Older Adult Participation in Cancer Clinical Trials: A Systematic Review of Barriers and Interventions

Mina S. Sedrak, MD, MS [1,2]; Rachel A. Freedman, MD, MPH[3]; Harvey J. Cohen, MD[4]; Hyman B. Muss, MD[5]; Aminah Jatoi, MD[6]; Heidi D. Klepin, MD[7]; Tanya M. Wildes, MD[8]; Jennifer G. Le-Rademacher, PhD[6]; Gretchen G. Kimmick, MD[4]; William P. Tew, MD[9]; Kevin George, BS[2]; Simran Padam, MD[2]; Jennifer Liu, BS[2]; Andrew R. Wong, BA[2]; Andrea Lynch, MLIS[10]; Benjamin Djulbegovic, MD, PhD[11]; Supriya G. Mohile, MD, MS[12]; William Dale, MD, PhD[11]; on behalf of the Cancer and Aging Research Group (CARG)

[1]Center for Cancer and Aging, City of Hope Comprehensive Cancer Center, Duarte, California [2]Department of Medical Oncology and Therapeutics Research, City of Hope National Medical Center, Duarte, California [3]Department of Medicine, Dana-Farber Cancer Institute, Boston, Massachusetts [4]Department of Medicine, Duke University Medical Center, Durham, North Carolina [5]Department of Medicine, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina [6]Department of Medicine, Mayo Clinic, Rochester, Minnesota [7]Department of Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina [8]Department of Medicine, Washington University School of Medicine, St Louis, Missouri [9]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York [10]Graff Library, City of Hope National Medical Center, Duarte, California [11]Department of Supportive Care Medicine, City of Hope National Medical Center, Duarte, California [12]Department of Medicine, University of Rochester, Rochester, New York.

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Corresponding Author: Mina S. Sedrak, MD, MS, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010 (msedrak@coh.org).

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Abstract: Cancer is a disease of aging and, as the world's population ages, the number of older persons with cancer is increasing and will make up a growing share of the oncology population in virtually every country. Despite this, older patients remain vastly underrepresented in research that sets the standards for cancer treatments. Consequently, most of what we know about cancer therapeutics is based on clinical trials conducted in younger, healthier patients, and effective strategies to improve clinical trial participation of older adults with cancer remain sparse. For this systematic review, the authors evaluated published studies regarding barriers to participation and interventions to improve participation of older adults in cancer trials. The quality of the available evidence was low and, despite a literature describing multifaceted barriers, only one intervention study aimed to increase enrollment of older adults in trials. The findings starkly amplify the paucity of evidence-based, effective strategies to improve participation of this underrepresented population in cancer trials. Within these limitations, the authors provide their opinion on how the current cancer research infrastructure must be modified to accommodate the needs of older patients. Several underused solutions are offered to expand clinical trials to include older adults with cancer. However, as currently constructed, these recommendations alone will not solve the evidence gap in geriatric oncology, and efforts are needed to meet older and frail adults where they are by expanding clinical trials designed specifically for this population and leveraging real-world data. **CA Cancer J Clin 2020;0:1-15. © 2020 American Cancer Society.**

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Introduction

Patients aged ≥70 years represent 42% of the overall cancer population.[1-3] However, older patients are vastly underrepresented in clinical trials that set the standards for the efficacy and safety of cancer treatments.[4-6] Only 24% of participants in trials registered with the US Food and Drug Administration (FDA) are aged ≥70 years,[4-6] and <10% of patients in this age group participate in National Cancer Institute (NCI)-sponsored clinical trials.[7-14] Even when older adults are enrolled in cancer trials, they typically have fewer functional impairments or comorbid conditions[15] than the average older patient treated in clinical practice.[9,13,14,16] Consequently, most of what we know about the risks and benefits of cancer therapeutics is based on clinical trials conducted in younger, healthier patients,[4,17] leading to systematic differences in treatment and disparities in health outcomes between older and younger patients with cancer.[18-31]

Although common barriers to enrollment of older patients in oncology clinical trials have been the subject of frequent inquiry, the participation of this population, particularly those aged ≥70 years and/or with poor health, has not changed substantially over time.[20,32-35] Several studies have described the barriers as complex and

multifaceted, often involving a combination of system, physician, and patient factors.[31,36-41] Specific efforts to improve the clinical trial enrollment of older patients with cancer have included a physician-directed educational intervention,[42] focused committees, policy statements,[43-47] and the development of a limited number of trials dedicated to older patients.[48-53] However, few studies[54,55] have synthesized this research. A clear understanding of barriers to clinical trial enrollment and interventions tested is needed to develop new, effective strategies to facilitate the inclusion of older adults in cancer clinical trials.

Beyond prior literature reviews,[55-58] which are limited to broad overviews of the evidence, only one systematic review by Townsley and colleagues[54] focused on the barriers that impede accrual of older patients with cancer. That systematic review, based on studies published from 1994 to 2004, was performed before adoption of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, which is the standardized framework for conducting and reporting systematic reviews,[59] and did not evaluate the quality of the evidence. Furthermore, the review focused on studies that assessed the barriers to clinical trial participation for older adults and did not assess intervention studies or efforts to remove these barriers, which are necessary to inform future efforts.

To advance knowledge based on the existing evidence and to address the limitations of the previous reviews, we conducted a systematic review focused on evaluating 2 questions: 1) What *barriers* hinder participation of older adults in cancer clinical trials? and 2) What *interventions* influence and improve their participation beyond trials designed specifically for their age group? Our goal was to synthesize prior research, which we hypothesized would be highly heterogeneous, under a uniform framework that can inform the development of new, evidence-based trial recruitment strategies for older adults with cancer and guide policy choices about how to direct future research and resources.

