Landmark manuscripts in geriatric oncology that review barriers to recruitment and provide recommendations for overcoming barriers

1. Kornblith et al. Survey of Oncologists' Perceptions of Barriers to Accrual of Older Patients with Breast Carcinoma to Clinical Trials. Cancer, 2002
2. Townsley et al. Systematic Review of Barriers to the Recruitment of Older Patients with Cancer onto Clinical Trials. JCO, 2005
3. Wildiers et al. End Points and Trial Design In Geriatric Oncology Research: A Joint European Organization for Research and Treatment of Cancer—Alliance for Clinical Trials in Oncology—International Society of Geriatric Oncology Position Article. JCO, 2013
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5. Hurria et al. Improving the Evidence Base for Treating Older Adults with Cancer: American Society of Clinical Oncology Statement. JCO, 2015
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    a. Kim et al. Broadening Eligibility to Criteria to Make Clinical Trials More Representative and Inclusive. Clinical Cancer Research
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Survey of Oncologists' Perceptions of Barriers to Accrual of Older Patients with Breast Carcinoma to Clinical Trials

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Supported by a grant from the National Institute on Aging and a grant from the National Cancer Institute (CA31946) to the Cancer and Leukemia Group B (Richard L. Schilsky, M.D., Chairman).

The authors are indebted to all of the physicians who took the time to participate in this survey. It also was clear that this study could not have been done without the clinical research associates and nurses at the major participating sites who juggled the complicated research procedures of the larger pilot study, including this survey. The authors' special thanks go to the following individuals: Ms. Sarah Beddingfield (Duke University Medical Center), Ms. Donna Galgano (North Shore-Long Island Jewish Medical Center), Ms. Jan Marie McEvilly (University of Chicago Medical Center), Ms. Donna Silver (Vermont Cancer Center), Ms. Laurie Smith (Washington University Medical Center), and Ms. Diane Gould (State University of New York Upstate Medical University).

The following institutions participated in this study: CALGB Statistical Office, Durham, NC (Stephen George, Ph.D.; grant CA 33601); Duke University Medical Center, Durham, NC (Jeffrey Crawford, M.D.; grant CA 33601); Mount Sinai School of Medicine, New York, NY (James F. Holland, M.D.; grant CA 04457); North Shore University Hospital, Manhasset, NY (Daniel R. Budman, M.D.; grant CA 35279); Roswell Park Memorial Institute, Buffalo, NY (Ellis Levine, M.D.; grant CA 02599); SUNY Upstate Medical University, Syracuse, NY (Stephen L. Graziano, M.D.; grant CA 21060); University of Chicago Medical Center, Chicago IL (Gini Fleming, M.D.; grant CA 41287); University of Maryland Cancer Center, Baltimore, MD (David Van Echo, M.D.; grant CA 31983); University of Vermont Cancer Center, Burlington, VT (Hyman B. Muss, M.D.; grant CA 21060); Wake Forest University School of Medicine, Winston-Salem, NC (David D. Hurd, M.D.; grant CA 03927); and Washington University School of Medicine, St. Louis, MO (Nancy Bartlett, M.D.; grant CA 77440).

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Received December 10, 2001; revision received February 28, 2002; accepted April 15, 2002.

BACKGROUND. Prior research has documented the under-representation in clinical trials of older patients with cancer. In part of a larger study to test the magnitude of these barriers to entering eligible older patients with carcinoma of the breast into clinical trials (Cancer and Leukemia Group B [CALGB] trial 9670), barriers to accruing eligible older patients to clinical trials were obtained from the physician's perspective.

METHODS. One hundred fifty-six physicians (85% oncologists) who treated patients with breast carcinoma at 10 CALGB institutions completed a questionnaire concerning what they perceived as barriers to enrolling older patients with breast carcinoma on clinical trials and possible interventions that may improve accrual.

RESULTS. Physicians' perceptions of the most important barriers to accrual of older patients were: 1) elderly patients have significant comorbid conditions that are not excluded by the protocol but that may affect how they would respond to treatment (16%); elderly patients have difficulty understanding what is required in a complicated treatment trial, resulting in poor compliance (16%); treatment toxicity (14%); and elderly patients often do not meet the eligibility criteria (15%). Oncologists most frequently suggested that the most effective interventions for improving the accrual of elderly patients to trials included making personnel available in the clinic to explain clinical trials to older patients and their families (25%) and providing physicians with educational materials concerning treatment toxicity in the elderly (18%).

