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Commentary Title

Enhancing Drug Evaluation in Diverse Populations and Older Adults: National Academies of Sciences, Engineering, and Medicine Considerations

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The total value to society of eliminating all life expectancy disparities attributable to underrepresentation of minorities for the three common conditions of diabetes, heart disease, and hypertension was approximately $11 trillion based on a commissioned analysis that applied the Future Elderly Model for the National Academies of Sciences, Engineering, and Medicine (NASEM) Committee on Improving the Representation of Women and Underrepresented Minorities in Clinical Trials and Research.[1] While older adults experience higher rates of these comorbidities[2] and polypharmacy[3] than the general population and are the major utilizers of medications,[4] they are considerably underrepresented in clinical trials and clinical research overall.[5] The prioritization of COVID vaccines for older adults as part of Phase 1 by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices was a prominent example of the importance of studying older adults and particularly older adults with chronic disease in clinical trials.[6]

To address the societally pressing challenge of the lack of older adults, women, and minorities in clinical trials and medical research in general, NASEM hosted a virtual workshop titled “Drug Research and Development for Adults Across the Older Age Span” in 2020. The following year through 2022, NASEM performed a Congressionally mandated consensus study with culminating report titled “Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups”. The goal of these NASEM activities was to examine and shed light on the challenges and opportunities in drug research and development for older adults, women, and underrepresented groups and to explore hurdles that impair clinical studies in these populations. The NASEM events described the array of consequences due to underrepresentation of women and minoritized populations as well as the salient conclusions based on the evidence (Table 1).

Barriers to necessary representation of underrepresented and excluded populations in clinical research in the current research system has reduced participation by a diverse

population in clinical trials and clinical research at multiple levels. Individual research studies, the institutions that conduct research, funders of studies, institutional review boards, medical journals, and the broader landscape of national policies and practices that govern research all contribute to barriers of populations historically excluded from clinical research.

At the level of an individual research study, the factors and problems that lead to the underrepresentation and exclusion of certain populations in clinical trials and research begin with and follow the life cycle of a project. Understanding and resolving underrepresentation and exclusion of these populations in research requires careful examination of almost every stage in the research process itself. This includes at the time research questions are developed. The composition, training, and attitudes of the research team must also be considered to foster the thoughtful dialogue and insight necessary to maximize representation of needed populations. Research site selection is also a key facet in bolstering access to priority populations for increasing representativeness. Intentionality in “meeting people where they are” has been identified as a key pillar in improving representativeness and validity of studies. Consideration on participant selection and study protocols in general that includes determination of sampling approaches, recruitment methods, inclusion and exclusion criteria must also be carefully evaluated. Appropriately performed this includes review of informed consent processes, remuneration for study participants, as well as development and inclusion of multilingual recruitment and consent documents. For older adults it has been noted that while most older adults with the most common chronic conditions that result in hospitalization in the US occur in older people with multiple conditions, having multiple conditions was often an exclusion criterion in NIH trials. This approach effectively ensured that the representative older population was systematically excluded from the studies. Deliberate considerations of the consequences of inclusion and exclusion criteria decisions on representativeness must be prioritized as fundamental to the research.

Institutional structures are also a barrier to appropriate inclusivity. Medical institutions of different types face a
range of structural barriers to inclusion in clinical trials. For example, although academic medical centers conduct 55 percent of the extramural medical research supported by the NIH, and operate 98 percent of the nation's 41 comprehensive cancer centers as of 2019, sustainably and meaningfully engaging underrepresented and excluded populations often does not align with the traditional incentive structures for researchers at these institutions. Recruiting diverse population groups and properly engaging with community members, which is time-consuming and requires investments to build and sustain trust, are only minimally considered in promotion and tenure decisions at academic medical centers. While community health centers serve a much more diverse community than academic medical centers, these institutions also face barriers to clinical trials and research recruitment, which include limited provider knowledge about available research opportunities and challenges with electronic health record (EHR) infrastructure, that can limit providers' ability to query the EHR using study inclusion and exclusion criteria.