Methods

Search Strategy

We conducted and reported this systematic review according to prespecified criteria [60] outlined by the PRISMA guidelines. [59] The study protocol was registered with the PROSPERO international prospective register of systematic reviews (registry number CRD42018085677; Center for Reviews and Dissemination, University of York).

One investigator (A.L.), a health information specialist, searched 6 databases: PubMed MEDLINE, Ovid MEDLINE, Embase, Scopus, PsycINFO, and the Cochrane Library. There were no specified date, age, sex, or language restrictions. The coverage dates for this review began from each database's inception (MEDLINE, 1946; Embase, 1947; Scopus, 1966; PsycINFO, 1806; and Cochrane Library, 1995) and ended on January 15, 2019. The search strategy contained 4 core components, which were linked using the AND operator: 1) clinical trials (eg, therapeutic research, human experimentation), 2) participation or recruitment (eg, eligibility, patient selection, patient participation), 3) older adults (eg, elderly, geriatric, aging), and 4) cancer (eg, neoplasms, malignancies, chemotherapy). Controlled vocabulary (ie, Medical Subject Headings [MeSH] terms) and keywords were identified for each of the 4 core components. The search was developed initially for PubMed and then adapted for each of the other 5 databases by mapping the search terms to additional controlled vocabulary and subject heading terminology. Search terms were reviewed by an independent health information specialist (consultant) at an outside institution to ensure that the search strategy was relevant and comprehensive (for full details of all search terms, see Supporting Tables 1-3 and the Supporting References).

Reference lists from previous reviews and key articles retrieved were also examined for relevant studies. In addition, reviewers with expertise in geriatric oncology from the Cancer and Aging Research Group (CARG)[47,61,62] were invited to nominate additional publications for possible inclusion.

Study Selection

Duplicate articles were removed in EndNote (version X9; Clarivate Analytics). Remaining articles were exported into a reference management software (Covidence; Veritas Health Innovation Ltd) for study selection. Titles and abstracts of studies were independently screened for eligibility by 2 reviewers (K.G., S.P.). Disagreements were adjudicated by a third reviewer (M.S.S.). All studies deemed eligible by title and abstract screening underwent a full-text review by 2 independent reviewers (S.P., J.L.) using the same criteria. Discussion or involvement of a third reviewer (M.S.S.) was used to address discordant eligibility ratings. Studies were eligible for inclusion if they: 1) were published in English; 2) had full text available; 3) were empirical, peer-reviewed experimental, quasi-experimental, or observational studies (ie, not reviews, letters, case series, or conference proceedings); 4) evaluated barriers to participation and/or interventions to improve the participation of older adults in oncology clinical trials; and 5) focused on patients aged ≥65 years with cancer. Studies were excluded if they: 1) described the problem (ie, reported underrepresentation) but did not examine the reasons for low enrollment of older adults, 2) reported interventions associated with improving enrollment of the general cancer population but did not examine how these

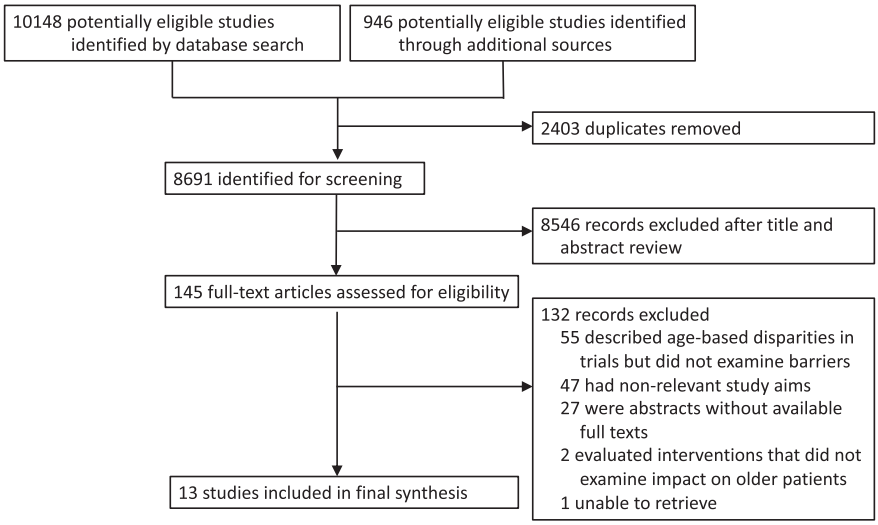

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

interventions increase representation of older patients with cancer, or 3) reported a specific therapeutic trial for older adults with cancer (ie, trials purposely designed for older patients).

Data Extraction

A standardized template, adapted from the Cochrane Collaboration,[63] was used to extract data on study characteristics (year of publication, authors, journal, geographic location, funding source), study questions (aims, design, duration, participants, cohort eligibility and size, study measures), results (outcomes, key findings), and authors' stated conclusions. Two paired reviewers (S.P., J.L.) independently extracted this information from each study and resolved any disagreements through discussion.

To structure data synthesis, we used the Accrual to Clinical Trials (ACT) framework,[64] in which the majority of reasons for low enrollment in clinical trials can be categorized as system, provider, patient, or caregiver factors. Two reviewers (A.R.W., J.L.) independently coded barriers and/or interventions identified from the studies using thematic content analysis.[65-67] Discordant coding was discussed and adjudicated by consensus.