CONCLUSIONS. Physicians viewed barriers to accruing older patients with breast carcinoma to clinical trials as multidimensional, with the most important involving

protocol requirements, treatment specific issues, and older patients' medical and cognitive characteristics. Thus, a variety of interventions would be needed to improve accrual of older patients to clinical trials, including increasing physicians' knowledge concerning treatment toxicity in the elderly, simplifying protocol requirements, and reducing treatment toxicity. ***Cancer* 2002;95:989–96.**

DOI 10.1002/cncr.10792

KEYWORDS: accrual, clinical trials, breast carcinoma, elderly patients, physician perspective.

Examination of accrual to National Cancer Institute (NCI)-sponsored cancer treatment trials from 1988 to 1992 revealed a clear age dependent relationship to accrual. More than 70% of children with cancer, 4.0% of adult patients age 20–49 years with cancer, and only 1.5% of adult patients age $\geq$ 50 years with cancer were entered on clinical trials.[1] These findings were supported further by Trimble and colleagues'[2] study of cancer patients age $\geq$ 65 years who were entered on NCI-sponsored clinical trials compared with the Surveillance, Epidemiology, and End Results (SEER) Program incidence rates for seven disease sites in the United States. With the exclusion of prostate carcinoma, which is overwhelmingly a disease of men age $>$ 65 years, the difference between the proportion of cancer patients with these diagnoses entered on NCI trials and SEER incidence data for those patients with these diagnoses age $>$ 65 years is striking. For men age $\geq$ 65 years with these diagnoses, the average proportion of patients entered on NCI trials among patients with lung carcinoma, colorectal carcinoma, pancreatic carcinoma, and leukemia is 37.5%, compared with the average SEER incidence rate for these diseases of 63.8%, an under-representation of older male patients in NCI trials of 26.3% ($P < 0.001$).[2] A similar picture emerged for women age $\geq$ 65 years, with an average proportion of patients entered on NCI trials for lung carcinoma, breast carcinoma, colorectal carcinoma, ovarian carcinoma, and pancreatic carcinoma of 25.9%, compared with the SEER incidence rate for these disease sites of 56.5%, an under-representation of older female patients on trials of 30.6% ($P < 0.001$).[2] For men, the greatest disparity between accrual of older patients to trials compared with disease incidence in the United States was among patients with leukemia (NCI trials, 9.6%; SEER trials, 55.6%); for women, the greatest disparities were among both patients with breast carcinoma (NCI trials, 17.3%; SEER trials, 47.7%) and patients with colorectal carcinoma (NCI trials, 46.2%; SEER, 74.7%).

Similarly, in a study of 16,396 patients with cancer on Southwest Oncology Group (SWOG) trials from 1993 to 1996 involving 15 disease sites, older patients with cancer accounted for 25% of patients on SWOG trials compared with 63% of patients with cancer in the U.S. population, an under-representation of 38% ($P < 0.001$).[3] The greatest disparity occurred for women with breast carcinoma (SWOG, 9%; SEER/U.S. population, 49%).

It was findings like these that prompted our pilot study to determine the barriers to accrual for older patients with breast carcinoma who were eligible to enter treatment trials, controlling for major confounding variables of treating physician, disease stage, comorbidity, and physical functioning.[4] Because the three studies discussed above[1–3] only posed possible reasons for the disparities in accrual by patients' age, it was important to obtain empiric evidence from both physicians and patients concerning their perceptions of barriers to the participation of older patients in clinical trials, even when it has been determined that patients are eligible to participate. This article presents the findings from a survey of 156 physicians, most of whom were oncologists who treated patients with newly diagnosed carcinoma during the year prior to protocol activation (CALGB 9670), with regard to their perception of the difficulties in entering older patients with cancer on clinical trials.

