what, if any, changes to NIH policies are needed. Because the workshop was configured to address the overall scientific barriers to and opportunities for the inclusion of younger and older populations in clinical studies, the ideas generated may be useful not only to NIH and other GRFs but also to the broader scientific community, including individual investigators, funding agencies, regulatory agencies, and scientific publishers. It is the hope of the workshop participants that this is the start of a broad change in approaches to the inclusion of younger and older populations in clinical research.

SUMMARY OF WORKGROUP DISCUSSIONS

For the June 2017 "Inclusion Across the Lifespan" Workshop, four workgroups were established to examine specific topics related to inclusion, including study population, study designs and metrics, ethical challenges in the enrollment of vulnerable populations, and data collection and reporting to support age-specific and subgroup analyses.

Prior to the workshop, core members of each workgroup met via conference call a minimum of three times, and used their own approaches to address the assigned topics. At the workshop, the workgroups were expanded to facilitate broader discussions on the assigned topics. The information gathered during the conference calls, discussions during in-person breakout sessions at the workshop, presentations on the second day of the workshop, and any other materials provided by workgroup members are summarized in this section, with a focus on the challenges and barriers identified regarding inclusion, and the workgroups' proposed strategies to address them.

STUDY POPULATION

Co-Chairs: Cynthia Boyd, M.D., M.P.H., Johns Hopkins University School of Medicine and Bloomberg School of Public Health; Tyra Bryant-Stephens, M.D., Children's Hospital of Philadelphia; and Michael Cohen-Wolkowiez, M.D., Ph.D., Duke University School of Medicine

Overview

The Study Population Workgroup was tasked with examining inclusion and exclusion criteria, age restrictions, and how to ensure representativeness of study populations in clinical trials.

The workgroup identified four main topic areas: 1) Inclusion and Exclusion Criteria; 2) Recruitment, Enrollment, and Retention; 3) Data Analysis and Study Interpretation; and 4) Government Requirements. For each topic, the workgroup identified challenges and strategies to address them.

Overarching Proposed Strategies

- **Provide training and education for investigators**. The training should focus on age considerations in inclusion and exclusion criteria, study populations, and enrollment, as well as policies on inclusion and exclusion criteria and enrollment. This training may be considered a key requirement in career development awards.
- **Provide resources, including guidance documents and funding allowances, for recruitment, enrollment, and retention**. Increased funding for institutions should be considered to aid in recruiting underrepresented populations. Funding and regulatory agencies should revise policies and guidance documents, as needed, to address inclusion of children and older adults in clinical trials. Best practices for recruiting and retaining pediatric and older populations should be shared more broadly across the scientific community.
- **Leverage current NIH infrastructure to provide assistance**. Existing structures, such as the Clinical and Translational Science Awards (CTSA) Program and Trial Innovation Centers (TICs) grants, could be used to build a consultant network that investigators can access.
- **Revise grant applications to include requirements**. Require grant applications for clinical studies and trials to include justifications for any age exclusions; a plan for enrollment of study

population; literature on the characteristics of affected populations in terms of age, comorbidities, or other characteristics; a description of how investigators will access the study population; and self-monitor enrollment numbers to ensure adequate representation across the age span specified in the target enrollment tables.

- **Consider legislation or policies to require the same inclusions and justifications for older adults in clinical trials as for children**. NIH has previously issued policies requiring the inclusion of children.[5] Legislation, such as after the Pediatric Research Equity Act (PREA)[6], authorizes the U.S. Food and Drug Administration (FDA) to require drug companies to study their products in children, using the same drug and for the same purpose as in the adult population. Currently, no policy or legislation provides the same inclusions for older adults.

Inclusion and Exclusion Criteria

The study population defined by the eligibility criteria should be representative of the population of people with the condition being studied. However, eligibility criteria often include arbitrary lower or upper age limits that exclude children and adolescents or older adults without a clear justification. These restrictions may reflect an altruistic intention to protect younger or older people, lack of expertise of the investigator, or limited access to pediatric or older populations. The inclusion and exclusion criteria included in the eligibility criteria should be objective and written in clear, concise language, and investigators should provide a scientific justification for each criterion.

Challenges and Barriers

- **Investigators must balance including a representative sample of the population while minimizing known risks and ethical considerations of study participants**. This can often lead to the exclusion of children and older adults who are considered more at-risk.
- **The restrictions in inclusion and exclusion criteria can create a disincentive for including populations that may be viewed as vulnerable**. Examples of these criteria include co-existing condition restrictions, age restrictions, and laboratory restrictions. The sheer number of exclusion criteria can also act as a disincentive. These restrictions can also inadvertently limit race/ethnicity and gender representation in the population.
- **Children and older adults often require additional consideration for the informed consent process**. This may be the result of physical or cognitive impairment in older adults and physiologic, physical, cognitive, and developmental changes in children.
- **Investigators need to balance efficacy and effectiveness**. Common exclusion criteria include age restrictions, comorbid conditions, and issues around the balance of efficacy vs. effectiveness of the intervention.
- **Investigators may reuse prior eligibility criteria in new studies**. The practice of reusing eligibility criteria from a previously designed protocol instead of developing a new protocol can promulgate unnecessary restrictions on enrollments.

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[5] Review and Award Codes for the NIH Inclusion of Children Policy. Retrieved from https://grants.nih.gov/grants/funding/children/pol_children_codes.htm

[6] Pediatric Research Equity Act (PREA) (2003, December 3). Retrieved from https://www.congress.gov/108/plaws/publ155/PLAW-108publ155.pdf

- **Limited numbers of individuals with the disease or condition affect the ability to implement traditional study designs**.

Proposed Strategies

- **Investigators should describe the epidemiology of disease or condition across age, comorbidity, and racial/ethnic characteristics in study design**. Investigators should review the epidemiology and then develop strategies for inclusion based on the results.
- **Any restrictions based on age, comorbidity, or gender/sex should be well-justified**. This will help address the challenge of balancing efficacy vs. effectiveness.
- **Technical assistance to sponsors and investigators could help them include children and older adults in clinical trials**. This could include providing opportunities to consult with research experts in older adult and pediatric populations.
- **Incentives and best practice strategies for researchers could help enroll underrepresented populations**. Examples include targeting Requests for Applications (RFAs) to address gaps in knowledge based on age, race, and gender, or sharing information and expertise on the best way to address recruitment and retention.
- **Add age to application enrollment tables**. Creating a place for the data to be collected would allow for better reporting and data collection, and would require researchers to consider age during the study design process.

Acceptable Justifications for Exclusion

The workgroup identified two acceptable justifications for excluding participants from a clinical study:

1) The study presents an unacceptable risk to the study participant relative to the knowledge gained from the study, and additional studies are needed to develop a safety profile before studying in pediatrics populations and older adults.
2) The disease or condition does not occur in the age group.

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. For example, a study may not explicitly list age-based exclusion of older participants, but they may be inadequately represented because of challenging logistics related to obtaining consent or barriers to retention across multiple follow-up appointments and procedures.[7]

Challenges and Barriers

- **Study structure and protocols may limit participants' ability to join**. Particular characteristics of a study population — such as degree of mobility, comorbidities, literacy, schooling, co-medications, and other psychosocial stressors — can impede enrollment and ongoing participation.

[7] Bourgeois FT, Orenstein L, Ballakur S, Mandl KD, Ioannidis JP. Exclusion of Elderly People from Randomized Clinical Trials of Drugs for Ischemic Heart Disease. *Journal of the American Geriatrics Society*. 2017; and Sardar MR, Badri M, Prince CT, Seltzer J, Kowey PR. Underrepresentation of women, elderly patients, and racial minorities in the randomized trials used for cardiovascular guidelines. *JAMA Intern Med*. 2014; 174(11):1868-1870.

- A limited number of patients with the disease or condition of interest can mean needing resources for reaching these patients across multiple sites and countries, increasing enrollment challenges.

- **Lack of stratification of enrollment participants.** Stratification by age would help ensure a representative population across the lifespan is enrolled in clinical study.
- **Challenges with obtaining consent**. Invasive procedures and assessments outside of standard of clinical care reduce consent rates; this may be a greater barrier for older adults and children. The risk of study procedures or drugs in children and older adults may also limit consent or ability to recruit/retain subjects.
    - Literacy and language requirements affect the ability for consent and follow-up study procedures/assessments. For children and older adults, it is important to consider how these requirements also could affect a legal guardian or proxy.
- **Lack of experienced investigators**. Investigators may have limited experience or knowledge on the best ways to identify, recruit, and retain populations needed for the study.
- **Lack of innovative enrollment techniques and new communication tools**. This can limit the ability for children and older adults to stay engaged in the study.
- **Attrition that occurs during follow-up periods**. Studies that require in-person follow-up of study participants increase the risk for attrition, particularly for older adults and children. For example, older adults are more likely than younger adults to have worsening physical function or other health issues that make in-person follow-up challenging. Older adults may also be on a fixed income, making it difficult for them to participate if there are travel or accommodation costs. Children enrolled in hospital studies who improve may become increasingly involved in school and their communities.

Proposed Strategies

- **Engage experts to assist in study design**. Engage pediatric and geriatric clinical trial specialists and biostatisticians at an early stage in the design and development of research protocols to gain their expertise and insights into approaches for identifying and enrolling children and older adults.
- **Design studies for ease of participants rather than investigators**. For example, mobility may be a major challenge for older adults or children to participate in enrollment and follow-up visits. To address this challenge, studies could be designed to use home visits, mobile units with research personnel to perform assessments and procedures at the location of the study participants, or accessible technologies that promote easier enrollment and follow-up data collection.
    - Adaptive trial designs may be useful to increase inclusion among specific participant groups. This would provide researchers more flexibility to recruit and retain underrepresented populations, and adjust the study as needed based on outcomes.

- **Use of innovative methods can improve recruitment of sub populations to ensure representativeness**.
  - New (e.g., social media, telemedicine) and traditional (e.g., phone) communication tools can be adapted for use by the focal study population or their caregivers and leveraged to engage and retain study participants.
  - Information about open clinical trials can be made available through EHRs and brochures or other communications materials available in waiting rooms (keeping ethics in mind, such that potential subjects do not feel coerced).
  - Leverage clinical trial networks, multi-site consortiums, and research funder resources (e.g., CTSA TICs) to find eligible participants with the disease or condition of interest for clinical studies.
  - Develop community engagement expertise and encourage funding agency support to provide infrastructure for community engagement.
- **Consider increased funding to support recruitment and retention of more inclusive study populations**. Achieving the correct population for a study may require multiple sites or multiple countries. If new techniques are used, such as mobile sites, this could increase costs.
- **Develop consent strategies to ensure inclusion.** Consent strategies should accommodate and incorporate age, language, disabilities, mobility, and literacy of populations across the age span.
- **Develop methods to ensure safety for participants who may be at higher risk during studies**. This could include minimal risk methods incorporated into the study design or individualized safety monitoring for people at higher risk.
  - Children and older adults should be a part of safety and efficacy studies if the use could apply to them.
  - Study interventions should be tailored to the needs of the study populations (e.g., liquid formulations, small tablet size) to facilitate administration of the intervention, as well as long-term compliance and retention.
- **Investigators should consider outcome measures that can be collected from proxy respondents to minimize loss to follow-up over time**.