Risk-of-Bias Assessment

Appraisal of study quality was performed using study quality-assessment tools from the National Heart, Lung, and Blood Institute, which are specifically tailored to the design of each study and include items for evaluating potential flaws in study methods or implementation (eg, source of bias, confounding, study power).[68] For each item in the assessments, quality reviewers could select *yes*, *no*, or *cannot determine/not reported/not applicable*. On the basis of their responses, the reviewers then rated individual studies as being of *good*, *fair*, or *poor* quality. A *good* study is considered to have the least risk of bias, and the results are considered valid. A *fair* study is susceptible to some bias deemed not sufficient to invalidate its results. A *poor* rating indicates a significant risk of bias. The quality rating for each study was independently assessed by 2 reviewers (A.R.W., J.L.), with any disagreements subsequently resolved through discussion and involvement of a third reviewer (M.S.S.).

Results

In total, 10,148 articles were identified from the 6 database searches, and 946 additional articles were identified from reference lists. After removing duplicate publications, 8691 articles were screened for eligibility. Of the 145 studies eligible for full-text review, 13 met the inclusion criteria (Fig. 1). Supporting Table 1 summarizes the study characteristics, designs, and findings. Given the limited size and marked heterogeneity of the evidence base, a quantitative synthesis (meta-analysis) of the identified studies was not possible, and our analysis focused on a qualitative synthesis.

Study Characteristics

Table 1 summarizes the characteristics of the studies included in the evidence synthesis. Most studies (12 of 13; 92%)[31,36-38,69-76] were observational studies (9 cross-sectional,[36-38,71-76] 2 cohort,[31,70] and one case-control[69]) and evaluated only barriers. Only one interventional randomized controlled trial (RCT)[42] met the final inclusion criteria. Six studies[31,38,73-76] were published in 2010 or later, and 2[36,69] were published before 2004. Most studies (8 of 13; 62%)[31,36,38,42,69,71,72,75] were based in the United States. Solid tumor malignancies were the most prevalent cancer type

TABLE 1. Characteristics of the 13 Studies Included in This Systematic Review

CHARACTERISTIC	NO. OF STUDIES, N = 13	REFERENCES
Year published		
Before 2004	2	Kornblith 2002,[36] Kemeny 2003[69]
2004 to 2009	5	Townsley 2006,[37] Kimmick 2005,[42] Puts 2009,[70] Moore 2004,[71] Basche 2008[72]
After 2010	6	Javid 2012,[31] Freedman 2018,[38] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Country of origin		
United States	8	Javid 2012,[31] Kornblith 2002,[36] Freedman 2018,[38] Kimmick 2005,[42] Kemeny 2003,[69] Puts 2009,[70] Moore 2004,[71] Basche 2008,[72] McCleary 2018[75]
Canada	2	Townsley 2006,[37] Puts 2009[70]
Netherlands	1	Hamaker 2013[73]
Ireland	1	Ayodel 2016[74]
Germany	1	Prieske 2018[76]
Minimum age used to define older adults		
65 y	11	Javid 2012,[31] Kornblith 2002,[36] Freedman 2018,[38] Kimmick 2005,[42] Kemeny 2003,[69] Puts 2009,[70] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] Prieske 2018[76]
70 y	2	Townsley 2006,[37] McCleary 2018[75]
Study population		
Provider	5	Kornblith 2002,[36] Freedman 2018,[38] Kimmick 2005,[42] Hamaker 2013,[73] McCleary 2018[75]
Patients	5	Townsley 2006,[37] Puts 2009,[70] Basche 2008,[72] Ayodel 2016,[74] Prieske 2018[76]
Both	3	Javid 2012,[31] Kemeny 2003,[69] Moore 2004[71]
Sample source		
Multiple institutions	9	Javid 2012,[31] Kornblith 2002,[36] Kimmick 2005,[42] Kemeny 2003,[69] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] McCleary 2018,[75] Prieske 2018[76]
Single institution	3	Townsley 2006,[37] Puts 2009,[70] Ayodel 2016[74]
Population-based	1	Freedman 2018[38]
Study design		
Intervention	1	Kimmick 2005[42]
Observation	12	Kornblith 2002,[36] Townsley 2006,[37] Freedman 2018,[38] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Cross-sectional	9	Javid 2012,[31] Kornblith 2002,[36] Townsley 2006,[37] Freedman 2018,[38] Kemeny 2003,[69] Puts 2009,[70] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Surveys	11	Javid 2012,[31] Kornblith 2002,[36] Townsley 2006,[37] Freedman 2018,[38] Kemeny 2003,[69] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Qualitative analyses	4	Townsley 2006,[37] Kemeny 2003,[69] Puts 2009,[70] McCleary 2018[75]
Cohort	2	Javid 2012,[31] Puts 2009[70]
Case-control	1	Kemeny 2003[69]
Cancer type		
Solid	11	Javid 2012,[31] Kornblith 2002,[36] Townsley 2006,[37] Kemeny 2003,[69] Puts 2009,[70] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Breast	6	Javid 2012,[31] Kornblith 2002,[36] Townsley 2006,[37] Kemeny 2003,[69] Hamaker 2013,[73] Ayodel 2016[74]
Colon	2	Townsley 2006,[37] McCleary 2018[75]
Lung	1	Townsley 2006[37]
Prostate	1	Townsley 2006[37]
Hematologic	3	Townsley 2006,[37] Basche 2008,[72] Ayodel 2016[74]
All types	2	Freedman 2018,[38] Kimmick 2005[42]

assessed and were the focus of 11 studies[31,36,37,69-76]; only 3 (23%) of 13 studies included patients with hematologic malignancies.[37,72,74] Five studies sampled patients,[37,70,72,74,76] 4 sampled providers,[36,38,73,75] and 3 sampled both patients and providers.[31,69,71] The interventional RCT was targeted for providers.[42] No studies sampled caregivers.