MATERIALS AND METHODS

Methods

The physicians who were surveyed in this study all practiced at 10 institutions in the CALGB that had taken part in the *parent* pilot study of the barriers to the participation of older patients with breast carcinoma in clinical trials (CALGB 9670).[4] For the purposes of this study, the 10 institutions were selected based on the largest accrual of patients with breast carcinoma to treatment trials in the CALGB across all ages. The primary objective of the parent pilot study was to test whether older patients with breast carcinoma who were *eligible* for an open treatment trial at their institution were placed on trials less frequently than their younger counterparts. The parent trial, CALGB 9670, had a case-control design in which an older patient (age $\geq$ 65 years) was paired with a

younger patient with the same disease stage and the same treating physician. Fifty-one percent of younger patients were offered a trial compared with 35% of their matched cohort of older patients ($P = 0.06$). However, when race, comorbidity, and functional status were controlled for in a regression analysis, age interacting with disease stage became the most important predictor of whether a patient would be offered a trial by a physician ($P = 0.03$).[4] Specifically, 68% of younger patients with Stage II disease were offered a trial compared with 34% of the remaining patients ($P = 0.0004$). Thus, older patients who had Stage II disease were at a clear disadvantage with regard to whether they were offered a trial compared with younger patients who had Stage II disease and both older and younger patients who had Stage I disease.

The views of older patients with breast carcinoma, their own treating physicians, and other oncologists at their institution who had treated at least one newly diagnosed woman with breast carcinoma in the year prior to protocol activation were assessed to examine different groups' perceptions of what the significant barriers were in accruing older patients to trials. The results presented here represent the views of oncologists other than the treating physicians. The sample was comprised of 156 physicians who were asked to complete a brief questionnaire about their perceptions of the difficulties in placing older patients with carcinoma on clinical trials. Clinical research associates at each of the participating institutions sent copies of the survey by interoffice or regular mail to physicians who were involved in the treatment of patients with breast carcinoma.

Because all participants in this aspect of the study were physicians, assent, rather than written informed consent, was obtained. The return of the completed questionnaires served as proof of their agreement to participate in the survey. Completed questionnaires were then mailed or sent by facsimile back to the clinical research associates.

Measures: Physicians' Assessment of Barriers to accrual

A brief questionnaire was constructed (by M.K. and A.B.K.) for the purposes of this study to assess physicians' views about why it was difficult to enter older patients with breast carcinoma on clinical trials (see Table 2). Because barriers to accrual of older patients were considered to be multidimensional, items included *protocol requirements* (e.g., older patients often do not meet the eligibility criteria), *treatment specific* issues (e.g., treatments are too toxic), *social support* (assistance at home not available for treatment administration or management of side effects), *logistic issues* (transportation not available; unable to pay for costs not covered by insurance), *physician attitudes* about the protocol (e.g., an arm of the protocol is viewed as less effective or unacceptable; best treatment for the patient is not included in the protocol), and *medical and cognitive characteristics* of older patients (comorbid conditions not excluded by the trial's eligibility criteria that still may affect patients' responses to the trial; difficulty of older patients understanding the trial). Although ageism (which is defined by Butler as a process of systematic stereotyping and discrimination against people due to their age[5]) may have influenced physicians' responses to many of these items, the only item that most clearly reflected ageism was the idea that the life expectancy of some patients may too short to justify their participation in clinical trials. Physicians could write in additional reasons why they thought it was difficult to accrue older patients to clinical trials.

Physicians were then asked to rank the three most important reasons why it was difficult to accrue older patients with cancer to clinical trials. Finally, physicians were asked to check off which of seven possible interventions they thought may be effective in improving accrual and to rank the three interventions that may be most effective. Examples of items include special educational lectures or materials for physicians concerning older patients with malignant disease, educational materials for patients and/or family members concerning clinical trials, providing the older patient with transportation to and from the clinic, and providing the physician with more personnel in the clinic to help explain the trials to patients (for a complete list of the items, see Table 3). Physicians also were able to write in additional approaches that they thought may be useful in improving accrual.

Separate from the Physician Survey of Barriers to Accrual, a different questionnaire was completed by the patients' own treating physician in the parent trial (CALGB 9670),[4] in which the oncologist reported whether the patient had been offered participation in a trial and, if not, why not. The results of this questionnaire are described in the parent trial[4] and are referred to briefly below (see Discussion).

Physicians' Characteristics

Basic characteristics of the physician were measured, including the physician's age, gender, ethnicity, medical specialty (e.g., medical, surgical, radiation oncology, etc.), the setting of their medical practice, and the proportion of their case load that involved patients age $>$ 65 years.

RESULTS

Sample Characteristics

One hundred fifty-six questionnaires were returned. The actual percentage of questionnaires returned from those distributed is unknown, because most institutions had not kept track of the number of questionnaires sent to physicians. The return rate of three institutions ranged from 33% to 100%, indicating a high degree of variability. One-third of the questionnaires were obtained from North Shore University Hospital (n = 50 questionnaires; 32%), with the other institutions contributing completed questionnaires as follows: Duke University Medical Center, n = 25 questionnaires (16%); Washington University Medical Center, n = 22 questionnaires (14%); University of Chicago Medical Center, n = 14 questionnaires (9%); State University of New York Upstate Medical University at Syracuse, n = 14 questionnaires (9%); and others, n = 31 questionnaires (20%).