Data Analysis and Study Interpretation

Appropriate data analysis and interpretation is critical to the synthesis of trial evidence and its application in treating patients. This includes careful consideration of certain sub-populations in the analysis, including children and older adults. The study of specific sub-populations 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.

Challenges and Barriers

- **Detailed information on the number of children and older adults in clinical trials is not easily accessible**. Trial publications typically do not include preplanned sub-group analysis of children and older adults, nor do they report the number of children and older adults included. This lack of reporting further reduces the clinical trial evidence available to guide clinical care of children and older adults.

- **Treatment effects from highly selective trials cannot be extended to populations that were not included.** The average effect of a clinical trial may not apply to all populations included in a pragmatic trial, and analytic strategies are not used to recognize issues with average effects vs. heterogeneity of effect.
- **Using age as the sole basis for analysis does not tell the entire story**. Health status can vary widely in participants who are the same age.
- **Attrition can result in incomplete data**. Studies that require multiple follow-up visits may have higher attrition rates, resulting in missing data, which can be problematic for effective analysis.

Proposed Strategies

- **Require reporting of key data**. FDA regulations and industry and federal government guidelines should encourage researchers to report by age, sex, race/ethnicity, and co-existing conditions.
- **Require reporting of study limitations**. Investigators should be required to inform funding agencies and publish limitations in generalizing study results when the population is not representative of the population with the disease or condition.[8]
- **Publications should include broader information on study enrollment**. Dissemination strategies should appropriately represent the actual study population (avoid extrapolation). Publications should include a broader range of information on who was enrolled in the studies in terms of age, comorbidities, and other markers of health status.
- **Evidence synthesis methods must assess the body of evidence in terms of the ability to generalize**. Appropriate analytic strategies can help maximize the potential knowledge gained from preplanned subgroups or stratified recruitment; multivariable risk models can help, highlighting the need for appropriately understanding risk across the life span (age can be continuous).
  - Stratification is necessary in analyzing data to expand the age range. But researchers must balance the need to compare subgroups with representing the average treatment effect for the population.

Government Requirements

In 1993, U.S. Congress passed the National Institutes of Health Revitalization Act of 1993[9], directing the NIH to establish guidelines to ensure the inclusion of women and minorities in NIH-supported clinical research. The statute directed the NIH to conduct outreach programs to support the recruitment of women and members of minority groups as participants in clinical studies and established clear criteria for exceptions to enrollment requirements. Since then, the statute has been amended to also provide guidance on the analysis and reporting of gender and racial differences.

These legislative requirements are a major advance in ensuring representative study populations, but notably do not address age-based exclusion from clinical studies and trials. In contrast, other agencies have recognized the need for such guidance. A guideline developed by the FDA in 1989 states that

[8] Weiss CO, Varadhan R, Puhan MA, et al. Multimorbidity and evidence generation. *Journal of general internal medicine*. 2014; 29(4):653-660; and Boyd CM, Kent DM. Evidence-based medicine and the hard problem of multimorbidity. *Journal of general internal medicine*. 2014; 29(4):552-553.

[9] National Institutes of Health Revitalization Act (1993, June 10). Retrieved from https://www.congress.gov/103/bills/s1/BILLS-103s1enr.pdf

"there is no good basis for the exclusion of patients on the basis of age alone, or because of the presence of any concomitant illness or medication, unless there is reason to believe that the concomitant illness or medication will endanger the patient or lead to confusion in interpreting the results of the study."[10] The International Conference of Harmonization also published a guideline in 1993 recommending that older patients be included in clinical trials for drugs that are likely to be relevant in this population.[11]

With respect to pediatric populations, since 1998 the NIH has had a policy that aims "to increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders and conditions that affect adults and may also affect children."[12] Sponsors must justify the age range of proposed participants and why children are being excluded. As Dr. Diana Bianchi noted in her presentation, however, based on clinical trials registered in ClinicalTrials.gov during the 10-year period from 2006 to 2017, only 19 percent of interventional studies sponsored by the NIH were open to subjects younger than 18, indicating that most trials provide justification for enrolling only adults (see Appendix IV). Currently, there are insufficient data to properly assess the effectiveness of the NIH policy on the inclusion of children.

There have been several legislative initiatives to increase the study of medicines in children, notably the Best Pharmaceuticals for Children Act (BPCA)[13], passed in 2002, and the Pediatric Research Equity Act (PREA)[14], enacted in 2003. These programs have increased both the pre-market and post-market study of pharmaceuticals in children and several indicators point to the considerable progress in pediatric drug development that has been achieved under these initiatives.[15] However, a number of limitations remain. BPCA is a voluntary program and typically applies to drugs that have already been introduced on the market and may already be used in children without pediatric safety and efficacy data. PREA, while mandatory and applicable to medicines prior to market availability, is compromised by broad exemptions and waivers and delays in the completion of mandated pediatric studies.[16] For example, PREA requirements do not pertain to orphan drugs—which constituted 41 percent of all novel drugs approved by the FDA in 2016—nor to classes of drugs typically used to treat diseases or conditions that occur primarily in adults, even if the same molecular targets apply to pediatric diseases or conditions. Delays are also pervasive, with as many as 55 percent of PREA studies receiving deadline extensions.[17]

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[10] Food and Drug Administration Center for Drug Evaluation and Research. Guideline for the study of drugs likely to be used in the elderly. 1989.

[11] International Conference on Harmonisation of Technical Requirements for Regulation of Pharmaceuticals for Human Use. Studies in support of special populations: Geriatrics E7. 1993; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Step4/E7_Guideline.pdf. Accessed September 1, 2015.

[12] National Institutes of Health. Inclusion of Children - Policy Implementation. 2016; https://grants.nih.gov/grants/funding/children/children.htm. Accessed May 11, 2017.

[13] Best Pharmaceuticals for Children Act (BPCA) -- https://www.congress.gov/107/plaws/publ109/PLAW-107publ109.pdf

[14] Pediatric Research Equity Act (PREA) -- https://www.congress.gov/108/plaws/publ155/PLAW-108publ155.pdf

[15] FDA Blog on progress in pediatric drug development -- https://blogs.fda.gov/fdavoice/index.php/tag/pediatric-research-equity-act-prea/

[16] Bourgeois FT, Hwang TJ. The Pediatric Research Equity Act Moves Into Adolescence. *Jama*. 2017; 317(3):259-260.

[17] Ibid.

Challenges and Barriers

- **Lack of requirements for older adult inclusion**. Most GRFs have no requirement for inclusion of older adults and generally do not monitor the age distribution of participants enrolled in trials.
- **Absence of reporting guidance**. The scientific community lacks guidelines or requirements around the reporting of trial enrollment of children and older adult participants.
- **Need for analysis on effectiveness of policies**. There is a lack of information on whether the 1998 NIH policy to increase the participation of children in research has resulted in any increases.
- **Existing mechanisms have led to a lack of available information**. Deferrals and waivers for pediatric studies under federal legislation limit availability of efficacy, safety, and dosing data in this population.

Proposed Strategies

- **Investigators should include a plan for the focal study population and comparison to epidemiological distributions** (e.g., in enrollment tables) by age, gender, race, and co-existing conditions. Specific age requirements and justification need reinforcement in the scientific review and incorporation into the research plan.
- **Consider incentivizing enrollment for certain patient populations based on age, gender, and race**. This could be promulgated through legislative actions or GRF policies, or use of RFAs for certain age groups. Federal agencies could consider increased funding for study of recruitment and accrual of older populations.
- **Encourage reporting of federally-funded clinical research by age and tracking of inclusion of children and older persons in clinical trials to inform next steps**. Clinical study reports would be enhanced by enrollment information for children and older adults as well as sub-analyses of these populations whenever possible to provide better clinical data on the safety and efficacy of interventions in children and older adults.
- **Evaluate current GRF and regulatory agency policies and guidance documents to assess effectiveness in inclusion of children and older people in clinical trials.** This type of collaboration could ensure there is an adequate study of drugs used in older adults and require the drug industry to create liquid formulations earlier in trials to improve inclusion.

STUDY DESIGN AND METRICS

Co-Chairs: Heather Allore, Ph.D., Yale University School of Medicine; and Scott Denne, M.D., Indiana University School of Medicine

Overview

The Study Design and Metrics Workgroup examined how to design studies to be more inclusive across all ages, using input from the entire study population (or from representatives such as caregivers or parents). The workgroup also identified challenges that investigators face when designing studies and how these challenges can impact clinical trials.

The workgroup discussed reporting requirements and the role that researchers, reviewers, and policymakers have in encouraging data collection from a larger sample of participants in all reaches of

the lifespan. In addition to increasing the body of data available, the metrics themselves should be harmonized to make storing data easy and increase the interoperability of data.

At a fundamental level, studies are optimally designed to show the basis for including certain participants instead of a justification for excluding certain populations. Investigators, IRBs, and reviewers should show why someone should be excluded, and the community would benefit from more education on the topic.

Challenges and Barriers

- **The higher costs for larger sample sizes and limited funding could prove to be significant barriers**. Reviewers and GRFs should be cognizant of this issue. There are times when it is simply difficult to recruit certain groups of participants to be a part of the sample, and there is concern that a mandated inclusion policy could lead to fewer trials (especially if a larger sample size is needed as a result).
  - A narrow sample would be harder to show as being beneficial at the large scale. There is a benefit to researchers having a large sample, but it can often be cost-prohibitive.
- **Age is currently not considered a variable in study design, data analysis, or reporting**. This can result in data not being collected or analyzed at the sub-group level.
- **Pediatric studies are not required to report the exact age of a child if he/she is under 18 years old** (currently, "under 18" is an acceptable metric). Reporting on an "under 18" population does not take into account the wide variability in physiological, cognitive, and behavioral development from birth to adolescence, nor does it consider variation within each developmental stage.
- **Guidelines tailored to the specific needs of older adults have not been established**. This is because the special needs of this population have not been fully appreciated since it has generally been assumed that no differences existed for older adults in trials.
  - The FDA utilized the methodology of bridging data to gather information on dosing in the pediatric populations. Pharmacokinetics or pharmacodynamics metabolic changes in development could apply to geriatric populations as well, using similar methodologies.
- **Previous illnesses or other conditions could result in selection bias against older adults**. A challenge with older populations could be that there is naturally some selection bias among those who survived other diseases or conditions, leaving them potentially susceptible to other illnesses and could complicate the study results.
- **Analysis is not conducted on age subgroups**. Analysis of participant age in clinical trials is further complicated by the fact that while investigators may collect this information, it is typically reported in the aggregate, with the raw data unavailable to GRFs and rarely published.
- **Some analyses tend to be underpowered**. Fewer variables may make analysis easier. As such, it can be harder to analyze and explain how a treatment/trial affects older/younger patients.