Studies Assessing Barriers to Older Adult Participation in Cancer Clinical Trials

Twenty-three subcategories of barriers were identified (Table 2) across the 12 observational studies. [31,36-38,69-76] Using the ACT framework, barriers were categorized as system, provider, patient, and caregiver factors.

Six (50%) of 12 observational studies[31,36,38,71,73,75] reported system barriers. All 6 (100%) of these studies[31,36,38,71,73,75] reported stringent eligibility criteria as a major barrier. Other system barriers noted were language used in consent forms[31,38,73] and appropriate trial availability.[38,71]

Nine (75%) of 12 observational studies[31,36-38,69,71,73-75] reported provider barriers. Seven (78%) of those 9 studies reported that providers are reluctant to enroll older adults due to the risk of increased toxicity, including concerns because of patient multimorbidities and potential toxicity profiles of investigational treatments.[31,36,38,69,71,73,75] Five (56%) of 9 studies found that providers were hesitant on the basis of patients' age alone.[31,36,38,73,75] Other provider barriers included time demands,[31,36,73,75] lack of personnel,[31,38,73] preferences for another treatment,[36,69,73] provider bias against research in general,[31,36,37,74,75] lack of awareness of available trials,[36,69] and provider discomfort with randomization.[31,75]

Ten (83%) of 12 observational studies reported patient barriers.[31,36-38,69,70,72-74,76] Six (60%) of those 10 studies reported limitations because of patient knowledge,[31,36-38,74,76] transportation issues,[31,36,38,72,74,76] time demands or burden associated with trials,[31,38,70,72,73,76] patient concerns about efficacy and toxicity of investigational drugs,[31,37,70,72,74,76] and concerns with experimentation.[31,36,69,72,73] Other identified barriers were patients' treatment preferences,[31,36,69,73] concerns about financial coverage,[31,36,38,72] age (eg, the patient believes they are too old),[37,74] and emotional burden.[38,70]

Although 4 (33%) of the 12 studies[31,36-38] reported caregiver barriers, none sampled caregivers directly. In all 4 studies, physicians and patients reported that barriers include caregivers' concerns[31,36-38] and, in 2 studies (50%), caregiver burden.[31,36]

Studies Assessing Strategies to Improve Older Adult Participation in Cancer Clinical Trials

Only one RCT[42] was identified. Published in 2005, this cluster-randomized study (N = 125 institutions) examined whether a physician-directed geriatric educational intervention could increase the accrual of older patients (aged ≥65 years) to NCI-sponsored cancer treatment trials. The educational intervention consisted of an educational symposium, geriatric oncology educational materials, a list of available protocols, monthly e-mail and mail reminders, and a case discussion seminar. Fifty-three institutions were randomly assigned to receive the educational intervention, and 72 institutions were assigned as controls, receiving standard educational information.

The study found that the intervention did not significantly improve accrual of older patients. Before the intervention, the overall percentage of older patients accrued to phase 2 and 3 treatment protocols reported was 40% in the intervention arm compared with 36% in the control arm ($P = .40$). During the first and second years postintervention, the percentage of older patients in clinical trials in the intervention and control arms was 36% versus 32% ($P = .35$) and 31% versus 31% ($P = .83$), respectively.

Quality of the Evidence

Risk of bias was assessed using National Heart, Lung, and Blood Institute study quality-assessment tools (see Supporting Figs. 1-3). Of the 12 observational studies, 3 were rated as having a low risk of bias (*good* quality),[69,70,72] 8 were rated as having an uncertain risk of bias (*fair* quality),[31,36-38,71,73,74,76] and one was rated as having a high risk of bias (*poor* quality).[75] The RCT[42] was rated as having an uncertain risk of bias (*fair*) based on study design factors, such as unclear adherence to the intervention, lack of blinding, and a reported power calculation.

Discussion

This systematic review identified 13 relevant empirical studies, including 12 observational studies examining barriers that hinder the participation of older adults in cancer clinical trials and one (negative) RCT aiming to increase the enrollment of older adults in trials.[31,36-38,42,69-76] Our findings starkly amplify the paucity of high-quality evidence that uniformly and comprehensively defines the barriers in various care settings, with even more limited research on interventions to address these barriers. Consequently, effective strategies to improve the participation of older adults in cancer clinical trials remain woefully underdeveloped.

Our systematic review findings underscore the complex, burdensome, and structural impediments that effectively exclude older and frail patients with cancer from clinical trials. To address these, the current research infrastructure must be modified to accommodate the needs of older patients and, if their inclusion cannot be operationalized, we must determine new ways to meet older adults *where they are* rather than where they *should be* to fit the current structure. Instead of the standard approach to cancer trials, we offer the following underused solutions to expand clinical trials to include older adults with cancer (Table 3).