Physicians participating in this survey were predominantly oncologists (85%) in academic medical centers (71%), and had a patient caseload in which one-third to two-thirds of their patients were age > 65 years (see Table 1). The majority were men (69%), white (87%), and had a median age of 43 years (range, 29–74 years).

TABLE 1
Characteristics of Physicians (n = 156)

Characteristic	%	No.
Gender		
Male	69	105
Female	31	48
Age (yrs)		
< 40	31	46
40–49	42	62
50–59	20	30
60–74	7	11
Ethnicity		
White	87	132
Black	3	4
Southeast Asian (Indian)	3	4
Other	7	11
Medical specialty		
Medical oncology	48	75
Surgical oncology	21	32
Radiation oncology	16	25
General surgery	12	18
Fellow	3	5
Practice setting		
Academic medical center	71	106
Private practice	25	37
Community-based hospital	5	7
Proportion of patients age > 65 yrs		
< 1/3	30	46
1/3–2/3	63	96
>2/3	7	11

Physicians' Assessment of Barriers to the Accrual of Older Patients with Breast Carcinoma to Clinical Trials

There were four reasons endorsed by ≥ 50% of physicians as to why it was difficult to accrue older patients with breast carcinoma to clinical trials: transportation needs (68%); comorbid conditions that were not excluded by the eligibility criteria but that physicians believed would affect how older patients felt or responded to treatment (53%); toxicity of the treatment regimens (51%); and patient difficulty in understanding the trial (50%) (see Table 2). Physicians wrote in other additional barriers to accrual that they felt were not captured in the reasons listed in the questionnaire. Because physicians had written in these barriers, their frequency of endorsement did not reflect the actual proportion of physicians who may have viewed these issues as barriers to accrual, because they had not been included on the list of items in the questionnaire. In fact, in the case-control study in which the patient's treating physicians filled out the parallel questionnaire to the survey regarding why their own patients had not been placed on a trial, even though they had been eligible, 8 of 45 physicians (18%) and 6 of 47 physicians (13%), respectively, reported that they were not aware that an appropriate trial existed for their younger and older patients.[4] This was in contrast to the surveys completed by 156 physicians in which only 1 physician had written this in as a reason why the accrual of older patients to clinical trials was difficult.

Three out of four of the most frequently endorsed barriers to accrual were also those that most frequently were ranked as the most important barrier to accrual. Transportation needs was the one exception, in that it was endorsed the most frequently, although it was not considered the most important barrier as frequently. Although *elderly often do not meet the eligibility criteria* was endorsed less frequently than other barriers, it was one of the top three barriers to accrual rated as most important. However, those that were ranked as the second most important barriers to accrual were transportation needs (17%) and toxic treatment regimens (17%).

When they were asked about various possible methods for improving the accrual of older patients to clinical trials, virtually all methods provided in the questionnaire were endorsed by 45–69% of physicians: having more clinic personnel available to explain trials to older patients (69%), providing patients (63%) and family members (59%) with educational materials about clinical trials, providing physicians

TABLE 2
Physicians' Assessment of Barriers to Accrual of Older Patients with Breast Carcinoma to Clinical Trials (Ranked in order of frequency of endorsement)

