Age Is Just a Number: Considerations for Older Adults in Cancer Clinical Trials

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Abstract

Older adults continue to be underrepresented in cancer clinical trials, despite most cancer occurrence peaking in the later decades of life. Consequently, diagnostic and management strategies are commonly extrapolated from data on younger patients, thus challenging the delivery of informed cancer care in this patient population. Several recommendations and calls to action have been released by cancer societies, advocacy organizations, and regulatory agencies to guide inclusion of older adults in clinical trials. Effective implementation, however, requires awareness and close collaboration between all stakeholders involved in the clinical trial journey. We herein provide insights and experience from a drug developer on key considerations to optimize participation and retention of older adults in cancer clinical trials and discuss those under 4 key domains: trial eligibility and design, assessments and endpoints, patients and oncologists, and data reporting.

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The use of eligibility criteria that explicitly exclude patients on the basis of age appears to be declining. In a recent study, upper age restriction criteria were identified in as low as 10.1% of 742 phase 3 randomized clinical trials (combined total enrollment of 449,720 patients), with a median age cutoff of 72 years (15). Thus, although enrollment criteria restrictions based on age cutoffs could be a prime cause of age disparities, they cannot fully explain the persistent underrepresentation of older adults in cancer clinical trials.

There is now increased understanding that reliance on age alone to determine clinical trial eligibility should be avoided. Alternate eligibility criteria that exclude patients on the basis of functional status, organ function, comorbidity or co-medication profile, and previous malignancy may also contribute to under-representation of older patients, especially when uniformly applied. These criteria are aimed to homogenize the study population and mitigate the risk of potential adverse reactions from experimental drugs; however, they are often included from one study protocol to the next with little scientific basis (8,16,17). Ideally, protocol design should begin with zero exclusions, and criteria added only based on specific compelling scientific or ethical rationale (8). Suggestions and recommendations to revise criteria such as creatinine clearance, previous malignancy, performance status, and frailty to maximize participation have already been made through joint statements by ASCO, Friends of Cancer Research, and the FDA (8,18). Seeking input from geriatric oncology specialists when such exclusion criteria are considered can help mitigate overuse (19). Moreover, when exclusions are necessary because participants with impaired organ function would be at higher toxicity risk, an appropriately specific measure of organ dysfunction should be used that does not lead to the unnecessary exclusion of older participants with milder dysfunction (17).

The inclusion of older patients in early phase studies would establish drug metabolism and clearance, drug-drug or drug-disease interactions, and concerns regarding vulnerability to a particular toxicity in older adults (17,20). Decisions on pivotal trial eligibility criteria and design could then stem from translational research and early phase trials to inform the impact of specific parameters on efficacy, safety, and dosing and should begin with zero exclusion assumptions (17). For example, in a retrospective analysis of patients enrolled in phase 1 clinical trials for gynecologic malignancies from 2010 to 2016, older patients (70 years and older) had similar toxicity profiles compared with younger patients, suggesting they do not need to be categorically excluded from further randomized trials (21).

Specific dose evaluation in older patients could prove noninferior in terms of overall treatment benefit and produce less toxicity in elderly, frail patients (8). A considerable gap persists in such “early” knowledge, and inclusion of older patients in early phase trials remains rare. Real-world evidence can provide valuable insights to inform trial designs by evaluating effectiveness and safety in older and diverse patients not represented in clinical trials (14,22).

Additional opportunities to address the evidence gap may include the use of adaptive clinical trial designs, starting with a narrower population with further cohort expansion to a broader diverse and older population, using lower or stepwise dose interventions in older patients if suggested by interim safety data (17,23). Stratification in randomized trials and assignment of parallel arms with older patients in open-label trials may also be used to evaluate efficacy and safety. Hierarchical testing could be used to evaluate the primary endpoint in a modified intent-to-treat population of younger patients for example, and secondary endpoints can be assessed in the overall intent-to-treat population including all age groups (20). Several innovative and contemporary trial design approaches have also been proposed (23,24). Pragmatic clinical trials conducted in the context of standard care are also an option to enroll older and more vulnerable patients with more flexible eligibility criteria (25).

