The Journal of Nutrition, Health and Aging 29 (2025) 100587

Contents lists available at ScienceDirect

The Journal of Nutrition, Health and Aging

journal homepage: www.elsevier.com/locate/jnha

Editorial

Advancing the methodology of clinical trials for aging populations: A call to innovation, inclusion, and global relevance

The ongoing global trend of population aging urges the design and implementation of clinical trials that are not only scientifically rigorous but also inclusive and tailored to the unique needs of older adults. Indeed, despite representing the largest and fastest-growing segment of health-care service users, older individuals remain underrepresented in clinical trials. It is especially concerning that clinical trials systematically exclude those who are representative of the typical patient populations that will eventually use the tested interventions [1]. Their omission is often justified due to chronological age, multimorbidity, frailty, cognitive impairment, disability, or logistical concerns [2,3]. However, the gap between trial populations and real-world patients compromises the external validity and generalizability of clinical evidence, while perpetuating health inequities and hindering person-centered care. As a matter of fact, older adults are often treated based on clinical guidelines and treatment protocols that are extrapolated from research conducted in younger, healthier, and more homogeneous populations, potentially leading to suboptimal (or inappropriate) care and outcomes [4].

The scoping review by Cesari et al. [5] provides a timely and practical response to the methodological limitations that affect research involving older adults. By screening over 4700 reports, the authors identified 80 relevant studies, yielding 1119 methodological insights on the design and deployment of clinical trials involving older adults. These entries were consolidated into 120 pragmatic recommendations, categorized across 13 clusters encompassing all stages of a clinical trial's lifecycle, from its planning to post-trial activities. The synthesis, enriched by consultations with experts from low- and middle-income countries (LMICs), underscores the need to address structural and contextual barriers limiting older adults' participation in clinical trials, including limited financial support, non-inclusive infrastructure, systemic ageism, and logistical constraints. The complexity of these issues is amplified in LMICs and low-resource settings, where additional limitations (e.g., suboptimal training in geriatrics of healthcare providers, restricted access to research facilities, low literacy among participants, frequent underdiagnosis of health conditions) further complicate clinical trial design and implementation.

Unlike most research guidance that is conceptualized for high-income contexts, the work by Cesari et al. [5] integrates expert input from seven LMIC-based researchers with direct experience in aging-related studies. This collaboration was instrumental in shaping the final set of recommendations, ensuring cultural, logistical, and ethical relevance in low-resource settings. According to the World Health Organization (WHO), by 2050, over two-thirds of the global population aged 60 years or older will be residing in LMICs [6]. These regions face the dual challenge of rising demands linked to chronic conditions and disabilities, along with systemic limitations in research infrastructure, training, and funding [7]. The LMIC expert panel identified several major context-specific challenges, including lack of ethics infrastructure, transportation barriers, seasonal inaccessibility, low health literacy, and legal constraints on participant compensation.

In response, Cesari et al. [5] propose practical and contextually appropriate solutions to enable the development of representative clinical trials in such contexts. Notable examples include the deployment of mobile assessment teams, the establishment of age-friendly facilities, the implementation of home visits, the simplification of consent procedures, and the use of culturally validated instruments. The identification of complementary measures (e.g., inclusion of reflexivity statements, translation of findings into local languages, proactive community engagement) plays a key role in the success of this approach and further reinforces adherence to principles of equity, cultural competence, and research sustainability [8].

Older individuals often exhibit multimorbidity, frailty, physical and cognitive disability, and social vulnerabilities, which interact in complex ways and challenge traditional models of trial design. In addition, their priorities frequently differ from those of younger populations, with greater emphasis placed on quality of life, functional and cognitive independence, and mental health rather than disease remission or life extension [9,10]. As such, a methodological recalibration is warranted to avoid conducting clinical trials whose findings are scientifically valid but practically irrelevant.

To address this critical gap, Cesari et al. [5] propose to focus on outcome measures that reflect the lived experiences and priorities of older adults, thus moving beyond conventional biomedical endpoints. Accordingly, priority should be given to domains like functional ability (e.g., mobility, daily living activities), psychosocial well-being, and independence, that are more representative of what older individuals value [10,11]. The call for co-designed outcomes reinforces the importance of engaging all relevant stakeholders in the choice of endpoints that maximize the relevance and translational potential of research.

A notable insight from the review is that many of the proposed methodological improvements are cost neutral. For example, simplifying consent forms, co-designing protocols with older adults, expanding eligibility criteria, or incorporating geriatric assessments can be implemented with minimal financial investment, while promoting significant impact [12]. This is particularly relevant in LMICs, where financial resources are limited, but innovation is crucial.

The review also directly addresses the issue of structural ageism in research, highlighting the widespread exclusion of older adults who reflect patients encountered in everyday clinical practice [13,14]. The authors argue for a shift toward eligibility criteria based on functional

http://doi.org/10.1016/j.jnha.2025.100587
Received 16 May 2025
Available online xxx

capacity rather than chronological age, recommending the use of evidence-based tools such as the comprehensive geriatric assessment to elaborate scientifically justified inclusion strategies. These recommendations align with and promote the principles of the United Nations Decade of Healthy Ageing (2021–2030) initiative and its plan of action for research and innovation [15]. They are also reflected in a resolution from the 75th World Health Assembly, which emphasizes the need to improve research outputs by adapting clinical trial methodologies to "the needs of major population groups that the intervention is intended to benefit, with a particular focus on under-represented populations" [16].

The review opens several avenues for further enhancement and research. The transition from conceptual recommendations to practical strategies will require a focused research agenda particularly tailored to the constraints and opportunities in low-resource settings. Future work should also establish a core set of indicators to monitor inclusivity, representativeness, and the use of age-relevant endpoints. These metrics are essential for tracking the adoption and effectiveness of methodological innovations. Comprehensive strategies need to be devised to foster engagement with older adults, as well as caregivers, community organizations, and policymakers. This is essential to enrich the recommendations and identify possible latent barriers [17]. Finally, the full potential of digital tools for recruitment, engagement, and follow-up should be harnessed to overcome traditional difficulties and foster a more accessible, person-centered approach to global clinical research in geriatrics.

In summary, the scoping review by Cesari et al. [5] is expected to serve as a valuable practical resource for advancing the methodology of clinical trials involving older adults. Their work not only collates a broad and fragmented body of evidence but also enhances it by incorporating global, ethical, and person-centered perspectives. The question now is not whether to act, but how quickly. Funders, regulators, trial networks, and scientific journals are called to operationalize these recommendations and their possible future refinements into standards, policies, and training. Only then can we ensure that the science of aging truly serves the population it is intended to benefit.

Declaration of Generative AI and AI-assisted technologies in the writing process

No Generative AI or AI -assisted technologies were used in the writing process.

Funding

This work was partially funded by the Italian Ministry of Health (Ricerca Corrente 2025) and Next Generation EU in the context of the National Recovery and Resilience Plan, Investment PE8—Project Age-It: "Ageing Well in an Ageing Society". This resource was co-financed by the Next Generation EU (DM 1557 11.10.2022). The views and opinions expressed are only those of the authors and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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