	Overall (n = 56)		Most important (n = 152)		Second most important (n = 149)	
Item	%	No.	%	No.	%	No.
1. Transportation often required for clinic visits is difficult, costly, or often not available to the elderly patient	68.0	106	6.0	9	17.0	25
2. Elderly often have significant other comorbid conditions, *not* excluded by protocols but would affect how they would respond or feel	53.0	78	16.0	25	14.0	21
3. Elderly patients have difficulty understanding what is required in a complicated clinical trial, resulting in poor compliance	50.0	80	16.0	24	11.0	16
4. Treatment regimens are too toxic for elderly	51.0	78	14.0	22	17.0	26
5. Assistance required at home for treatment administration or management of side effects often is not available	40.0	63	5.0	7	7.0	11
6. Elderly often do not meet eligibility criteria	36.0	56	15.0	23	8.0	12
7. Some costs for medical care in clinical trials often are not covered by health insurance	34.0	53	3.0	4	5.0	7
8. Physicians feel that an arm of protocol is less effective or is unacceptable	25.0	39	5.0	7	7.0	10
9. Best treatments for an elderly patient often are not included in clinical trial	21.0	33	5.0	7	4.0	6
10. Life expectancy of some patients is too short to justify participation in clinical trials	17.0	27	0.6	1	3.0	5
11. In many trials, likelihood of success is often low	6.0	9	1.0	2	0.7	1
12. Other						
Patient refusal; not interested in aggressive treatment	5.0	8	—	—	—	—
Patient unwilling to be randomized	2.0	3	—	—	—	—
Influence of family members	1.0	2	—	—	—	—
Patient feels one arm of trial is superior	1.0	2	—	—	—	—
Patient lives too far away, making it difficult to manage care	0.6	1	—	—	—	—
Trial was not offered to patient	0.6	1	—	—	—	—
MD not aware of an available trial	0.6	1	—	—	—	—
Additional testing required could be toxic	0.6	1	—	—	—	—

with educational lectures and materials about the toxicity of treatments in older patients (45%), and having more protocols available with fewer exclusion criteria related to comorbid conditions (49%). However, only a minority of physicians (19%) felt that educational lectures and materials concerning older patients' physical and mental capabilities would be effective in improving accrual (see Table 3). The need for more clinic personnel to explain trials to older patients was selected most frequently by physicians as the most important method for improving accrual (25%).

DISCUSSION

The findings in our survey support the original contention that physicians' perceptions of barriers to accrual of older patients with cancer are multidimensional, primarily consisting of those that reflected *protocol requirements*, *treatment specific issues*, *social support*, *logistic issues*, and the *medical and cognitive condition of older patients*. Additional barriers that physicians wrote in broadened the types of barriers to include *patient attitudes* about participating in a research study (e.g., not wanting to be randomized, not wishing to be used as a *guinea pig*, lack of interest in aggressive treatment), *family attitudes* (e.g., family advising against the patient's participation), and *lack of physician awareness of existing protocols*. This latter finding emerged in Siminoff and colleagues' study[9] as well, with surgical and medical oncologists significantly more likely to offer clinical trials to patients when they were aware that there was an open trial for which a patient was eligible ($P \leq 0.01$).

Many of the barriers to accruing older patients with cancer to clinical trials that were suggested in the literature[2,3] were endorsed frequently by physicians in this survey as well. These included transportation difficulties, treatment toxicity, and significant comorbid conditions that had not eliminated an older patient but were believed to affect how the patient would respond to the treatment trial.

TABLE 3
Physicians' Suggestions for Improving Accrual of Older Patients with Breast Carcinoma to Clinical Trials (Ranked in order of frequency of endorsement)

	Overall (n = 156)		Most important (n = 151)	
Method	%	No.	%	No.
1. Make personnel available in the clinic to explain clinical trials to elderly patients and their families	69.0	108	25.0	38
2. Provide patients with better educational materials concerning clinical trials	63.0	99	13.0	19
3. Provide transportation to make it easier for elderly patients to participate in trials	63.0	98	14.0	21
4. Provide family members with better educational materials concerning clinical trials	59.0	92	5.0	7
5. Provide protocols with few exclusion criteria related to comorbid conditions	49.0	77	9.0	14
6. Provide MDs with lectures, courses, articles concerning toxicity of cancer treatments in the elderly	45.0	70	18.0	27
7. Provide MDs with lectures, courses, articles concerning physical and mental capabilities of the elderly	19.0	29	1.0	2
8. Other				
Eliminate extra examinations and testing; simplify trials	3.0	4	—	—
Reduce extra costs; provide insurance coverage	2.0	3	—	—
Provide MDs with lists of available protocols and brief summaries	1.0	2	—	—
Provide home care	0.6	1	—	—
Use less toxic regimens in protocols	0.6	1	—	—
Train MDs in how to present clinical trials to patients	0.6	1	—	—
Simplify informed consents	0.6	1	—	—

Two issues that appeared to be much more important to physicians when considering a trial for older patients compared with younger patients were the toxicity of the regimen and comorbid conditions. Although these factors did not exclude a patient from the trial, they were believed to affect a patient's treatment response. In the case-control parent study,[4] 11 of 33 treating physicians (33%) reported that treatment toxicity was one of the three most important reasons for not offering a trial to their older patients; no physician stated this as a reason for not offering a trial to younger patients.[4] Furthermore, the finding that younger patients with Stage II disease were offered trials significantly more often than all other remaining patients, including older patients with Stage II disease,[4] suggests that treatment toxicity was most likely a major reason for the difference: Protocols for Stage II patients often include chemotherapy.