Proposed Strategies

The workgroup developed proposed strategies for more inclusive study design; ensuring a representative study population; expertise needed to improve study design; and metrics to assist in meeting the goal of being more age-inclusive.

Study Design

- **Any age exclusion should be fully justified**. This requirement currently exists for children, but not for older adults. There should be no arbitrary upper age limits in the design of trials. Upper age limits on studies should not be an arbitrary number, and studies must provide a justification for doing so. The GRF application should allow for the explanation of exclusion to be included.
  - This would place emphasis on understanding more practical, real-world conditions of diseases, rather than identifying factors that would exclude participants.
  - Minimize acceptable exclusion criteria to balance scientific justification vs. generalizability. Peer review should consider generalizability as a strength.
  - Pragmatic trials that are generalizable to the population and include multivariable risk-based analytic methods are needed to address heterogeneity.
- **Consider the age distribution of the disease/condition/study topic in the general population**. This should be done as part of the study design and recruitment plan to ensure a representative population. This will also help direct purposeful recruitment to better match and represent the population being studied.
  - This is not a small commitment, and mandating it could potentially set researchers up for failure, based on the cost requirements. However, it is an important principle that can and should be achieved on the front end. One option is to include it as part of the application or write it into the proposal.
- **Include age as a standard variable**. Similar to sex/gender, age should be considered a standard variable in research design, analysis, and reporting.
- **Involve key stakeholders in planning study design and participation**. For older adults, this includes older adults with the disease/condition as well as their caregivers. For children, this could include the children themselves and their parents. Working closely with stakeholders during the study design can help anticipate and avoid potential barriers to recruitment and retention.
- **Design interventional studies to address the focal population**. For example, interventional studies in children should be designed specifically for children. Similar considerations should be made for older adults. This should be done with the recognition that there are certain exceptions for rare diseases/conditions and other factors.

Ensuring a Representative Study Population

- **Examine recruitment strategies.** Studies should use purposeful recruitment that represents the population being studied, and GRFs should work with stakeholders to understand potential barriers to recruitment and retention.
  - Currently, England and France mandate including participants in the study process from start to finish. Their progress as well as that of other international policies/programs doing similar work should be examined.
  - Consider proactive recruitment strategies, including working directly with older or younger populations and going out into communities.
  - Create a panel for pre-review of clinical studies and trials to ensure they include representative populations. This would also mean that it would not be the responsibility of the investigator to search for/include additional research staff with expertise in epidemiology and demography.

- **Conduct an evaluation of inclusiveness of GRF-sponsored studies.** An evaluation across all GRFs could assess inclusivity by comparing anticipated enrollment in the application vs. actual enrollment vs. published enrollment.
- **Consider alternative study designs to allow for greater inclusion**. There are a number of different trial types, such as adaptive trials (i.e., sequential, multiple assignment, randomized trials) and platform trials (i.e., trials with flexible features such as dropping treatments for futility, declaring one or more treatments superior, or adding new treatments to be tested during the course of a trial) that could allow for greater inclusion.
  - Consider preference and other designs for non-drug interventions.

Expertise Needed

- **Appropriate expertise for the population being studied**. Research teams must include appropriate pediatric expertise for studies that include children and expertise in aging for studies involving older adults.
- **Expertise needed as part of review**. Reviewer expertise in these areas should be available for evaluations of study design.
- **Experience in recruiting and retaining specific study populations**. The recruitment plan should be explicit in how specific study populations will be recruited, enrolled, and retained, requiring expertise in these areas.

Data Collection and Reporting

- **Facilitate reporting on specific ages**—particularly in pediatric populations—which would better consider the wide variability in physiological, cognitive, and behavioral development from birth to adolescence, and the variation within each developmental stage. This information would be valuable for informing future trials.
- **Revise and simplify data collection and reporting.** Create uniform collection forms for clinical trials that include standard information such as data on demographics and common comorbid conditions. The reporting structure should also be standardized across GRFs and journals.
  - Expand information available on underrepresented populations by making greater use of observational data.
- **Provide greater access and transparency of data**. Make government-funded clinical trials data and applicable bio-specimens, if any, available publicly.

Metrics

- **Collect age-specific and other appropriate data with race/ethnicity data in GRF reporting requirements**.

  As an example, age categories could be grouped as follows:
  - 0 – 28 days
  - 29 days – 364 days
  - 1 – 5 years
  - 6 – 12 years
  - 13 – 15 years
  - 16 – 18 years
  - 19 – 21 years
  - 22 – 25 years
  - 10 year increments up to 65 years
  - 65+ in five-year increments

  As appropriate, the following variables should also be collected:
  - Functional status
  - SES

- Relevant comorbidities
- Gestational age
- Assessment of physiological age
- Assessment of functional outcomes

> **Increase awareness of existing metrics**. GRFs should provide guidance and information on existing data sets, including metrics currently being collected. Making data widely available allows studies to identify gaps in existing work/recorded data that could be addressed.

Ethical Challenges and the Enrollment of Vulnerable Populations

Co-Chairs: Tamera Coyne-Beasley, M.D., The University of North Carolina at Chapel Hill Translational and Clinical Sciences Institute; Joshua Grill, Ph.D., University of California-Irvine, School of Medicine

Overview

When making decisions about the inclusion or exclusion of specific groups in clinical studies and trials, the greatest ethical consideration is the need to recruit representative populations that will further scientific understanding and inform improved patient care. Currently, some rules designed to protect vulnerable populations may actually contribute to their underrepresentation in research, even though these groups stand to benefit from participation and may have great impact on furthering scientific understanding. To mitigate this disconnect, a culture shift is needed, whereby *protection from research* is replaced by *protection through research*. One critical recognition is that persons enrolled in disease- or condition-related research may be vulnerable as a result of their health condition. To accelerate the design of effective therapies, these factors must drive participant inclusion.

Historically, age has been a metric for assessing patient vulnerability and eligibility for inclusion in clinical studies and trials. Children under 18 and older adults have been arbitrarily excluded from research too often. While age is a metric often used to benchmark other health factors, it should not be the exclusive indicator for assessing a patient's eligibility for inclusion. Instead of assessing vulnerability based on extraneous factors like age, investigators must focus on their scientific question, assessing patient eligibility based on physiological or clinical metrics (e.g., onset of puberty). Additionally, investigators should ensure deliberate representative inclusion of eligible participants by age—as well as by sex, race, and ethnicity—in line with the scientific issue in question. To protect vulnerable individuals through research rather than from research, the medical community must shift the cultural default from exclusion to inclusion.

Defining Vulnerability

Defining what makes an individual or population vulnerable is complex. Vulnerable populations can be loosely defined as individuals at increased risk for undue influence, coercion, or exploitation. Protecting the rights and welfare of vulnerable groups—which include children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons as defined in the revised Common Rule regulations[18]—requires additional safeguards. The ultimate assessment of an individual's vulnerability should be based on their cognitive ability and capacity to make autonomous

[18] Common Rules regulations (2009, January 15). Retrieved from: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

decisions and provide informed consent; this vulnerability may necessitate additional safeguards or may justify exclusion if there are safety concerns.

Challenges and Barriers

- **Referring to a given population or individual as "vulnerable" can be alienating and construed as paternalistic**. As the medical community transitions to patient-centered care, investigators should avoid making assumptions about an individual's ability or interest in enrolling in clinical studies and trials based on an assessment of an individual's or group's need for protection.
- **Assessing patient risk relative to potential benefit is challenging**. Current processes tend to default to excluding populations in clinical research and trials when there is personal risk associated with their participation. This risk is difficult to assess, particularly when these individuals stand to significantly benefit from participation.

Proposed Strategies

- **Make widespread changes to language used to define vulnerable groups to avoid alienation**. The scientific community should refer to underrepresented groups with increased respect and understanding. For example, rather than referring to individuals over 65 as "elderly," they should be referred to as "older adults."[19] Similarly, groups historically referred to as "minorities" should be described by their race or ethnicity. Investigators should seek to understand better the historical and social context of historically vulnerable and consistently underrepresented groups to ensure their improved recruitment and representation in clinical trials and research.
- **Assess an individual's vulnerability based on his or her ability to make autonomous decisions and criteria for enrollment relative to the research's scientific question**. Rather than arbitrarily assessing eligibility for inclusion based on age, investigators should assess the cognitive function of children under 18 and older adults to determine their ability to provide informed consent. If individuals meet eligibility criteria and can provide informed consent, they should be allowed to enroll. If individuals meet eligibility criteria and cannot provide informed consent, they should be allowed to enroll through surrogate consent and assent.

Acquiring Consent of Children and Older Adults in Clinical Research

Many similarities exist when considering the inclusion of children under 18 and older adults in clinical studies and trials. Both groups may be mischaracterized as vulnerable, due to their assumed inability to provide consent, need for a proxy decision-maker, and or reliance on others in functional, healthcare, or legal arenas. While there are potential safety challenges associated with including these groups related to ongoing organ development in children or organ dysfunction in adults, it is critical for the scientific community to assess other factors that have historically led to the exclusion and therefore underrepresentation of these groups in clinical studies and trials. The eligibility of all potential trial participants should be based on cognitive ability and capacity to provide informed consent, rather than chronological age or physical performance.

[19] Lundebjerg, N. E., Trucil, D. E., Hammond, E. C. and Applegate, W. B. (2017), When It Comes to Older Adults, Language Matters: Journal of the American Geriatrics Society Adopts Modified American Medical Association Style. *J Am Geriatr Soc*, 65: 1386–1388. doi:10.1111/jgs.14941

Challenges and Barriers

- **Adolescents may be eligible for participation and capable of providing informed consent, but their current grouping with children of all ages may lead to their frequent exclusion**. Many adolescents are physiologically or developmentally the same as 18-year-olds, but unlike 18-year-olds, adolescents are not allowed to receive treatments without parental permission. The revised Common Rule regulations would allow current state laws regarding required parental consent for medical care to be extrapolated to consent for participating in medical research as well. This legal age of consent currently varies by state, reinforcing that this age-based restriction is arbitrary rather than scientifically based. In some situations, adolescents are legally permitted to consent to medical care without parental permission, but not able to consent to research participation for the same medical condition.
- **Participation of older adults may be impacted by residence status.** Some adults that live in continuing retirement communities or nursing homes may be willing and interested in participating in clinical studies and trials, but the community may have restricted access that limits their participation.

Proposed Strategies

- **Develop a universal assessment for a participant's capacity to provide consent**. The scientific community should develop better methods for assessing capacity to consent in subjects based on their understanding of the study and its potential risks and benefits. The scientific community should implement this assessment tool universally, regardless of participant age or the disease or condition under study. The assessment process must be as objective as possible (i.e., not affected by culture, education, IQ, or socioeconomic status) and standardized.
- **Develop a more robust assent process for individuals without the cognitive function needed to provide consent**. Participants who cannot provide informed consent should be required to provide their assent for participation, whenever possible. Assent should be documented via a standardized, objective means.
- **Define the unique abilities of adolescents to provide consent**. Given that adolescents have more rights and abilities than pediatric patients, they should be provided with an increased potential to provide consent if they demonstrate the cognitive ability to do so. The use of technology, including virtual reality, could help communicate needed information in a way that can be more easily understood by these groups.