TABLE 2. Identified Barriers to Clinical Trial Participation of Older Adults With Cancer

	REFERENCE											
BARRIER	36	69	71	37	72	70	31	73	74	75	76	38
System												
Eligibility criteria	•		•				•	•		•		•
Consent form language							•	•				•
Trial availability			•									•
Provider												
Concern for toxicity	•	•	•				•	•		•		•
Concern for patient age	•						•	•		•		•
Time/burden	•						•	•		•		
Preference for another treatment	•	•						•				
Lack of personnel							•	•				•
Preference against research in general	•			•			•		•	•		
Unaware of available trials	•	•										
Patient												
Knowledge	•			•			•		•		•	•
Transportation	•				•		•		•		•	•
Time/burden					•	•	•	•			•	•
Concern about efficacy and toxicity				•	•	•	•		•		•	
Against experimentation	•	•			•		•	•				
Treatment preferences	•	•					•	•				
Finances	•				•		•					•
Age (eg, believing they are too old)				•					•			
Emotional burden						•						•
Caregiver												
Preferences	•			•			•					•
Burden	•						•					

Operational Modifications to the Current Cancer Research Infrastructure

There are several ways to modify trial designs to accommodate the needs of older adults. The CARG, in collaboration with the National Institute on Aging (NIA) and the NCI, held a series of conferences funded by a U13 grant to identify and address gaps in knowledge about the care of older adults with cancer. The group has published several white papers, including one focused on how to modify clinical trials for older adults with cancer.[47] Here, we highlight several of these recommendations and how they have been incorporated into current trials.

Design trials specific to older adults

Clinical trials can specifically focus on older adults and address questions that are most pertinent to the geriatric oncology population. An example of this is the Cancer and Leukemia Group B (CALGB) 49907 phase 3 RCT (ClinicalTrials.gov identifier NCT00024102), which compared standard adjuvant polychemotherapy versus monochemotherapy in patients aged ≥65 years with breast cancer.[48] Similarly, single-arm phase 2 studies can be designed specifically for older adults. The Alliance for Clinical Trials in Oncology (Alliance) A171601 trial (ClinicalTrials.gov identifier NCT03633331) is a single-arm, open-label, phase 2 study assessing the tolerability of palbociclib in patients aged ≥70 years with metastatic breast cancer.[77] This study design is advantageous because it incorporates standard-of-care practices (using FDA-approved drugs), captures adverse events in a population that was underrepresented in the registration trials, and advances our understanding of tolerability (how treatment affects aging and quality of life) as well as age-related changes in the pharmacology of cancer treatment.

TABLE 3. Recommendations to Expand the Inclusion of Older Adults in Cancer Clinical Trials

OVERARCHING SOLUTIONS	SPECIFIC STRATEGIES	EXAMPLES FOR IMPLEMENTATION
Operational modifications to the current cancer research infrastructure	Geriatricize trial design	• Design trials specifically for older adults (eg, single-arm phase 2 A171601)[a] • Extended trial design (no precedent) • Adaptative design (eg, phase 3 CALGB 49907)[b] • Prospective cohort design (eg, TLC study)[c] • Postmarketing surveillance cohorts/registries (eg, NRMI Genentech study)[d] • Embedded study (eg, A041202, EA2186)[e]
	Measure relevant endpoints	• Concurrent differential dosing trials (eg, FOCUS2, GO2)[f] • Composite endpoints (eg, *Overall Treatment Utility* or *Therapeutic Success*, which combines efficacy, toxicity, and patient compliance) • Treatment failure-free survival • Time to treatment failure • Patient-reported toxicity (eg, PRO-CTCAE) • Aging-related measures (eg, single or multiple domains of GA and other measures to capture function or cognition) • Quality-of-life–related measures (eg, PROMIS, EORTC, Q-TWIST) • Was It Worth It (WIWI) questionnaire
	Broaden (further) eligibility criteria	• Use measures of function (eg, gait speed) or other evaluations of biological age rather than performance status • Incorporate standardized, objective measures of multimorbidity, such as the Charlson Comorbidity Index (consider a hierarchy of comorbid conditions) • Engage (early) with patient advocates, geriatricians, or geriatric oncologists
	Address site/stakeholder-specific barriers	• Avoid shotgun, *one-size-fits-all* approach • Evaluate specific site and stakeholder barriers • Develop multilevel, tailored interventions to meet unique needs
Expand the reach of cancer and aging research beyond standard clinical trials	Design pragmatic clinical trials	• Consider cluster-randomized trials (eg, COACH trial)[g] • Expand to community-practices (eg, NCORP)
	Leverage real-world data	• Use EHRs, tumor registries, claims data, and other sources • Link cancer (eg, SEER) and aging data (eg, HRS)

Abbreviations: CALGB, Cancer and Leukemia Group B; COACH, Communicating About Aging and Cancer Health (COACH) clinical trial; CTCAE, Common Terminology Criteria for Adverse Events; EHR, electronic health record; EORTC, European Organization for Research and Treatment of Cancer; GA, geriatric assessment; HRS, Health and Retirement Study (sponsored by the National Institute on Aging and the Social Security Administration); NCORP, National Cancer Institute Community Oncology Research Program; NRMI, National Registry of Myocardial Infarction; PROMIS, Patient-Reported Outcome Measurement Information System; PROs, patient-reported outcomes; Q-TWIST, Quality-Adjusted Time Without Symptoms and Toxicity; SEER, National Cancer Institute Surveillance, Epidemiology, End Result Program; TLC, Thinking and Living With Cancer Study.
[a]A171601 is an Alliance for Clinical Trials in Oncology trial (ClinicalTrials.gov identifier NCT03633331).
[b]The ClinicalTrials.gov identifier for CALGB 49907 is NCT00024102.
[c]The ClinicalTrials.gov identifier for the TLC study is NCT03451383.
[d]The ClinicalTrials.gov identifier for the Genentech NRMI trial is NCT00669045.
[e]A041202 is an Alliance for Clinical Trials in Oncology trial (ClinicalTrials.gov identifier NCT01886872), and EA2186 is Eastern Cooperative Oncology Group trial 2186 (ClinicalTrials.gov identifier NCT04233866).
[f]FOCUS2 is Medical Research Council (UK) trial MRC-CR09 (ClinicalTrials.gov identifier NCT00070213), and GO2 is Cancer Research UK trial CRUK/12/022.
[g]The ClinicalTrials.gov identifier for the COACH trial is NCT02107443.