Six of 33 treating physicians (18%) reported that one of the three most important reasons for not offering a trial to an older patient was that their comorbid conditions, were viewed as affecting patients' responses to the treatment, even though they were not excluded by the protocol. None stated this as a reason for not offering a trial to a younger patient. Although the sample sizes were not large, these findings indicate that treatment toxicity and comorbidity were critically important to oncologists when deciding whether to offer a trial to an older patient.

It was not possible to estimate the degree to which ageism influenced physicians' perceptions of barriers to the accrual of older patients to clinical trials. Two items in the questionnaire were more openly suggestive of ageism: *difficulty of older patients understanding the trial* and *life expectancy too short to justify an older patient's participation in a trial*. The former was endorsed by 50% of physicians, whereas the latter was endorsed by only 17% of physicians. The vast majority of physicians did not endorse the most blatant item concerning ageism—*short life expectancy*—as a significant barrier to accrual. However, *difficulty of older patients understanding the trial*, which is a more subtle ageist item that clearly would apply to some older patients, was endorsed heavily. Most of the barriers listed in the questionnaire may very well be valid reasons that explain the difficulties in offering trials to older patients with cancer. There are very toxic treatment regimens; older patients have more comorbid conditions that increase their frailty and, thus, may influence their response to treatment; they may need help at home with treatment regimens that is not available, etc. However, a number of items also may have reflected stereotypical attitudes toward older persons, justifying the physician's decision not to offer them a trial: assumptions of transportation needs, other comorbid illnesses that affect patients' responses to treatment, difficulty of older patients understanding a trial, and treatment toxicity. In the case-control parent study, age interacting with disease stage remained the significant predictors of whether patients were offered participation in a trial, after controlling for comorbidity and physical functioning.[4] This analysis, which controlled for factors that commonly exclude patients from clinical trials, in conjunc-

tion with the finding that there was no significant difference between older patients and younger patients accepting trial participation once it was offered,[4] suggested that ageism played a role in whether physicians offered trial participation to their older patients with Stage II disease.

In most cases, the types of barriers that physicians perceived to accruing older patients with cancer to clinical trials have been cited in the literature concerning difficulties in accruing *any* patient with cancer to clinical trials.[6–9] With clinical trial participation of newly diagnosed adult patients with malignant diseases estimated at 2.5% across all adult age groups,[10] it is abundantly clear that barriers to accrual to clinical trials are pandemic. Furthermore, barriers that we believed may be especially problematic in the accrual of older patients with cancer have all been mentioned in other studies in relation to difficulties in accruing all adult patients with cancer to clinical trials, irrespective of their age:[6,9,11] restrictive eligibility criteria due to comorbid conditions, difficulty in patients' understanding and compliance with protocol requirements, and the extra time required to enroll patients in trials and, thus, the need for extra personnel.

Interventions to Improve Accrual

Given the complexity of the problem, a variety of interventions is likely to be needed to improve accrual of older patients with malignant disease to clinical trials. The methods that physicians frequently endorsed for improving accrual of older patients to clinical trials reflected the multidimensional aspect of the problem: educational efforts directed to the physician, patients, and family members; greater resources for the patient (transportation) and physician (more personnel in the clinic to explain clinical trials to older patients); and simpler, less restrictive, and less toxic protocols. Providing oncologists with medical information to help them determine whether a clinical trial should be offered to their older patients with cancer may improve accrual to trials, particularly because not all studies demonstrate that older patients tolerate these regimens as well as younger patients (e.g., see Giovanazzi-Bannon et al.[12] and Crivellari et al.[13]). However, with only a limited number of studies addressing treatment tolerance of older patients with cancer, there is an insufficient body of knowledge to inform physicians adequately regarding this issue.

Based on this survey's findings that physician education would improve the accrual of older patients to clinical trials, an educational intervention is being tested through the CALGB (CALGB 360001) that involves a geriatric symposium combined with monthly E-mail reminders of available CALGB protocols. With 13% of treating physicians in the case-control parent study reporting that they were not aware that an appropriate trial existed for their older patients, it is possible that increasing oncologists' awareness of open trials for their eligible older patients, in itself, may substantially improve the frequency with which trials are offered to older patients with malignant disease.