Ethically Justifiable Reasons for Exclusion

While many groups have historically been excluded from participating in clinical trials and research for arbitrary reasons, several ethically justifiable reasons for exclusion do exist. Appropriate exclusion factors that better align with the scientific process and historical and social context include the following:

1) Lack of disease or condition presence within a group
2) Presence of a comorbid condition that presents an unacceptable safety risk to the participant

Challenges and Barriers

- **HHS Regulatory Requirement Protections (Subpart D) require justification for the exclusion of children in clinical research, but similar guidelines do not exist for the exclusion of older**

adults. Without such guidelines for the justification of exclusion for older adults, investigators and reviewers may lack adequate incentive to meaningfully change current practices.

- **Investigators and institutions fear potential repercussions from including children and older adults in studies**. For example, a traditional concern about including children in clinical trials is that a poor outcome in a child may hurt chances for drug approval or may be subject to legal ramifications that may negatively influence the project or research institution. This scenario is rare. Similarly, many believe that if IRBs waive parental permission for adolescents in studies of some conditions – for example, sexually transmitted infections (STIs) – the parents may sue the institution, though there are also few documented instances of this actually occurring.

Proposed Strategies

- **Improve understanding associated with the legal environment of inclusion and exclusion in clinical trials**. The scientific community should compare consent laws and criteria for inclusion and exclusion across states and provide suggestions for revisions based on scientific research. Concordance should be sought between legally permissible situations for children to consent to medical care and parallel opportunities to participate in research.
- **Consider revising GRF grant applications and review processes to elevate the need for inclusion**. To ensure that investigators adequately consider the populations that should be included in study design, GRFs should consider revising the grant application structure to require consideration of population inclusion as part of the upfront discussion of the project impact and significance. Investigators could be instructed that representative inclusion—including by age, socioeconomic status, race, ethnicity, and sex—will be part of the application scoring process.
- **Develop checklists, guidance, and training for investigators, reviewers, and IRB members to ensure that any exclusions are ethically justifiable and that included populations are representative of the issue being studied**. To help ensure that application development and review focuses primarily on advancing science and available treatment options, the scientific community should publish checklists, guidance, and training to overcome implicit biases and establish inclusion, not exclusion, as the default in study design.

Considerations for Informed Consent from Non-Familial Caregivers

While some subjects may not be able to provide their own consent based on their level of cognitive ability, these subjects may stand to benefit significantly from participation in clinical studies and trials. In these cases, a study's IRB can decide who is eligible to be a consent surrogate for these subjects. Identifying the appropriate person to provide consent in these situations can be challenging since, in many cases, participants without decision-making capacity may not have an obviously appropriate individual who can make decisions on their behalf that protect their rights and welfare.

Challenges and Barriers

- **While parents are natural surrogates for their children, they may not be the most appropriate people to provide consent in all instances**. For example, parents of children may not be the most appropriate consent surrogate when parents have impaired cognitive ability, or when children, particularly adolescents, are estranged from their parents.
- **Older adults with impaired cognitive ability do not have natural consent surrogates**. The best advocate for an older adult could be a spouse or adult child, or less obvious and consistent options like a long-term friend or a neighbor. Adequate guidelines are not currently in place to

provide non-familial caregivers with surrogate consent capabilities, even if they are best suited to protect the subject's rights and welfare, and available guidance/regulations may vary substantially from state-to-state.

Proposed Strategies

- **Provide more detailed guidance for IRBs related to assessing the appropriateness of non-familial caregivers for providing surrogate consent**. To help IRBs more consistently decide who can provide surrogate consent for children under 18 and older adults who lack the capacity to provide informed consent, the scientific community should develop consistent guidance that provides additional opportunities for inclusion, rather than exclusion due to the complicated nature of non-familial consent.

Safeguards for Vulnerable Populations

The Common Rule states that safeguards should be included in studies for vulnerable populations, but these safeguards are not specified. Investigators are ultimately the first line of defense in protecting vulnerable populations. To provide adequate safeguards, researchers must design studies with representative populations of participants and adequate monitoring, engaging any underrepresented or vulnerable groups during the study design process. To ensure that needed safeguards are in place to protect the rights and welfare of vulnerable populations, IRBs may require third party consent monitors or disease/condition advocates with an understanding of the needs of a vulnerable group to ensure that these groups can be adequately recruited and retained. These safeguards are critical for ensuring that studies include the necessary representation to maximize scientific advancement while simultaneously protecting participants. Studies must avoid exploitation as well as their deliberate or unintentional exclusion.

Challenges and Barriers

- **Safeguards for vulnerable groups are not consistently defined**. While the Common Rule requires safeguards for vulnerable subjects, the scientific community lacks consistent definition and guidance on potential safeguards and their implementation.
- **It is difficult to identify the investigator's role in acknowledging and alleviating the burden of participation for children and older adults in clinical trials and research**. To participate in clinical trials, children often must miss school, caregivers often must miss work, and older adults may face struggles associated with transport. Participation can also be time-consuming, frustrating, and tedious. Studies must be designed to better acknowledge and alleviate these burdens.

Proposed Strategies

- **Involve affected populations in study designs**. As the medical community transitions to more patient-centered care, the research community should also transition to involving affected subjects in study planning and participation.
- **Engage advocates in review processes**. If investigators are enrolling subjects requiring special consideration, it is critical to include advocates on the review board who can instruct the associated care requirements (e.g., staffing, technology) of that group based on experience.

- **Use consent monitors**. Especially in cases in which vulnerable populations may be enrolled in high-risk protocols, the use of consent monitors may further ensure participant interests and autonomy are protected.

Data Collection and Reporting to Support Age-Specific and Subgroup Analyses

Co-Chairs: Jerry Gurwitz, M.D., University of Massachusetts Medical School; Roger F. Soll, M.D., University of Vermont College of Medicine; and Elizabeth Tipton, Ph.D., Teacher's College at Columbia University

Overview

Data on participants enrolled in clinical trials is limited in terms of age and other demographics (e.g., race/ethnicity, sex, socioeconomic status [SES]). Researchers conducting meta-analyses of trial results to determine whether subgroup analyses according to age (and other demographic groups) are feasible are challenged by the need for more generalizable clinical data. Similarly, a lack of standardization of both trial data repositories and trial results reported in scientific journals hinders the performance of meta-analyses. Although age provides important information that is correlated with developmental status in pediatric age groups, in older adults, age in and of itself is a characteristic with substantial limitations, as it is not necessarily indicative of other important characteristics in the enrolled study population. Age, for instance, is not always correlated with a person's functional ability or burden of multimorbidity.

Overall, the problem with data collection and reporting is two-fold: researchers should report on information about the population from which the trial sample is drawn (e.g., prevalence of the condition of interest) in addition to providing adequate information about the representativeness of the trial sample, including characteristics and outcomes, according to age and other demographics.

Challenges and Barriers

- **Researchers not reporting full demographic data.** Clinical trial researchers do not typically report information on population prevalence by age or other demographics, nor do they consistently report adequate information on those participating in trials with respect to outcomes by age.
- **Lack of standard reporting guidelines for journal editors**. When publishing clinical trial outcomes in scientific journals, authors use reporting standards specific to their journal, which even for the same journal can be inconsistent. Performing meta-analyses of age-related enrollment and results from clinical trials using articles from different journals requires significant time to search through articles for relevant data.
- **Need for a central data repository.** Researchers conducting meta-analyses must reference clinical trial datasets from many different sources. Each source designs their data repositories differently, presenting challenges in efficient data gathering. Having one central repository would reduce burden on both researchers and authors reporting on trial outcomes.

Proposed Strategies

The workgroup identified several strategies to improve data collection, reporting, and analysis. As part of its evaluation, the workgroup also identified other factors in study design and inclusion that can affect data collection.

Data Collection, Reporting, and Analysis

- **Begin/maintain data collection in pediatric and older adult inclusion**. GRFs should gather metrics on pediatric inclusion, and publish metrics on older adult inclusion in an ongoing way, both of which are key requirements for performing meta-analyses in clinical trials.
- **Have GRFs standardize data repositories**. GRFs could work with the scientific community to standardize clinical trial data repositories as an alternative to creating one central repository.
- **Encourage development and use of available technologies for automatic data collection**. Gathering data on participants in clinical trials could be expedited by using smartphone apps to automatically collect certain data (e.g., age, sex/gender, race, SES), reducing the burden on participants as well as trial sites.
- **Review unused data**. A significant amount of participant data (e.g., data on comorbidities) is often collected but is not reported or used. Analyzing these data could serve as a starting point for meta-analyses or provide further data for additional studies.
- **Coordinate efforts to standardize data collection and reporting**. Bring together funders (e.g., GRFs), IRBs, regulatory agencies (e.g., FDA), journals/editors, and the Consolidated Standards of Reporting Trials CONSORT Group[20], with input from patients/families and other stakeholders, to develop standards for data collection and reporting. Discussion and planning on how to coordinate efforts across the different stakeholders is still needed.
- **Improve how age information is reported in clinical trials**. Researchers conducting clinical trials use methods of reporting age information that do not accurately represent the age characteristics of the people in the trial (e.g., reporting that a study of 10 people in their fifties and one person in their seventies had an age range of 50–70). Changing the way information on age is reported would provide more granular clarity to age-related trial data.
- **Change the way data are reported and/or stored.** Consider two possible strategies to increase the quality of data collection and reporting for age-specific and subgroup analyses.
  - House anonymized research data centrally online for everyone to access (which might take a long time, in terms of technology development and resources required).
  - Have researchers report outcomes by age group, but without significance testing (which would be easier and faster to begin with). The ultimate goal to move to open data sources, while important, is a longer-term goal.
- **Use age strata on GRF websites**. Establishing new age strata standards or the reporting of age as a continuous variable for a large clinical trial data repository website like ClinicalTrials.gov will make it easier to harmonize standards across other repositories and in published reports and journal articles.
- **Consider revising the CONSORT form, used to reflect progress through the phases of a clinical trial, to include study population information**. Adding population breakdown to the CONSORT form could ensure reporting on trial results which would include information (e.g., ages,

[20] CONSORT Group. Retrieved from http://www.consort-statement.org/

sex/gender, race, SES) on participants in the trial. Revisions to the CONSORT form could allow journals to adopt and help standardize the change. This would help keep researchers accountable for describing the focal study population, compared to what it should have been.