At Pfizer, we have established the Diversity in Clinical Trials Center of Excellence to support our clinical trial teams and promote considerations of diversity from the earliest stages of study design. The center provides demographic data on epidemiology of the disease we are targeting to help drive diverse and representative enrollment as well as support appropriate trial site identification based on population distribution. We have also designed technology platforms that allow real-time patient recruitment and retention data and provide early signals on where we should deploy additional recruitment tactics. Thus, our general approach entails consideration of the epidemiology of the disease and design of studies that reflect the age distribution, beginning with no age exclusion. For example, in some of our recent trials recruiting heavily pretreated men with metastatic castration-resistant prostate cancer, which naturally implies an advanced age group, removal of upper age cutoffs from eligibility criteria and reliance on functional measures that have a scientific rationale allowed recruitment of a trial sample with a median age of 69 years and up to 84 years (TALAPRO-1, NCT03148795) (26). Beyond data from clinical trials, we also rely on real-world evidence studies to further our understanding of treatment patterns and functional and quality-of-life outcomes in older patients; for instance, the PalomAGE study (EUPAS23012) is a prospective observational study that we recently initiated specifically to understand experience of women aged 70 years and older with locally advanced or metastatic breast cancer (27).
Assessments and Endpoints

Optimized inclusion of older adults in cancer clinical trials should be accompanied by the addition of appropriate endpoints for this patient subgroup. In a review of endpoints of all phase 1-3 trials reporting data from elderly patients in 2001-2004 and 2011-2014, overall survival was the most common primary endpoint, and a shift was noted in the reporting of tumor-centered endpoints to composite endpoints. Disease-specific survival was very infrequently reported despite its importance in distinguishing deaths from cancer-unrelated causes. The use of functional endpoints and patient-reported outcomes was notably rare across both time periods (28). This surely needs to be revisited considering the value and weight of quality of life and functional independence in older patients compared with prolongation of life (8,23).

Collection of typical geriatric assessment data including functional status, cognitive function, frailty measures, nutritional status, and comorbidities during the trial would help further establish the benefits and risks of interventions in older patients and identify independent predictors of morbidity and mortality (19,23,29). Sponsors could work closely with patient relatives and caregivers, social and behavioral scientists, patient advocates and advocacy groups, geriatricians, and geriatric oncologists to consider the relevance and feasibility of clinical trial assessments and endpoints in older adults, which could also help materialize treatment value during drug approval and reimbursement discussions (20,22). Developing appropriate strategies to capture and manage adverse events in older patients may also facilitate retention and completion of clinical trials (20).

We have had successful experience in using geriatric assessment tools in studies targeting older patients with cancer. For example, in a real-world observational study analyzing outcomes in advanced or metastatic breast cancer [POLARIS, NCT03280303 (30)], assessment of functional status and degree of dependence using the Activities of Daily Living (31) and of frailty using the Geriatric 8 (32) screening tools in women aged 70 years and older provided us with further insights on the role of therapy in this age group beyond what we could have realized using conventional assessment of Eastern Cooperative Oncology Group performance status alone. In the aforementioned PalomAGE study (27), we are also using the DIALOG Geriatric Core Dataset (G-CODE) as a standardized, validated, and reproducible set of tools for geriatric evaluation across 7 domains: social environment, autonomy, mobility, nutritional status, cognitive status, mood, and comorbidities (33). This would be the first prospective study to incorporate the DIALOG G-CODE questionnaire in a population of patients with advanced breast cancer.

Patients and Oncologists

Elderly patients are usually willing to consider participation in cancer clinical trials but cite lack of information on opportunities being readily available to them as a barrier to participation (23,34,35). Oncologists may not consider older adults for participation in clinical trials, with bias, toxicity concerns, and insufficient time or support being recognized as key factors in failing to offer clinical trials for their older patients (23,36). Community oncologists additionally report that patient attitudes, beliefs, and understanding are among the main barriers for inclusion of their older patients in clinical trials (36). A large proportion of older adults receive their cancer care in the community, with limited access to clinical trials conducted at large urban centers (36).

The accelerated adoption of digital tools for data capture, passive collection of patient information, and decentralized study design brought about by the COVID-19 pandemic should be further leveraged to improve diversity of clinical trial participants including those in rural areas as well as patients with limited mobility or lacking access to research institutions, including older adults (17). More trials can be open in the community setting by reducing the institutional burden on participation through improved technology (22), coupled with improving awareness and education about clinical trials through adapted materials and collaboration with community health educators to better reach older patients (19). Offering caregiver support and mitigating the challenges of trial logistics through alternative approaches to site visits and support when they are necessary will encourage participation (20).

Recruitment challenges can be addressed during study design by placing the patient experience at the center of the process with a focus on reduced burden of participation and ease of monitoring via alternative approaches such as local imaging and home visits so that we can meet older and frail patients where they are (14,17). Routine patient care costs during clinical trials may not always be covered, especially for underrepresented groups, and add to the disparity in clinical trial inclusion. Efforts to reduce such cost and coverage barriers are necessary to optimize participation (37,38).