Modify trial design to collect more data on older adults

Clinical trials can be adapted to collect more evidence on older adults through extended and adaptive designs. Extended trial design allows for the addition of a cohort of older patients to the treatment arm that was shown to be superior in an RCT. Adaptive trial design allows for modification of a trial design as the study proceeds, based on interim data analysis.[43] In CALGB 49907, for example, an adaptive Bayesian design was used that allowed for interim analysis of the accumulated data at a specified time point. At that time point, the treatment effect in one of the treatment arms satisfied a predefined futility boundary, and, as a result, accrual to that arm was terminated. By using this approach, accrual to the other treatment arm can be continued until the planned total sample size is reached. This study design is advantageous because of the potential for a smaller sample size requirement if the underperforming study arms are eliminated after interim data analysis, and it overcomes the costly and lengthy limitations of large trials.

Leverage population cohort studies

Prospective cohort studies can be used to answer commonly posed questions in geriatric oncology regarding the feasibility, dosing, and toxicity of a selected regimen.[24,78,79] This can be used to add data if older adults cannot be included in the pivotal clinical trials. There are many examples of cohort

studies in geriatric oncology. Several cohort studies were used to develop clinical risk-prediction models, such as the CARG Chemotherapy Toxicity Score and the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score.[20,34,35] Similarly, longitudinal cohort studies can provide important insights into the late-term effects of cancer treatment on aging in older cancer survivors, as has been done in the Thinking and Living With Cancer (TLC) Study (ClinicalTrials.gov identifier NCT03451383).[80]

Establish postmarketing surveillance studies

Postmarketing surveillance studies use cohort designs to longitudinally monitor populations underrepresented or not studied in the registration trials. This may be an important opportunity for advancing the evidence base in geriatric oncology. Investigators and treatment centers should partner with pharmaceutical companies for postmarketing surveillance of the efficacy and toxicities of cancer drugs in the older and frailer population. A successful example of this is the National Registry of Myocardial Infarction (NRMI), a Genentech-funded study including more than 2.2 million patients with cardiovascular disease across 1600 hospitals (ClinicalTrials.gov identifier NCT00669045).[81] Similar registries may be developed in geriatric oncology.

Embed biological or functional age evaluation in trials

An embedded study (ie, correlative or ancillary study) can be used to identify the characteristics of patients at high risk for toxicity and evaluate the toxicity profile of new drugs. An example is Alliance A041202 (ClinicalTrials.gov number NCT01886872), which embeds a comprehensive geriatric assessment (GA) within the schema of a phase 3 trial evaluating the efficacy of ibrutinib, either alone or in combination with rituximab, relative to chemoimmunotherapy in patients aged ≥65 years with untreated chronic lymphocytic leukemia.[82] Similar trials have used this approach, including Eastern Cooperative Oncology Group trial EA2186 (ClinicalTrials.gov identifier NCT04233866). These companion substudies are important to fill critical knowledge gaps in the care of older adults and can identify specific aging measures that may predict overall survival and treatment-related mortality for this population.

Conduct concurrent differential dosing trials for older adults

Concurrent differential dosing trials can fill the dearth of information regarding the optimal dose and schedule of cancer therapeutics for the geriatric population. Providers have many concerns about the patient risk of treatment toxicity in older and frail patients, and their willingness to deliver the full chemotherapy dose with the first cycle of treatment may be influenced by age-related vulnerabilities, particularly if the treatment goal is palliation. Studies such as the Fluorouracil, Oxaliplatin, and CPT-11 (irinotecan): Use and Sequencing 2 (FOCUS2) trial (ClinicalTrials.gov identifier NCT00070213)[51] for older and frail adults with metastatic colorectal cancer used a reduced first dosing of treatment, then allowed providers to escalate to the standard dosage if the patient tolerated treatment well. Another example is the GO2 phase 3 trial (Cancer Research UK trial CRUK/12/022), which examined dose de-escalation arms in older patients with advanced gastroesophageal cancer.[83] Efforts should be directed toward conducting dose de-escalation and dose titration studies to examine optimal strategies that improve treatment tolerability without compromising efficacy in this population.

Measure relevant endpoints

Sponsors and investigators should carefully consider *what* endpoints matter to older patients. Cancer clinical trials are often well poised to collect a narrow set of cancer-specific endpoints (eg, response rate, survival, toxicity) to demonstrate drug safety and efficacy. Most of these studies use subanalyses based on chronological age to determine toxicity in the geriatric population. However, given the heterogeneity in the health status of older adults and the strong evidence that chronological age alone does not adequately characterize health status in this population,[84-86] there is a need for greater attention to patient-specific endpoints that measure clinical and biological aging-related consequences of cancer treatment.[87] Understanding how a drug affects outcomes, such as function or cognition,[88] is essential information needed by clinicians and patients to make informed treatment decisions.[89] Furthermore, broader endpoints tailored specifically for the geriatric oncology population, such as coprimary or composite measures of tolerability, treatment efficacy, and GA endpoints/patient-reported outcomes (eg, overall treatment utility), are needed to capture what is most important to older adults.[90-94]