Other Key Points Relating to Improving Data Collection and Reporting

- **Ensure investigators have expertise in older and pediatric populations**. Investigators must be trained on appropriate inclusion of older adults and children in clinical trials. Alternatively, supplementing existing research teams with individuals with expertise relating to those populations could accomplish the same goal.
- **Change the terms used for older adults in studies**. Adults over a certain age are often referred to as "elderly," "elders," "seniors," and "the aged" in studies, which can alienate this population. The preferred term "older adults" should be standard for use in studies and reports.[21]
- **Create guidelines for all demographic categories**. Demographic categories (e.g., age, race, sex, and possibly SES) need guidelines for consistent reporting. Consideration should also be given for guidelines for reporting comorbidities.
- **Ensure that inclusion of pediatric and geriatric populations in clinical trials is meaningful.** The inclusion of children and older adults must be part of the overall objectives of the study. Some trials will focus solely on these age groups to the exclusion of others for studies of specific diseases and conditions that affect these age groups.
- **Eliminate upper age limits for participants unless risk-justified**. Putting upper age restrictions on trial participants can result in a study that does not analyze people who most experience the disease or condition under study. Removing upper limits on age would ensure more generalizable trial results. Older adults should be included in studies unless there is a significant health risk associated with participation.
- **Develop specific age ranges for older adults**. Pediatrics uses several different age categories for children between birth and 21 years of age,[22] and the same should be standardized for older adults (i.e., older adults should not be lumped into broad age categories like 65+ or 75+).

[21] Lundebjerg, N. E., Trucil, D. E., Hammond, E. C. and Applegate, W. B. (2017), When It Comes to Older Adults, Language Matters: Journal of the American Geriatrics Society Adopts Modified American Medical Association Style. *J Am Geriatr Soc*, 65: 1386–1388. doi:10.1111/jgs.14941

[22] Williams K, Thomson D, Seto I, Contopoulos-Ioannidis DG, Ioannidis JP, Curtis S, Constantin E, Batmanabane G, Hartling L, Klassen T; StaR Child Health Group. Standard 6: age groups for pediatric trials. *Pediatrics*. 2012 Jun; 129 Suppl 3:S153-60. doi: 10.1542/peds.2012-0055I. PMID: 22661762

APPENDIX I. REGISTRANT LIST

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Minzhi Ye, Case Western Reserve University

Giovanna Zappala, NIH, NIA

Susan Zieman, NIH, NIA

Steve Zullo, NIH, National Institute of Biomedical Imaging and Bioengineering

APPENDIX II. INCLUSION ACROSS THE LIFESPAN PLANNING COMMITTEE MEMBERS

Committee Co-Chair: Jane Atkinson, NIH, National Institute of Dental and Craniofacial Research (NIDCR)

Committee Co-Chair: Samir Sauma, NIH, National Institute on Aging (NIA)

Lawrence Agodoa, NIH, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Jennifer Alvidrez, NIH, National Institute on Minority Health and Health Disparities (NIMHD)

Monica Basco, NIH, Office of Research on Women's Health (ORWH)

Marie Bernard, NIH, NIA

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

Jodi Black, NIH, Office of the Director (OD)

Jonca Bull, U.S. Food and Drug Administration (FDA)

Kristin Burns, NIH, National Heart, Lung, and Blood Institute (NHLBI)

Patricia Brennan, NIH, National Library of Medicine (NLM)

Redonna Chandler, NIH, National Center for Advancing Translational Sciences (NCATS)

Janine Clayton, NIH, ORWH

Dawn Corbett, NIH, National Institute of Mental Health (NIMH)

Lauren Davis, NIH, NIA

Jerry Fleg, NIH, NHLBI

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Marjorie Jenkins, FDA, Office of the Commissioner (OC)

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Mia Lowden, NIH, NIA

Martin Mendoza, FDA

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Susan Schafer, NIH, NIAID

Donna Snyder, FDA

Erica Spotts, NIH, OBSSR

Paris Watson, NIH ORWH

Lynne Yao, FDA, Center for Drug Evaluation and Research (CDER)

APPENDIX III. WORKGROUP TOPICS AND CO-CHAIRS

Four workgroups were formed to examine specific topics related to inclusion. Below is a list of the topics and co-chairs who led each effort.

STUDY POPULATION: INCLUSION/EXCLUSION CRITERIA, AGE RESTRICTIONS AND THEIR IMPACT ON STUDY POPULATIONS OF CLINICAL TRIALS AND CLINICAL STUDIES

- **Co-Chair**: Cynthia Boyd, M.D., M.P.H., Johns Hopkins Bloomberg School of Public Health
- **Co-Chair**: Tyra Bryant-Stephens, M.D., Children's Hospital of Philadelphia
- **Co-Chair**: Michael Cohen-Wolkowiez, M.D., Ph.D. Duke University School of Medicine

STUDY DESIGNS AND METRICS

- **Co-Chair**: Heather Allore, Ph.D., Yale University School of Medicine
- **Co-Chair**: Scott Denne, M.D., Indiana University School of Medicine

ETHICAL CHALLENGES AND THE ENROLLMENT OF VULNERABLE POPULATIONS

- **Co-Chair**: Tamera Coyne-Beasley, M.D. The University of North Carolina at Chapel Hill Translational and Clinical Sciences Institute
- **Co-Chair**: Joshua Grill, Ph.D., University of California- Irvine, School of Medicine

DATA COLLECTION AND REPORTING TO SUPPORT AGE-SPECIFIC AND SUBGROUP ANALYSES

- **Co-Chair**: Jerry Gurwitz, M.D., University of Massachusetts Medical School
- **Co-Chair**: Roger F. Soll, M.D., University of Vermont College of Medicine
- **Co-Chair**: Elizabeth Tipton, Ph.D., Teacher's College at Columbia University

APPENDIX IV. PRESENTATION SUMMARIES

As part of the "Inclusion Across the Lifespan" plenary session, experts presented background information and the results of analysis. This appendix includes a brief summary of each presentation.

INCLUSION OF CHILDREN IN NIH-FUNDED CLINICAL RESEARCH

Diana W. Bianchi, M.D., Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Dr. Bianchi presented an analysis on the discrepancy between NIH grants' intent and actual inclusion of children under the ages of 21 and 18. Within the research community, there is a broad concern on the inclusion of children in clinical trials. Appropriate inclusion is generally decided on a case-by-case basis, and the threshold age for the inclusion recently decreased from 21 to 18 in 2016-2017.

The analysis reviewed studies from 2007 to 2016 to determine how many grants were submitted with a plan to include children under the age of 21. A preliminary review of the data showed that 65 percent of NIH grants planned to include children, while 7 percent of NIH grants planned to only include children. Limitations of these data include the definition of children as under the age of 21, whereas most individuals consider children to be under the age of 18. Additionally, information in grant applications was prospective and indicated planned inclusion as opposed to actual inclusion. Grant application information often described exclusion of children, rather than the specific actions taken to include them, and many times studies were not fully developed at the time of application.

In total, 336 grants from 2007 to 2011 were reviewed and coded for the analysis, representing 130 distinct conditions ranging from blood disorders to cancer. The results showed that out of the NIH Phase III grants that planned to include children under 21, 52 percent of the grants planned to include children under the age of 18, and 45 percent had no plans to include a change to the age. Publication results showed that 97 percent of the grants had at least one publication, and 82 percent of grants published clinical trial results by April 2017. Overall, 31 percent of the published results included children under the age of 18, resulting in a 29 percent deviation from planned inclusion in a grant application to actual inclusion in study results. Of the publications that included any analysis by age, 36 percent deviated from their original analysis plan. These results serve to further the argument that there is currently a discrepancy between the intent and the implementation of including children in clinical trials.

During the post-presentation question and answer session, meeting participants commented that the presentation made a compelling case for reporting requirements and asked whether the issue would be best addressed as part of study design or the IRB process.

Key Takeaways

- Approximately 65 percent of all NIH grants plan to include children under the age of 21, and about half of those grants include children under the age of 18.
- 60 percent of NIH Phase III clinical trial grants that originally planned to include children did not report or analyze results by age.
- Over 80 percent of NIH Phase III grants stated an intention to include children under the age of 18, but did not report any children under 18 in published results.

- Overall, 30 percent of grantees diverged from their original analysis plan in their published results.

The Persistent Exclusion of Elderly Patients in Clinical Research

Florence Bourgeois, M.D., Assistant Professor of Pediatrics, Harvard Medical School

While pediatric trials have not kept pace with the growth of clinical trials overall, there is a similar underrepresentation in older adult patients. Individuals 65 and older make up just 14 percent of the population, yet these individuals represent 60 percent of all cancer patients, 65 percent of patients hospitalized with heart disease, and 35 percent of all healthcare expenses. The challenges of studying older adult patients include concerns about safety, the capacity to provide consent, co-existing medical conditions, increased costs, and practical barriers to study activities, such as poor hearing and cognitive slowing. Based on these challenges, there is empirical evidence supporting the case that older adult patients are excluded from many clinical studies.

Given the burden of disease among older adult patients, Dr. Bourgeois sought to examine the underrepresentation of older adult patients in clinical trials. A total of 839 trials studying ischemic heart disease over a 10-year period showed that 53 percent of trials excluded older adult patients, 43 percent had upper age limits of 75 and 80, and 17 percent of trials without upper limits did not enroll patients above 80. The mean age of participants in these trials was 62.7, compared to the real-world mean age of individuals with acute coronary syndrome of 70. These findings were consistent with results from a number of other studies. For example, one study showed that 66 percent of type 2 diabetes studies excluded older adult patients, while another demonstrated that the mean age of patients in osteoarthritic studies was 63 despite the mean real-world age of 79. Additionally, 33 percent of non-small-cell lung cancer trials excluded older adult patients altogether.

Older patients are often willing to participate in research, but different strategies and approaches are required to both enroll and retain this population throughout the clinical trials. Some strategies that have been employed are early in-depth planning, minimizing exclusion criteria, use of an advisory board, careful review of the benefit-risk ratio, and detailed strategies for how to retain patient participants over time.

To address the gap of under-representation, some studies focus on conditions most pertinent to older adult patients. Moving forward, the alignment of disease burden and conditions, as well as the explicit inclusion of older adult patients, must increase to address the underrepresentation of older adult individuals in clinical trials.

Following the presentation, workshop participants brought up a number of additional challenges including the lack of funding available to conduct clinical trials or research focused specifically on older adults, the higher rate of renal dysfunction in older adults leading to additional risks and potential exclusion, and the need to make chronological age just one factor in a broader calculation of inclusion. One proposed solution was to include older adults in early phases of clinical trials, not just when the trials reach Phase III.

Key Takeaways

- Many clinical trials exclude older adult patients based on age limits, even for diseases predominately affecting the older adult population.
- Enrolled clinical trial patients are not representative of real-world patient populations.

- The underrepresentation of older adult patients is not being compensated for with older adult exclusive studies.
- Conditions studied are often poorly aligned with actual disease burden in the older adult population.

Going Beyond Inclusion – Women and Clinical Trials

Janine Clayton, M.D., Director, NIH Office of Research on Women's Health

The mission of the NIH Office of Research on Women's Health is to expand women's health research, to advance the inclusion of women in NIH-sponsored clinical research, and to promote the advancement of women in science. NIH recognized the problem of lack of inclusion of women in clinical trials, coupled with the application of study results to women's health. NIH inclusion reports indicate that enrollment by sex/gender in NIH Phase III clinical trials now includes slightly more women than men; however, this trend portrays an incomplete story.