At Pfizer, we have adopted several initiatives to optimize awareness and access to clinical trials in underserved and underrepresented populations, especially in the community setting. In some programs, we are offering study sites augmented staffing with a clinical recruitment coordinator to facilitate community reach. Moreover, the Patient Centricity Initiative launched by Pfizer Oncology in 2019 utilizes partnerships with various cancer patient and professional advocacy organizations to prioritize health equity and health literacy and involve underrepresented patients in clinical research. The Blue Button Program at Pfizer was also first of its kind to give patients participating in our trials their clinical data, with the hope that this can build trust in the clinical trial process and study sponsor and mitigate any concerns an elderly patient may have with regards to experimentation. We have also joined other industry partners in the Center for Information and Study on Clinical Research Participation (www.ciscrp.com), a first-of-its-kind cross sponsor collaborative dedicated to educating and informing the public, patients, medical and research communities, the media, and policy makers about clinical research and the role each party plays in the process. The initiative provides an opportunity to share best practices, identify barriers to recruitment in clinical trials, and co-create actionable solutions. Although the use of telemedicine in clinical care and research has considerably evolved over the past 2 decades, the COVID-19 outbreak forced us to implement these changes more quickly and on a larger scale. We have shared our experience and best practices in a recent industry report (39) and echo the recent call from ASCO to utilize learnings from this experience to improve clinical research especially as this pertains to optimizing access for older patients (40). We already had positive experience with the use of novel mobile applications to capture patient-reported functioning and quality of life in metastatic breast cancer studies recruiting patients aged 84 years and younger (41), further highlighting feasibility of using digital technology even in the oldest patients. In addition to these design and planning elements, proactive discussions with
investigators addressing our intention to include representative populations and specifically encouraging enrollment of older adults avoid hesitancy on the part of investigators to approach older patients.

**Reporting**

There is great room for improvement in clinical trial data reporting that should help shed more light on outcomes specific to older patients. Although there is a trend for improved reporting of elderly subgroups in phase 3 trials, especially in industry-funded studies, international trials with large sample size, and trials published in high impact factor journals (42), requiring authors to submit detailed age distribution of study populations and age-based analysis and adding geriatric oncology experts to journal reviewers would further the quality of evidence for older patients (19). Among patients older than 65 years of age, stratification of data for incremental age groups can further differentiate outcomes for subpopulations in the elderly (20).

Even when subgroup or stratified analysis in elderly patients is not feasible or done in individual trials, one approach we have previously taken in our breast cancer studies is the use of pooled analysis from several trials to generate and report efficacy and safety findings in larger sets of older adults, which also allowed further stratification of outcomes by incremental age groups among the elderly (43).

A multilayered strategy needs to be adopted with collaboration between various stakeholders to ensure appropriate representation of older adults in cancer clinical trials (Figure 1). Over the past 10 years, several recommendations have become available through a dedicated Institute of Medicine report; ASCO statements; action items from an ASCO-FDA Workshop; proceedings of a U13 conference held by the Cancer and Aging Research Group in collaboration with the NCI, the National Institute on Aging, and the Alliance for Clinical Trials in Oncology; and FDA guidance documents to the industry—all summarized in this commentary (8,17,19,20,22,23,29,44). These resources provide valuable advice on considerations for trial design but require active and serious adoption by study sponsors and clinical trial teams. Continued amplification of such recommendations and potentially using them as regulatory or funding incentives may further encourage inclusion of older patients in oncology research. Similar to directions under the Pediatric Research Equity Act and Best Pharmaceuticals for Children Act, a call has been made in a recent FDA-ASCO workshop for the FDA to highlight incentives for companies to enroll older adults in registration trials during pre-Investigational New Drug and end of phase 2 meetings (22). Similarly, pharmaceutical companies can require applicants for research grants to outline how the study design and execution promotes inclusion of older adults. Grant programs dedicated to cancer research in older adults can also be established. Collaborations between several pharmaceutical companies, including Pfizer, and cancer societies on grant programs that intend to promote diversity and representation in cancer research are already underway (45,46), and the same channels may be used to optimize representation of older adults in cancer clinical trials. All stakeholders in cancer care have a responsibility to improve representation of older adults in oncology research and thus improve applicability of evidence and quality of care for the older oncology patient.

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Data Availability
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