However, if ageism is a significant underlying barrier to offering a trial to older patients with cancer,[14,15] then an additional type of intervention will be needed to reduce negative attitudes toward older patients. Possible approaches may include *increasing knowledge* about older patients *in conjunction with positive experiences* with these patients; funding for additional staff to provide the extra time that often is required to determine whether an older patient is eligible, to describe the study, and to obtain informed consent; development of combined *geriatrics/oncology training programs* and *institutional leadership*, with strong encouragement for oncologists to improve clinical, research, and teaching practices related to older patients with malignant disease.

Study Limitations

These results were part of the parent study, which was conducted at the 10 institutions with the highest accrual to breast carcinoma treatment trials in the CALGB.[4] Consequently, our findings are not based on a representative sample of oncologists who treat patients with breast carcinoma in the United States or oncologists across all specialties. Therefore, our findings may not reflect the true prevalence of oncologists' views of barriers to offering clinical trials to older patients with cancer. Nor did all physicians who treat patients with breast carcinoma at these 10 institutions complete this survey, as indicated by the return rate of three of the institutions ranging from 33% to 100%. This most likely biased the findings. Additional research is necessary to test whether our findings can be replicated. However, our results suggest what oncologists perceive as the major barriers to offering trials to older patients with cancer, thus serving as a springboard for possible interventions.

When the items were developed for this trial (by M.K. and A.B.K.), we focused on areas that had been identified either in the literature or by clinical experience as barriers to the accrual to clinical trials of older patients with cancer. Consequently, the questionnaire did not include all reasons that may serve as barriers to accrual of *any* patient to a trial, such as patient refusal, their family objecting to their participation, and patient fears of being included in an *experimental* treatment, among others. Because these are relevant

barriers to accrual across all age groups, this questionnaire should be revised to include the full range of reasons why it is difficult to enter older patients with cancer onto trials.

Conclusions

All those involved in clinical trials research fully understand that an accrual of 2.5% of cancer patients to clinical trials is unacceptable for both ethical and scientific reasons. That this rate of accrual may be diminished further by virtue of being an older patient is disheartening. Accrual to clinical trials is a multidimensional problem that requires multidimensional interventions to affect improvement. To the degree that the different barriers outlined above are independent of each other, each intervention may improve accrual incrementally. However, if there are underlying issues that are not addressed adequately, such as insufficient knowledge among physicians about how to treat older patients effectively as well as a lack of awareness about ageist attitudes, then there will be only a minimal improvement in the frequency with which older patients with cancer are offered participation in clinical trials.

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VOLUME 23 · NUMBER 13 · MAY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Systematic Review of Barriers to the Recruitment of Older Patients With Cancer Onto Clinical Trials

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Submitted August 2, 2004; accepted February 2, 2005.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2313-3112/$20.00

DOI: 10.1200/JCO.2005.00.141

A B S T R A C T

Purpose
Older patients are significantly underrepresented in cancer clinical trials. A literature review was undertaken to identify the barriers that impede the accrual of this vulnerable population onto clinical trials and to determine what specific strategies are needed to improve the representation of older patients in research studies.

Methods
A systematic literature search was undertaken using several different strategies to identify relevant articles.

Results
Nine of 31 relevant papers from 159 citations were included. Age is a significant barrier to recruitment; only a quarter to one third of potentially eligible older patients are enrolled onto trials. Physicians' perceptions, protocol eligibility criteria with restrictions on comorbid conditions, and functional status to optimize treatment tolerability are the most important reasons resulting in the exclusion of older patients. Other barriers include the lack of social support and the need for extra time and resources to enroll these patients. Conversely, older patients do not view their age as an important reason for refusing trials.

Conclusion
Specific clinical trials confined to older patients should be conducted to evaluate tumor biology, treatment tolerability, and the effect of comorbid conditions. Protocol designs need to stratify for age and be less restrictive with respect to exclusions on functional status, comorbidity, and previous cancers, such that results are generalizable to older patients. Physician education to dispel unfounded perceptions, improved access to available clinical trials, and provision of personnel and resources to accommodate the unique requirements of an older population are possible solutions to remove the barriers of ageism.