Women in the United States are less likely to survive to the age of 50 when compared to 21 other high-income countries. Mortality rates for women have risen in nearly 43 percent of counties in the United States. These results point to the need to think beyond aggregate enrollment of women in clinical trials and to consider, instead, the context of the entire research continuum, including preclinical work and how clinical research is meant to generate knowledge towards improved health.

Inclusion of women should be considered at each stage of the research process, with some of the most significant implications for inclusion occurring in the design, analysis, reporting, and knowledge-transfer stages. Clinical research has not done a good enough job of examining the biological factors of sex and age, and how these factors affect health. Gender differences begin as early as birth, such as in autism spectrum disorders. These disorders have a five percent higher occurrence in boys, meaning girls are less likely to be diagnosed and may be left out of clinical trials due to under diagnosis. Another example is asthma, which affects more boys than girls before puberty, yet more women than men in adulthood.

The implications of sex and gender in health and disease also affect later stages of life. One example is that women with gestational diabetes have a higher risk of developing type 2 diabetes later in life. In addition, stroke has a disproportionate effect on women due to their longer life expectancy. Moreover, quality of life and functional outcomes following stroke are generally poorer in women than men. While depression can affect individuals at any time in life, the risk is frequently reported as being two times greater in women. Literature points to a complexity of factors differentiating the patterns of depression in men and women. The implications of these findings suggest that studies must account for relevant differences between women and men in trial design, and that research must improve sex/gender reporting to address pervasive sex and gender influences on health and disease.

Workshop participants also highlighted the need to include pregnant and nursing women in clinical studies. The frequent exclusion of these women from clinical trials means that doctors have little information to make evidenced-based decisions for the treatment of pregnant and nursing women. Another issue identified in the question-and-answer session was the challenge of enrolling women who have caregiving responsibilities for children and/or parents and other older adult relatives, which may pose additional barriers for their participation in clinical trials.

Key Takeaways

- Sex and gender differences exist in the diagnoses and impacts of diseases and conditions.
- Sex should be accounted for as a biological variable in study design, analysis, and reporting.
- Sex and gender influences have implications for disease/condition impacts throughout all stages of life, including pregnancy.
- Screening questionnaires for clinical trial enrollment as well as inclusion and exclusion criteria should be designed and selected with sex and gender influences in mind.
- Studies should be designed with the inclusion of women in mind.
- The inclusion of women should occur at all stages of the research process, with the greatest implications for impact occurring at the design, analysis, reporting, and knowledge-transfer stages.

Inclusion across the Lifespan: The Importance of Considering Race/Ethnicity and Socioeconomic Status

Eliseo J. Pérez-Stable, M.D., Director, National Institute on Minority Health and Health Disparities

The inclusion of minority racial and ethnic groups in NIH-funded trials has largely remained unchanged over the years, with minority inclusion in clinical trials representing around 26 percent to 28 percent of total trials today. Understanding the importance of race/ethnicity and SES will contribute to improved health outcomes such as infant mortality and cancer screenings.

SES assessments are poorly conducted in clinical research, with years of formal education as the primary metric used. Additional measures of SES should be implemented, including geographic location, household income, and assets. Despite the limitations of utilizing income as a marker of SES, national data has shown that individuals below the poverty line (annual household income <$25,000) are three times more likely to die from any cause compared to those in the upper middle class (annual household income >$115,000).

The prevalence of colorectal cancer has implications for both race and SES, as screening rates differ across both of these factors, with 66 percent of White patients and over 71 percent of college graduates screened, compared to 45 percent of those screened at a high school or lower education level. Mortality rates are predominately driven by social class, considering such factors as national origin, religion, language proficiency, and residence in rural versus urban locations.

It is important to consider that age variance in disease onset, progression, and premature mortality can lead to exclusion of minority groups across the lifespan. Including diverse participants leads to better science and makes common and economic sense as minorities are currently 40 percent of the U.S. population. Studies do not need to be powered or include all racial and ethnic groups, but study participants should be as representative of the population as possible to provide meaningful examinations of the relationships between ancestry, environment, and social factors. Understanding these relationships and interactions will expand the knowledge of disease pathology and therapeutic options for everyone.

Key Takeaways

- While it can be difficult to recruit minorities and often takes more resources and a different set of skills to do so, NIH should implement accountability on recruitment and add measures of SES in all funded projects with human participation.
- Underrepresentation of minorities leads to decreased knowledge of disease pathology and economic strains.
- Race and SES have significant implications in evaluating disease onset and progression.
- Age variance in disease onset, progression, and mortality can lead to the exclusion of minority groups across the lifespan.
- Scientific discoveries are only possible of minority groups are included in clinical sample trials and results are assessed by racial and SES breakdown.

Ethical Considerations when Including Vulnerable Populations in Clinical Trials

Christine Grady, Ph.D., Chief, Department of Bioethics, NIH Clinical Center

Clinical research should generate knowledge that is useful for understanding and improving human health. At the same time, there is an ethical responsibility to protect the rights and welfare of the individual participants who make such research possible. Since the goal of research is not to benefit individual participants, ethical considerations in protecting the rights and welfare of study participants are essential and become more complicated when considering enrollment of vulnerable populations. There are competing tensions between emphasizing protection from research when it poses a burden and access to research when it offers a benefit.

Vulnerable populations were originally described in U.S. federal regulations as including children, prisoners, pregnant women, mentally disabled persons, and economically or educationally disadvantaged persons. In the final revisions to the Common Rule published in January 2017, this list was modified to remove pregnant women and mentally disabled persons and instead include adults with impaired decision-making. Many commentators and guidelines have expanded the list of populations labeled as vulnerable in the context of clinical research over time. However, if everyone is labeled as vulnerable, then it is harder to protect those individuals who are actually vulnerable. One widely accepted definition of "vulnerable" in clinical research is individuals who have diminished ability to protect their own interests, often through an inability to understand information or their circumstances, or an inability to make a voluntary decision.

Age is a blunt indicator to describe vulnerability, as people at different ends of the age spectrum may have decreased capacity to understand information or decreased ability to make decisions. However, age alone is insufficient for determining vulnerability. Groups or individuals may be vulnerable for different reasons, and in different ways.

Clinical research is faced with the decision to protect vulnerable groups by excluding them from trials, or by enabling participation while recognizing individual needs and integrating additional safeguards as appropriate. Fair subject selection should be based on scientific appropriateness, considerations of risk and benefit, and a determination of whether prospective participants may have a compromised ability to protect their own interests.

The Belmont Report (1979) argued that either vulnerable participants should be excluded, or investigators should follow an order of preference in selection, and when vulnerable groups are included, research should focus on conditions that affect them. The Council for International Organizations of Medical Sciences' (CIOMS) 2016 Guideline states that children, adolescents, and adults incapable of giving consent should be included in research unless there is a good scientific or risk reason to justify exclusion.

Decisions about inclusion of vulnerable populations are also guided by considerations of risk and benefit. Many agree that inclusion is acceptable in studies that offer a prospect of clinical benefit or are minimal risk. Vulnerable individuals and groups should be included when appropriate, but safeguards should be added (e.g., limiting risk, including representation on IRBs, including surrogate consent, utilizing independent consent monitors, using advocates to support the views and voices of vulnerable populations).

One workshop participant noted that the use of the word "vulnerable" starts the conversation off in a place of exclusion rather than inclusion because of the desire to protect populations considered vulnerable. There is the need for a cultural shift to focus on the value of inclusion, and finding responsible ways to include these populations rather than categorically excluding them. As Dr. Grady stated, "The only way we learn how to treat people is by including them in research." Still, she added that inclusion for inclusion's sake is inadequate, as exclusion is justified in some cases. This is why study context is so important.

Key Takeaways

- There should be a case-by-case determination of who might be vulnerable in a particular study as it looks different across groups, individuals, and studies.
- When promoting research to address health needs of vulnerable groups, it is important to consider types of vulnerability and integrate appropriate additional protections for those who are vulnerable.
- Exclusion of vulnerable populations may be appropriate in some cases.
- Researchers should ask the following questions: Who do we want to include? How are these groups vulnerable? Can their vulnerability be adequately addressed?

Pediatric Product Development, Successes and Challenges

Donna Snyder, M.D., Medical Officer, Office of Pediatric Therapeutics, U.S. Food and Drug Administration (FDA)

Legislation encouraging pediatric product development has brought about a variety of successes and challenges to research and clinical trials. Children metabolize and respond to drugs differently than adults, leading to concerns about liability and harm towards the children. These concerns often lead to the exclusion of children from pediatric product development.

Despite different responses to drugs, children deserve to be treated with products that have been shown to be safe and effective for their conditions and should therefore be included in pediatric studies. PREA, established in 2003, requires drug companies to submit pediatric assessments, assess the drug's safety for the claimed indication in relevant pediatric populations, and establish efficacy through extrapolation from adults to children when effects are sufficiently similar.

BPCA provides an incentive for pediatric studies by providing marketing exclusivity for stand-alone pediatric development programs. Under BPCA, NIH has the authority to conduct and submit studies to the FDA in support of pediatric labeling.

Orphan Drug Exclusivity (ODE) established that drugs must be designated and approved to treat diseases affecting fewer than 200,000 patients in the U.S. where no current therapy exists or where the product will significantly improve existing therapy. Following approval, the FDA is barred from approving any other application of the same drug for the same orphan disease for seven years.

Pediatric Rare Disease Vouchers are provided to rare pediatric diseases that qualify for orphan designation and have serious, life-threatening manifestations primarily affecting individuals 18 and younger.

Successes within pediatric product development have included pediatric labeling changes, increased pediatric studies, and increased participants in clinical trials. In total, 684 labeling changes have occurred as a result of the BPCA and PREA incentives. Despite these increases, there are still challenges facing pediatric product development. There is a lag time of about nine years between when a product is approved for use in adults, to when the product labels are updated to include pediatric data, leading to off-label use during this period. Extrapolation may be used in pediatric trials to establish the efficacy of the product if the disease is similar and the response to therapy is expected to be similar; dosage and safety cannot be extrapolated. Ways to streamline pediatric development include national and international collaborative efforts, and the development of consortiums and networks to study pediatric-specific diseases. Outcome assessments, biomarkers, and appropriate study endpoints are needed to further pediatric product development.

Following the presentation, workshop participants asked whether any additional confirmatory study is conducted if extrapolation is used. Although separate studies are not conducted, the determination to use extrapolation is based on data available on its appropriateness for that situation. Participants also mentioned the need to begin gathering data on off-label use of drugs to help identify risks and potential dosage information, as well as encouraging pediatric studies to start earlier.

Key Takeaways

- FDA has requirements and incentives in place to encourage pediatric product development, including PREA, BPCA, ODE, and Pediatric Rare Disease Vouchers.
- Successes include 684 labeling changes and increasing the number of completed clinical trials and pediatric patients across a range of ages.