Broaden (further) eligibility criteria

Our findings, consistent with prior literature,[9,31,46,71,95,96] highlight that narrow eligibility criteria remain a major barrier to older adult access to available trials. Recent efforts to address this problem include the *Inclusion Across the Lifespan Policy* from the National Institutes of Health and several publications from American Society of Clinical Oncology (ASCO), Friends of Cancer Research, and FDA working groups that recommended changes to the most commonly used exclusion criteria.[15,43,97,98] However, concrete steps to implement these recommendations are needed. For example, efforts to establish a hierarchy of comorbid conditions and which ones could be acceptable for clinical trial criteria are needed to provide guidance for investigators and sponsors. Furthermore, the

use of measures of function (eg, gait speed) or other evaluations of biological age, rather than performance status (which has been demonstrated as a suboptimal measure of function in older adults), is recommended for increasing inclusion of older adults in trials. Incorporating standardized, objective measures of multimorbidity, such as the Charlson Comorbidity Index, can also be used to establish criteria for older adult inclusion. Sponsors and investigators should engage with patient advocates, geriatricians, or geriatric oncologists to better understand the needs of older adults when designing oncology trials.[44,99]

Advance regulatory and policy efforts

Since the 1980s, the FDA has made a concerted effort to encourage enrollment of patients aged ≥65 years in registration clinical trials.[100-102] Under FDA regulations, new drug applications must include efficacy and safety data presented by age, sex, and racial subgroups and, when appropriate, other subgroups of the population of patients treated, such as patients with renal failure. Specific information pertinent to the drug's experience in older adults is contained in the *Geriatric Use* subsection of the package inserts of approved products.[103] However, for many newly approved cancer treatments, there is inadequate prescribing information about the efficacy and safety data for patients aged >65 or >75 years; consequently, sparse data or conclusions can be drawn from the product labeling.[104] Recognizing this, the FDA partnered with ASCO in 2017 to conduct the first public workshop on geriatric oncology.[44] Building on discussions from the workshop, in 2020, the agency published the first oncology-specific guidance for including an adequate representation of older adults, specifically those aged >75 years, in registration trials.[105] These are important first steps and highlight the agency's leadership and willingness to work on this important issue. However, the current guidance functions as recommendations, not requirements. Future efforts are needed at the regulatory and policy level to translate these recommendations into action. For example, efforts to work with sponsors during the planning process for new drug applications can highlight incentives for companies to enroll older adults, including the potential for broader label indications and the possibility that clinicians may use treatments in larger patient populations if this evidence is collected. In addition, postmarketing commitments for companies, where appropriate, may be another approach to obtain more data on older adults in registration trials.

Evaluate and address site/stakeholder-specific barriers

Beyond the structural barriers, efforts should be directed to identify site-specific, provider-specific, patient-specific, and caregiver-specific barriers, such as those highlighted in this review. It is unlikely that there is a *one-size-fits-all* approach to addressing site and stakeholder barriers. Knowledge of specific barriers is therefore useful to develop tailored strategies and may be more effective than attempting to develop generic strategies for global barriers that may not be relevant to a heterogenous population.[106]

Our findings, consistent with others, highlight that practical impediments, such as lack of access, insurance constraints, inconvenience, and cost, limit older patient participation in cancer clinical trials.[54,72,107] Tailored approaches to overcome these barriers are needed. To help reduce the burden of travel, for example, strategies using innovations such as telehealth may reduce the number of in-person visits required for a study.[108,109] Alternatively, travel assistance programs, launched through partnership with organizations, such as the American Cancer Society, and companies, such as Uber, can provide logistical and financial support for patients, which may be helpful to facilitate research participation.[110] The FDA also recently updated its guidance on payment and reimbursement of research participants to clarify that reimbursement for travel expenses and associated costs, such as airfare, parking, and lodging, are not considered *undue influence* and are *generally acceptable*.[111]

In addition to addressing practical barriers, nonpractical psychosocial barriers, such as knowledge gaps and negative attitudes among both patients and their caregivers, cannot be ignored. Efforts to increase older adult and caregiver engagement and to provide clarification of patient preferences and values may allow individuals to be better prepared to consider participation in a clinical trial if presented as a treatment option. Education about clinical trials and the importance of participation in research will improve knowledge, attitudes, and preparation for decision making about enrollment in clinical trials.

Engage referring providers in the clinical trial process

Referring providers play an important role in facilitating patient access to clinical trials. Referring providers often introduce the concept of clinical trials to their patients and refer patients to oncologists who participate in clinical trials. This may be of particular significance in the older patient population, in which studies have shown that lack of primary provider support or a reluctance to travel to university centers where trials are most often conducted are key deterrents to clinical trial participation.[54,72,112] Thus educating referring providers, such as primary care providers or local community oncologists, is an important yet overlooked mechanism for increased accrual of older adults to cancer clinical trials. Building relationships with referring providers may promote a research-oriented

culture that can facilitate older adult participation in clinical trials.

Expanding the Reach of Cancer and Aging Research Beyond Standard Clinical Trials

Design pragmatic clinical trials

Merely increasing the enrollment of older adults in efficacy trials as currently constructed will not remediate the evidence gap in geriatric oncology, and designing pragmatic studies dedicated specifically to the older population is a promising solution. Many older adults have health conditions or other limitations that preclude enrollment in most RCTs; and, despite aggressive efforts to broaden the eligibility criteria, it is not realistic for these patients to participate in efficacy or early phase studies, which must be rigorously controlled and constrained.[43,44] However, pragmatic, older adult-specific trials could examine whether these novel treatments can be broadly implemented, if approved. Moreover, these studies can evaluate whether the risks and benefits of new treatments apply to a more demographically, socioeconomically, and clinically diverse patient population, including less fit and even frail older adults who otherwise may not have been eligible for the efficacy study.