Institutional review boards can also present barriers to diverse participation in clinical trials by limiting the types and amount of compensation given to research participants to avoid the impression of coercion or undue influence. However, limiting incentives may ultimately compromise beneficence and justice, two of the ethical principles for research with human subjects detailed in the *Belmont Report*.[7]

Research funders also have several roles and responsibilities that can influence the diversity of clinical trials. These include setting funding priorities, deciding which projects ultimately get funded, providing adequate funding to recruit and retain participants, requiring transparent reporting, and evaluating research outputs. Most clinical trials are funded by pharmaceutical firms. These trials present barriers, including out-of-pocket costs for participants, which are

often not discussed in the informed consent process, industry pressures to gather data quickly, and the selection of easy-to-recruit samples often being incentivized. It should be noted that some of these barriers are not solely unique to industry-sponsored trials.

Peer-reviewed medical journals serve as the gatekeepers to scientific advancements in clinical practice and health. Their editors yield great power for what is, and is not, published in their pages. Lack of representation on editorial boards and other journal leadership position may contribute to biases in publication. Recent focused efforts have been formalized to improve representation on journal editorial boards. This included the release of The Journal of the American Medical Association priorities to Strive for and Promote Diversity, Equity, and Inclusion (DEI) that included the following Key Approaches: Update Journal Mission Statements to include inclusivity aims, Appoint an Editorial Director of Equity, Improve Editorial Diversity, Promote Awareness of and Responsibility for DEI, Formalize Process for Assessment and Reporting, Expand Editorial Fellowship Program, Hold Seminars on Excellence in Scientific Writing, Continue to Publish Articles on DEI, Identify and Invite Peer Reviewers and Authors of Opinion Articles With DEI Expertise, Encourage Authors to Address Systemic and Structural Problems to Advance DEI, Review and Update Inclusive Language Guidance for Authors and Editors Update Statistical Analysis Guidance, Participate in International Collaboration on Standards and Policies.[8] While the JAMA effort is a necessary step, many more journals must plan, execute, and monitor their efforts to ensure representativeness regarding inclusivity.

These activities from NASEM developed an array of policy considerations and recommendations to narrow the inclusiveness gap for minorities, women, and older adults in clinical research. In terms of bolstering reporting, transparency, and accountability, the NASEM report recommended that The Department of Health and Human Services (HHS) create a research equity task force within HHS charged with coordinating data collection and designing study subject recruitment and accrual monitoring that would track across federal agencies, including the Food and Drug Administration (FDA), National Institutes of Health (NIH), Centers for

Disease Control and Prevention (CDC), Agency for Healthcare Research and Quality (AHRQ), Health Resources Services Administration (HRSA), Indian Health Services (IHS), and the Centers for Medicare & Medicaid Services (CMS). This task force would submit an annual report to Congress on the status of clinical trial and clinical research enrollment in the United States that would include patient counts recruited into clinical studies by phase and condition. Mandated data would include the study patients age, sex, gender, race, ethnicity, study location, and recruitment site. The annual report would also describe to what degree the study population was representative of the conditions studied as well as the sponsors of the research. Creating a real-time, data dashboard was offered as an example of a tool to make data more accessible and transparent continuously. The report also recommended clarifying how "representativeness" was determined and evaluated for protocols and product development plans.[1] This would serve to not only help discern the older adult representation, but allow for stratification of the older adult categories by minority, gender, and location to ensure that studies line-up with actual disease prevalence for older adult sub-populations. This coordinated with a frequent comment that heterogeneity of older adults must be better tracked with improved tools and technology to enhance knowledge and treatment outcomes to increase the proportion of heterogeneous older adults in clinical trials. The improved use of modern tools was also broached in terms of better use of technology such as social media to improve recruitment of older adults from diverse backgrounds into trials.[9] For a path towards equitable compensation to research participants and their caregivers, the NASEM report recommended developing specific guidance that would include systematically modified compensation for those who will experience a financial burden when participating in research activities. Receipt of a detailed recruitment plan should be required by The FDA no later than at the time of Investigational New Drug and Investigational Device Exemption application submission.

To facilitate that trial characteristics are consistently labeled throughout the database and can be easily disaggregated, exported, and analyzed by the public, NIH should standardize the submission of demographic characteristics to ClinicalTrials.gov beyond current guidelines. A