Challenges include reducing the lag time from the time of adults' approval to pediatric labeling, finding ways to streamline pediatric drug development, and a need for better outcome assessments, biomarkers, and appropriate study endpoints to further pediatric product development.

FDA Guidance on Inclusion of Older Adults in Clinical Studies

Robert Temple, M.D., Deputy Director for Clinical Science, Center for Drug Evaluation and Research, FDA

Before the 1980s, there was a reluctance to include older adult participants in clinical trials of new drugs because of concerns about concomitant illness and unexpected mortality with possible attribution to

the drug. This led to exclusion of older adults and those with concomitant risk factors. Since 1983, the FDA has released a series of discussions and guidelines on including older adults in trials. These guidelines enunciated common principles on the inclusion of older adults in clinical trials to support drug approval and called for analysis of safety and effectiveness by age, as well as other demographic characteristics, like sex and race.

Specifically, the guideline principles focused on the full evaluation of pharmacokinetics (PK) differences, inclusion of older adult participants, analysis of effectiveness by age, and clarity on the definition of older adults. Age-related effects can arise because of PK or pharmacodynamics (PD) differences. It is easiest to examine PK differences first, with particular interest in the effects of decreased renal function or altered cardiac function, which are both more common in older adults. The guidance called for a "PK screen," or population PK, which involved getting blood levels for all patients to look for PK variability not anticipated and allowing for the assessment of concentration-response relationships (PK/PD).

The inclusion guidelines state that there is no good reason to exclude participants from clinical trials based on advanced age alone, and also suggests including young and old patients in the same clinical trials which would allow better analysis. The guidelines further outlined that for both individual studies and integrated analyses, there should be an analysis by age, sex, race, renal function, concomitant illness, and other baseline characteristics.

While the 1989 FDA guidelines and the ICH E-7 guidelines both highlight interest in patients over 75 , the specific definition of older adults in both guidelines is people over 65 years old, and there is a long-standing societal definition of older adults as over 65. The Studies in Support of Special Populations (1993) urged the elimination of arbitrary age cutoffs and the revision of the paper in 2012 emphasized the importance of enrolling participants over 65 using pooled data to look at the effects in age groups.

While there is no rule requiring specific inclusion levels by age, race, or sex, a drug needs to be shown to be safe and effective in the population using it. In the absence of these rules, it is important to examine inclusion rates over the years. A U.S. Government Accountability Office (GAO) review of studies of drugs approved since January 1988 to mid-1990 found a great deal of variation in inclusion of older adults by disease or condition, with oncologic drugs having a relatively high percentage of inclusion and psychiatric drugs having a quite low percentage. Recently, as part of Health and Human Services' working group on Multiple Chronic Conditions (MCC), the FDA looked at demographic characteristics and found a 19 percent inclusion rate of individuals 65 and over. Looking specifically at studies of new anti-coagulant and new anti-platelet drugs, there has been substantial inclusion of patients over 75 years of age.

Findings support regulations for analysis of safety and effectiveness results by demographic group to be included in drug labeling. Moving forward, there is a broad interest in avoiding unnecessary exclusions of all kinds, not just age.

Following the presentation, the discussion focused on how to better require and incentivize the inclusion of older adults in clinical trials, specifically earlier in the trial process, in Phase I and Phase II studies, and when studying oncology interventions. One possibility is developing incentives for inclusion of older adult patients, similar to those used to encourage inclusion of children in clinical drug studies. Workshop participants also highlighted the need for greater transparency and availability of data to allow for better analysis. While some data are made available, there is often a lag or delay in access.

Inclusion is important in clinical drug trials to better understand the response to drugs in different populations. It is also critical to examine the multiple demographic factors without overwhelming the study and analysis.

Key Takeaways

- In the early 1980s, there was a reluctance to include older adults in clinical trials due to concerns about concomitant illness.
- Guidelines released by the FDA outlined principles on the inclusion of older adults in clinical trials and regulations called for analysis of safety and effectiveness by age.
- There is no good basis for the exclusion of patients on the basis of advanced age alone.
- The long-standing definition of older adults as above 65 places an arbitrary age cut off on this population and recent ICG guidance has urged inclusion of patients over 75.
- A review of clinical trial studies has found the inclusion of older adults to vary widely by disease or condition, but cardiovascular outcome studies of anti-coagulant and anti-platelet drugs have had a substantial inclusion rate of patients over 75 years old.
- Moving forward, studies should avoid unnecessary exclusions of all kinds.

Clinical Research Data Collection at the Individual Level

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Over the years NIH has heard and responded to concerns around inclusion in clinical research by age. Some of these concerns were highlighted in an article in the Journal of the American Geriatric Society released in 2010. The article highlighted the difficulty of obtaining informed consent, justifying the criteria for exclusion and inclusion by age, and measuring comorbidities as some barriers to inclusion of older adults in clinical trials. Many of the concerns are relevant in both pediatric and geriatric populations. As NIH considers the issues of inclusion, it is valuable to look back at a timeline of NIH inclusion policies and participation in data collection.

The late 1980s and early 1990s saw policies encouraging the inclusion of women in clinical research. In 1998, NIH issued a policy requiring the inclusion of children, and a notice released in 2015 changed the definition of child from under 21 to under 18. Most recently, the 21st Century Cures Act was passed requiring data on inclusion by age. The 21st Century Cures Act requires "data on study populations of clinical research […] which specifies the inclusion of women, members of minority groups, and relevant age categories, including pediatric subgroups."

The purpose of NIH inclusion policies is to ensure that the distribution of participants reflects the population needed to accomplish the scientific goals of the study. Ensuring inclusion of appropriate individuals increases the rigor, reproducibility, and generalizability of research, and informs general clinical care. Current data is limited because there is no way to know the number of individuals in any given age category, and there are limited subgroups. This leads to many unanswered questions, such as the percent of epilepsy trials involving toddlers.

The NIH Office of Extramural Research's proposed plan to address these limitations includes allowing submissions of participant age information in the competing application and progress report, collecting

age data at the individual participant level as a continuous variable, using age at enrollment rather than date of birth to protect identity, and including flexible measurement units.

Moving forward, grant application forms submitted for due dates after January 25, 2018 will include a proposed age range of participants. Additionally, in the progress report, recipients will be able to upload individual-level data on sex/gender, race, ethnicity and age, and data in a .csv format for maximum flexibility and ease of use. Benefits to collecting individual-level data include the leveraging of the types of data that many investigators are already collecting, eliminating the step of data aggregation, allowing for annual submission and better monitoring, and increasing maximum flexibility for analyses.

Following the presentation, workshop participants discussed the need to consider age groupings and provided clarity that if grant proposals use age at enrollment, it would not necessarily represent the full age range of participation. There were concerns that limited information is provided by collecting age range, but the effort is a first step in collecting information and data that are not currently collected/available. It would also be difficult to ask investigators to retroactively provide data that they have not collected. There were additional concerns that data submission would be voluntary, and it was clarified that those decisions have not yet been made. NIH will be prepared to collect and aggregate the influx of new data.

Key Takeaways

- The 21st Century Cures Act requires data on study populations, specifically including women, minority groups, and relevant age categories.
- NIH inclusion policies ensure that the distribution of study participants reflects the population needs.
- Including appropriate study participants increases the rigor and generalizability of clinical trials, and informs clinical care.
- Current data are limited by the lack of information on individuals in any given age category.
- Submissions on participant age information will address the gap in individual level data to increase the ability to conduct analyses and lead to better monitoring.

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APPENDIX VI. RESPONSES TO REQUEST FOR INFORMATION

The purpose of the RFI on Inclusion in Clinical Research Across the Lifespan (NOT-OD-17-059) is to augment information gathered during the June 1-2, 2017 workshop on appropriate age groups to be included in research studies involving human subjects. The comments gathered from the RFI will be reviewed when considering any policy changes pertaining to human subject research. The RFI was published on April 26, 2017 and was open for comment through June 30, 2017.

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

1) Best study designs that ensure the inclusion of participants from a broad range of ages, sex/gender, and race/ethnicity in clinical trials or clinical science
2) Strategies that are successful to ensure all ages are included when appropriate
3) Potential ethical challenges when including those individuals under 18 years of age, or frail or cognitively impaired older adults in trials
4) Ethical justification for excluding vulnerable populations
5) Strategies to expand current successful practices for inclusion of these populations
6) Age-related individual level data and/or summary statistics that could reasonably be provided as part of standard clinical trial reporting for NIH applicants, grantees, and ClinicalTrials.gov reports
7) Metrics that would be most helpful for interpretation of clinical trial study results – age groups, mean age with SD, median age with SD, or some other metric
8) Approaches to standardized reporting of age-related enrollment, data analysis issues, and results that would be most helpful to moving science forward
9) Potential barriers to and the opportunities for inclusion of pediatric and older populations in clinical studies
10) Any inclusion/exclusion criteria that might have the unintended consequence of reducing enrollment of pediatric and older populations in clinical trials
11) Any inclusion/exclusion criteria that might facilitate enrollment of pediatric and older populations in clinical trials
12) Any other concerns that NIH should consider in the recruitment of pediatric and older populations into clinical studies

Responses

As of June 30, 2017, the NIH had received a total of 16 responses. The common themes and key points from the responses are summarized below.

Overarching Themes Raised in the Responses

Every respondent to the RFI stated that inclusion of all relevant age groups in research studies will ensure that the findings are applicable to the widest possible range of individuals and, conversely, that exclusion from clinical research at each end of the age spectrum makes findings from that research less applicable to those populations.

Most respondents provided input on specific age groupings on which NIH-funded investigators should be required to enroll and report. Respondents were mixed on the need to collect individual level data.

Broadly, signals to the research community from NIH – whether through specific language in Funding Opportunity Announcements (FOAs) or setting additional review criteria regarding inclusion of age groups – would go far to encourage researchers to include relevant populations. Most respondents expressed appreciation that NIH held the June 2017 workshop to inform potential policy changes.

1. Best study designs that ensure the inclusion of participants from a broad range of ages, sex/gender, and race/ethnicity in clinical trials or clinical science

Eight responses addressed some aspect of how study design could ensure inclusion of participants from a broad range of age groups. One respondent stated the belief that the best design is to collect the same information on all participants, with subgroups for detailed questions. Three agreed that due to transportation and economic issues, locally available clinical trials would encourage participation from older populations at all economic levels. Two additional respondents echoed the findings presented at the workshop that encouraged investigators to design studies for participants rather than investigators, including enrollment and follow up near participants' homes (e.g., mobile units, community health workers), using new technologies that accommodate participants' needs, and utilization of pragmatic trials that leverage standard of care in clinical sites that are generalizable to the at-risk population. Still another respondent suggested that while recruitment of older, sicker adults would better represent the overall population being studied, once an adequate sample is achieved, these older age groupings could be closed out and the study refocused on remaining age groups.