To facilitate the development and implementation of these trials, collaboration between patient advocates, geriatricians, and oncologists should take place to ensure that these studies are amenable to the participation of older and/or frail patients and that the endpoints measured meet their needs.[44,90,113] Furthermore, efforts should be made to ensure that these pragmatic trials are open in community settings, where the vast majority of older patients are treated.[114] As our findings highlight, older adults may face more challenges than younger patients with travel, caregiver support, and other logistics associated with trial participation. Infrastructures, such as the NCI Community Oncology Research Program (NCORP), a national network designed to open participation of NCI-approved studies at community-based practices, should be leveraged to support a larger and more diverse patient population, accelerate accrual, and increase generalizability of trial findings.[115,116] One successful example of this is the Improving Communication in Older Cancer Patients and Their Caregivers (COACH) study (ClinicalTrials.gov identifier NCT02054741), a cluster-randomized clinical trial of community oncology practices within the University of Rochester NCORP that examined whether a GA summary with recommendations to oncologists can reduce toxicities and improve communication in patients aged ≥70 years with advanced cancer.[117] Future efforts are needed to increase the design and conduct of geriatric-specific pragmatic trials through partnership with NCORP, the NCI National Clinical Trials Network (NCTN), and the national infrastructure for geriatric oncology research through CARG, supported by the National Institute on Aging.[118-123] Our hope is that increased conduct of pragmatic trials designed for older adults in diverse health care settings will represent the seeds of a more inclusive clinical trial system to improve the evidence base for treating cancer in older adults, especially those who are frail or have comorbidities.

Leverage real-world data

We should expand our use of real-world data, which include higher numbers of older patients, to fill the evidence gap on older adults with cancer. Real-world data can be retrospectively analyzed from multiple sources of large population-based observational cohorts. For example, investigators can link cancer data from the Surveillance, Epidemiology, and End Results program and Medicare with geriatric information from aging databases, such as the Health and Retirement Study (sponsored by the NIH and the Social Security Administration), [124] to conduct epidemiology and health services research. Alternatively, real-word data from electronic health records (EHRs) or other health information technology databases that combine data from multiple EHRs across multiple practices (eg, CancerLinQ or Flatiron Health) may help fill the evidence gap. [125-127]

Geriatric oncology researchers should work with other stakeholders to develop a framework for using real-world data in clinical research and to establish the benefits and limitations of these new data. Many of these databases remain limited because they fail to capture measures of the GA domains, and future efforts are needed for improved collection and integration of functional or biological age (GA data) as standard elements into EHRs and other large population-based cohort studies. An example of this is the ongoing Life and Longevity After Cancer Study, a cancer survivor cohort embedded within the Women's Health Initiative, which collects both cancer and aging measures to fill knowledge gaps regarding how cancer and its treatment affects the aging process.[128]

Limitations and Strengths

Our study has limitations. First, to maintain our focus on barriers and interventions, we excluded studies that described age-based gaps in clinical trials or that examined interventions in the general adult population, which may have provided additional insight. We also excluded interventions that could improve the evidence base for treating older adults, such as dedicated trials designed specifically for older patients, as our focus was on strategies aimed at improving clinical trial enrollment and not the evidence base per se. Second, because of the heterogeneity of barrier

and intervention studies, a meta-analysis could not be conducted, and our analysis was limited to a qualitative synthesis of the data. Third, most of the studies included were observational in nature and thus were vulnerable to the effects of confounding. We tried to mitigate these effects by assessing and reporting the risk of bias. Finally, we categorized the barriers as system, provider, patient, and caregiver factors using the ACT framework; however, many of these factors are interrelated, and the barriers are more complex than can be conceptualized in a single uniform model.

Despite these limitations, our systematic review also has several strengths. First, to our knowledge, this is the first systematic review to synthesize the literature on barriers to older adult participation in cancer clinical trials and strategies to overcome them. Despite our comprehensive search for interventional studies on this topic, we found only one interventional trial—a sobering fact that underscores the need for further work in this area. Second, this study extends previous knowledge by including research published after 2004, conducting a quality assessment of the evidence, and reporting the findings according to PRISMA guidelines. Third, incorporating these studies into a unified framework enabled the identification of gaps and opportunities in the design and implementation of interventions to facilitate older adult participation in cancer research. We offer solutions building on findings from this review, prior position papers,[43,44] and ongoing dialogues among stakeholders in CARG,[47] the FDA, the National Institutes of Health,[129] the Society of International Geriatric Oncology,[130] the American Geriatrics Society,[131] and ASCO.[43,44] Finally, our findings and recommendations can guide future policy choices on how to direct research and resources aimed at improving the health and well-being of older adults with cancer.

As the world's population ages, older adults with cancer will make up a growing share of the oncology population in virtually every country. Hence the lack of evidence to treat older adults is relevant to all those who provide care for patients with cancer. Therefore, our review is a *call to action* across disciplines: All oncologists and primary care providers, not just geriatric oncologists, need to encourage their older patients to participate in clinical trials. This is a crucial time to rigorously evaluate the barriers to clinical trial participation in the geriatric population, and it is imperative for the health care system to address these issues to ensure that all patients with cancer receive the highest quality, evidence-based care.

Conclusions

Our findings emphasize the complex, multifaceted barriers to enrolling older adults in cancer clinical trials. Building on this, we offer specific recommendations for increasing the enrollment of older adults in existing clinical trials. However, as currently constructed, we believe this alone will not solve the evidence gap in geriatric oncology, and efforts are needed to expand clinical trials designed specifically for this population and to leverage real-world data. ■

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