theme across the NASEM activities was that NIH can better leverage its role as a funder to motivate improved inclusiveness of older adults and minorities. The score-driving criteria that measure the scientific integrity and overall impact of a NIH grant proposal should formally include participant representativeness data. Patient representativeness data should be components of the assessment of the scientific approach, including whether it is appropriate for concluding insights for the populations to whom the results are intended to generalize. In the 2020 NASEM workshop, Alzheimer's Disease research was referenced as an area in which representation of older adults would be expected. The concept of requiring a justification for not including older adults was described on several occasions.[9] The NIH should also assess in its annual review of progress reports of funded studies whether a given study has met the proposed enrollment goals of representativeness by race/ethnicity, sex, and gender, and should establish a plan for remediation that includes criteria for pausing funding that has not met predefined recruitment goals. Journal publisher, editors, and the International Committee on Medical Journal Editors should 1) require information on the representativeness of studies for submissions to their journals in context to the affected population; 2) consider this information in acceptance decisions; and 3) publish this information for manuscripts that are accepted. The overall representativeness of the trial, including how well the study population aligns with the target population should be evident in the publication. The Office of Human Research Protections (OHRP) and the FDA should advise local institutional review boards (IRBs) determine and report the representativeness of clinical trials as one measure of sound research design. Study protocols in which the pre-specified enrollment departs markedly from the disease prevalence would trigger request for a justification statement or possible remediation. The commitment to and value of educating review bodies across the clinical development continuum to incorporate considerations of age, gender, and minority status dimensions was a prevailing theme.

In terms of coverage and payment, CMS should revise its guidance for coverage with evidence development to require that study protocols include a plan for recruiting and retaining participants that are representative of the affected beneficiary population in age, race, ethnicity,

sex, and gender. Congress should direct the FDA to enforce accountability measures already present, as well as establish a taskforce to study new incentives for new drug applications for trials that achieve representative enrollment. This recommendation has in fact been enacted in the Food and Drug Omnibus Reform Act of 2022 (FDORA)[10] that requires sponsors of phase 3 or other pivotal medication studies to submit diversity action plans by the time the study protocol is submitted. A synthesis on the current environment was recently detailed in the special article "Current status of inclusion of older groups in evaluations of new medications: Gaps and implementation needs to fill them" in this journal.[11] Incentive programs should be designed to improve representativeness in clinical research and ensure they do not impede access to new therapies. Expedited coverage decisions should be considered for therapies based on clinical programs that achieve representativeness of the populations most affected. To incentivize community providers to enroll, participants in trials CMS should develop reimbursement approaches for the time and infrastructure that is required. Development of new payment codes would allow CMS to reimburse activities associated with clinical trial participation including data collection and personnel to support research education and recruitment endeavors. The Government Accountability Office (GAO) should assess the impact of previously enacted policies reimbursing routine care costs associated with CMS trials.

To foster equitable compensation to research participants and their caregivers, federal agencies, including the OHRP, NIH, and FDA, should develop guidance to direct IRBs on appropriate remuneration for study participation. This new guidance should encourage and allow for variable compensation to research participants and their caregivers commensurate with time commitment and financial burden of participating. There are trial designs tested that offer the prospect for increasing enrollment of older adults, including adaptive platform trial designs, home-based trials, mechanistic modeling, simulations, real-world data, and pragmatic clinical trials. Clinical trials can now be successfully completed in many non-traditional clinical trial environments that have included barber shops and pharmacies.[9]

Similarly, all sponsors of clinical trials and clinical research (e.g., federal, foundation, private and/or industry) should ensure that trials provide adequate compensation for research participants. A diverse, inclusive, and representative workforce, particularly in leadership circles, should be maintained for all organizations involved in clinical research. Recognition of research, training, and professional activities to promote community-engaged scholarly efforts and other research to enhance clinical trial representativeness should be included as areas of excellence for promotion or tenure considerations. The HHS should substantially invest in research infrastructure in the community. To bolster capacity of community health centers and safety net hospitals to participate in clinical research funding should be directed to agencies such as the HRSA, NIH, AHRQ, CDC, and IHS. These recommendations and recent advances to date in each area are summarized in Table 2. Progress has been made at the government level with passage of FDORA as well as coordinated efforts to improve representativeness in clinical research by other agencies, academic institutions, foundations, and non-governmental organizations. Yet, recommendations on changing the composition of the workforce and individual academic entities will require a longer timeframe and concerted effort as will building trust across all communities.

Bridging the inclusion gaps for older adults, minorities, and women in clinical research is achievable and necessary. However, it will demand intentional and committed policy efforts with coordination from an array of stakeholders. Fortunately, informed guidance now exists that we must immediately harness and apply to reverse our flagging population health outcomes and move us closer to peer nations.

AUTHOR CONTRIBUTIONS

Dr. Watanabe contributed to the concept and design and preparation of the manuscript.

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