Two respondents stated that NIH should instruct investigators to identify age as a variable (recognizing when disease burden is greatest), similar to race/ethnicity, and incorporate it into their study designs. A specific age inclusion recruitment plan should be part of every clinical trial application. Another encouraged NIH to consider adaptive trials and platform trials with flexible features such as dropping treatment for futility and greater use of observational data to expand information for underrepresented populations (meta-analyses). On the same note, another respondent suggested that if investigators who are running clinical trials were required to collect and record age-related information on all participants, future meta-analyses could be conducted to achieve generalizability. This same response also suggested that if the FDA were to require that data submitted for medication approval be posted publicly, re-analyses might be feasible.

2. Strategies that are successful to ensure all ages are included when appropriate

Most respondents recognized that certain research studies may be age- and condition-specific (e.g., a study on prostate cancer does not need to include adolescent girls). However, these respondents stated that enrollment in clinical research should operate under the assumption that all ages be included unless there is valid scientific justification for excluding one or more age groups. Several respondents said that NIH should immediately make this a requirement.

Five respondents specifically urged NIH to require appropriate expertise (e.g., pediatric, geriatric) on study sections to ensure that the peer review process can adequately evaluate applications for inclusion and appropriate research design for the study population. Reviewers should be provided with detailed plans for enrollment of all relevant age groups, as well as justifications for any exclusions. Included in the review should be an evaluation of consent documents and strategies to accommodate age, language, disability, mobility, and literacy across the age span. In addition, one respondent recommended that training be provided for reviewers on how to assess for, evaluate, and recommend recruitment and retention strategies known to be effective with minority populations, and that

incentivizing funds be offered to cover translation and other recruitment strategies to ensure adequate representation. Another respondent said that it would help reviewers to know the expected number and age range of participants, including children.

Three respondents suggested that NIH work more closely with patient organizations and their outreach networks to assist in recruitment.

Another respondent outlined a list of successful strategies to engage individuals in research studies, including telephone calls, text messages, email, post mail, paper and electronic flyers, and suggestions/referrals by health care providers during medical appointments. To engage youth in studies, text messaging has proven to be most effective. The same respondent cautioned that communications in all platforms should be done with lesbian, gay, bisexual, transgender (LGBT) and gender-expansive cultural competence.

3. Potential ethical challenges when including those individuals under 18 years of age, or frail or cognitively impaired older adults in trials

One respondent pointed out that chronological age itself does not indicate susceptibility to risk or vulnerability to undue influence, but rather that an individual's capacity to consent to participation in research varies, depending on a range of cognitive abilities and situational factors at different stages of life. Thus, ethical inclusion in research of individuals across the lifespan requires the recognition of common vulnerabilities and risks within each stage of life.

Another respondent who sought greater inclusion of the patient population in research urged more training for staff who approach patients about obtaining informed consent.

4. Ethical justification for excluding vulnerable populations

Three responses addressed ethical issues related to the inclusion of vulnerable populations (or justification for exclusion) in clinical studies, recognizing that many of these groups – older individuals, children, individuals who are cognitively impaired, and pregnant women – are understudied. One respondent stated that the broad concept of justice demands the responsible inclusion of these populations in research so they may benefit, and provided a list of major bioethics reports that include a fuller discussion of these issues. Another respondent asserted that applicants should be required to justify age-based, comorbidity, or functional inclusion/exclusion with strong scientific rationale. The third respondent wrote that while poor physical or mental health may provide justification for exclusion, neither end of the age spectrum should be used as reason for precluding participation in research.

5. Strategies to expand current successful practices for inclusion of these populations

Based on the assumption that study populations should mirror the demographic prevalence of conditions in the community, half of the respondents provided feedback on how to expand enrollment in clinical research to a wider range of participants. Both a strong statement from NIH about the need for all clinical trials to actively recruit older adults and using preferred terminology (i.e., "older adults" or "older people") when describing a study population (including NIH-issued FOAs) would be helpful. Two respondents said that NIH should provide active support by developing "toolkits" to help investigators recruit participants from across the lifespan into their studies; making these tools available would greatly assist next-generation scientists with less experience. Another respondent suggested that local academic institutions could be prepared to answer questions and help address problems concerning clinical trials. Another respondent suggested that IRBs should incorporate and update training modules

on LGBT cultural competency, so that researchers working with human subjects could be better prepared to recruit LGBT individuals.

Two responses provided specific strategy suggestions for expanding inclusion of older populations, again focusing on taking the research into the community, integrating it into holistic elder care, and using tools such as remote assessments and community health centers. Another response noted that NIH/institutional support for community engagement infrastructure would assist in recruiting representative study populations.

Another respondent noted that, once recruited, inclusion of these populations requires appropriate oversight, such as ongoing identification of impairment in decision-making capacity, efforts to obtain a legally authorized representative should a participant's cognitive ability decline, and constant engagement of family and other caregivers in the research process. This idea was echoed by another respondent, who suggested that when grantees are not meeting their enrollment targets by race, ethnicity, or language, NIH should offer evidence-based strategies to improve recruitment and retention, along with possible consultation from a mentor.

6. Age-related individual level data and/or summary statistics that could reasonably be provided as part of standard clinical trial reporting for NIH applicants, grantees, and ClinicalTrials.gov reports

Five respondents stated that NIH should immediately require inclusion of all relevant ages in NIH-sponsored research; this information should be collected and reported annually, and made available publicly. Individual data for each study could be reported using existing mechanisms, such as the NIH Research Portfolio Online Reporting Tool and ClinicalTrials.gov.

One respondent suggested mandating that all studies list the number of participants who are over 75 years of age.

7. Metrics that would be most helpful for interpretation of clinical trial study results – age groups, mean age with SD, median age with SD, or some other metric

Nearly all the respondents felt that NIH leadership in establishing a standardized data template with specific age groupings would provide an analytic tool for the research community and, ultimately, the users of the data, whether or not the NIH chooses to move forward with the plan to collect individual-level data. However, there was not complete accord as to what ages (in years) should comprise those groupings.

Several respondents reiterated that the current "grouping" of children under 18 years of age is inadequate for the purposes of pediatric research. Four respondents provided specific suggestions/tables for age groupings (in years) for use by investigators as they enroll participants in clinical trials. Three focused on pediatric age groups but recommended that the groupings be created according to developmental stage (even including fetal): preterm neonates, neonates, infants, toddlers, early/middle/late childhood, early/late adolescence. Three respondents further suggested moving the upper age limit of late adolescence to 26 years, to reflect recent developmental research.

Three respondents provided specific input on groupings (in years) that might be used for older study participants, beginning at 65 years.

Respondents cautioned NIH to regularly assess inclusivity with evaluations comparing anticipated enrollment described in grant applications with actual enrollment outlined in progress reports. One

respondent suggested that NIH require investigators to include a comparison of their actual enrollment to epidemiological distributions of target conditions by age, gender, race, and co-existing conditions.

8. Approaches to standardized reporting of age-related enrollment, data analysis issues, and results that would be most helpful to moving science forward

Seven respondents supported reporting the age of participants in clinical research at the time of enrollment, strongly encouraging a standardized approach to facilitate compilation and presentation of data across all NIH Institutes and Centers. They stated that such required reporting would assist investigators in ensuring that participants of appropriate ages are included throughout the study, making it simpler to answer the research questions posed, and allow other investigators to identify gaps for purposes of future studies. One respondent suggested that the "default" on grants.gov and NIH reporting tables be "no upper age exclusion."

One respondent preferred that age information be collected at study entry, throughout the study, and at study end to capture age span. One respondent stated that NIH should require investigators to publish as a limitation of their research whether the population studied adequately represents the population with the disease. Another recommended that NIH develop standardized policies outlining expectations of program officers in working with investigators to remedy any gaps in study populations.

Several respondents urged NIH to make these data public, and to implement age-reporting requirements fully and quickly, referencing the 21st Century Cures Act provisions.

One respondent offered a single, standardized table to capture age, sex/gender, and ethnicity, stating that a single format for reporting would greatly assist the research community. Another respondent suggested that NIH adopt the FDA's Drug Trials *Snapshots* program to facilitate access to information about patient representation in clinical studies, and that the information presented in these reports include specific ages and information on sexual orientation and gender identity.

9. Potential barriers to and the opportunities for inclusion of pediatric and older populations in clinical studies

Five respondents stated that to address the specific health needs of pediatric and older populations, targeted FOAs should be published, in addition to the new policy on FOAs for clinical trials, and that age inclusion should be stated as a review criterion.

Two respondents urged that peer review groups include reviewers with sufficient expertise (e.g., pediatric and geriatric) to judge whether proposed studies adequately include relevant populations.

One respondent stated that potential participants' comorbidities may pose a barrier to their eligibility for a clinical trial. However, another respondent recommended that NIH provide guidance and incentives for investigators to plan explicit enrollment strategies for older adults in the highest age strata and those with multiple chronic conditions.

10. Any inclusion/exclusion criteria that might have the unintended consequence of reducing enrollment of pediatric and older populations in clinical trials

None of the respondents identified any criteria.

11. Any inclusion/exclusion criteria that might facilitate enrollment of pediatric and older populations in clinical trials

One respondent listed several criteria that might help with benchmarking and facilitate enrollment of older populations, including expanded comorbidity to enable cumulative deficit assessment, a brief indicator of cognitive assessment, a brief indicator of mobility status, and a brief indicator of independence. Another respondent recommended that functional measures (e.g., gait speed) should be included in trials involving older adults, and that cognitive status, especially executive function and memory, should be assessed.

Another respondent focused on biological, rather than chronological, age, suggesting the development of tools to be used by investigators.

12. Any other concerns that NIH should consider in the recruitment of pediatric and older populations into clinical studies

Three respondents raised other concerns related to the inclusion of older populations in clinical studies. One pointed out that using a younger age limit for diseases primarily affecting older individuals (Parkinson's) would skew research results. Another suggested ongoing education about the value of research to payers and to the general public through public education campaigns. One respondent suggested that the FDA establish a Geriatrics Advisory Committee to regulate drugs and devices specifically for use in individuals over age 75 years. Another noted that younger and older LGBT people are especially vulnerable as they negotiate their sexual and gender minority status while dependent on parents or caregivers.

Respondents provided many references and links to reports to augment their comments on inclusion across the lifespan. Review of ideas from groups that have discussed these issues, such as the "Integration Across the Lifespan Domain Task Force," was also encouraged.

Conclusion

NIH would like to thank the respondents for their thoughtful comments. This feedback will help to inform NIH's deliberations about potential policy changes and future study designs that could be aimed at facilitating inclusion of appropriate populations in research studies.

Organizational Respondents to the RFI (NOT-OD-17-059)

- Florida Breast Cancer Foundation
- Federation of American Societies for Experimental Biology
- Society for Pediatric Research
- March of Dimes Foundation
- Elizabeth Taylor Medical Center
- Public Responsibility in Medicine and Research
- The American Geriatrics Society
- Alpha-1 Foundation
- American Academy of Pediatrics
- The Gerontological Society of America

In addition to the organizations list above, there were five individuals who responded to the RFI.