J Clin Oncol 23:3112-3124. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Cancer is a leading cause of death in North America, second only to heart disease, and it accounts for more than 500,000 deaths annually.[1] Also, it is a disease primarily of older people and estimates for 2001 indicate that one half of new cases and more than one half of cancer deaths in the United States, will occur in those aged 70 years or older.[1] When the oldest baby boomers reach 70 years in 2011, the proportion of people 70 years and older will increase significantly, resulting in an exponential growth in seniors with cancer.[2] Ensuring that older patients are kept healthy and independent for as long as possible is a vital goal to optimize the physical function and quality of life for this important segment of our population. The geriatric population represents a significant challenge to the medical system, not only because of increasing numbers but also because of complex health issues, which often develop with increasing age. Diseases in older patients can be more difficult to treat effectively for a variety of reasons including presence of

physiologic changes due to aging, risk of multiple comorbid illnesses, significant heterogeneity in their health status, and inconsistent reporting of symptoms.[3] Moreover, the physiologic changes associated with aging, the presence of comorbid illnesses, and the prevalence of polypharmacy can increase the risk of adverse events from medications in older patients. In addition to their medical needs, many older patients are socially isolated, and the delivery of adequate health care requires the concomitant provision of sufficient support services.

Despite the fact that older patients account for the greatest proportion of those with cancer, they are disproportionately underrepresented in many areas of cancer services utilization. For example, age has been found to be inversely related to the receipt of adjuvant and palliative radiotherapy in multiple cancer types,[4,5] of chemotherapy in metastatic lung cancer,[6] and of aggressive surgery in brain, lung, or colorectal cancers.[7,8] In order to completely understand how to correctly administer cancer treatment and to increase the utilization of cancer services by this population, clinical trials with an adequate representation of older patients need to be performed. Participation in well-designed clinical trials for potentially eligible patients may afford them the optimum treatment.[9] Unfortunately, because older patients are not well represented in cancer clinical trials, determining the best treatment for this group becomes difficult.[10,11]

Age is no longer a valid eligibility criterion in and of itself, and the majority of adult cooperative group clinical trials no longer specify an upper age limit. In fact, the Food and Drug Administration issued in 1989 a recommendation that older patients not be excluded from clinical trials.[12] However, despite this mandate, there are still widespread perceptions that older patients tolerate chemotherapy and radiation poorly.[13,14] Several studies[15,16] over the past two decades have refuted this belief. A study by Giovanazzi-Bannon et al[17] a decade ago found no significant differences between older and younger patients enrolled onto phase II clinical trials for seven treatment-related variables, including the number of grade 3 or greater toxicities. Despite this, the underrepresentation of older patients in trials continues to be a problem. In an effort to better define clinical trial accrual rates in older patients and assess the barriers specific to their recruitment, we have chosen to review literature from the past decade relevant to this topic.

METHODS

The focus of this review was to specifically address the unique barriers to recruitment onto clinical trials that face older patients with cancer. The term "older patients" was defined as older than 65 years for the purpose of this review. A systematic search of Medline, Embase, and the Cochrane Central Register of Controlled Trials was undertaken using several different search strategies and the following Medical Subject Headings terms and keywords as applicable: "clinical trials," "patient selection," "cancer," "neoplasm," "tumor/tumor," "aged," "elderly," "participate," "recruit," or "enroll." The search was restricted to articles written in English and dated within the last 10 years, from 1994 to 2004. This resulted in 140 citations of relevance to problems associated with the participation of older patients in cancer clinical research. Manual searches of the bibliographies of recent review articles and key references were also undertaken to identify relevant articles. An additional 19 citations were identified through the manual review, resulting in a total of 159 citations. All 159 titles and abstracts were independently reviewed by two of the authors (C.A.T. and R.S.). A priori inclusion criteria were established. To be eligible for inclusion, studies had to be primary research articles specifically addressing barriers to recruitment of older patients onto cancer clinical trials, or describing strategies to overcome recruitment barriers in this population. All phases of clinical trials and all tumor sites were potentially eligible for inclusion. Studies were excluded if they did not focus on the recruitment of the older patient onto trials as their primary objective set a priori, or if they addressed only treatment-related outcomes or toxicity of certain treatment modalities specific to the older patient without reporting on participation rates or assessing barriers to recruitment. Studies were also excluded if they were reviews on the subject or if they commented on supposed barriers without including primary research. Published abstracts without complete articles were excluded because of the inability to obtain detailed information regarding specific barriers. Thirty-one of the 159 citations were selected for further review of the entire article, which was done independently by all three authors. Differences in opinion were resolved by consensus. Nine of the 31 studies were included in the final analysis. A description of the remaining 22 studies and the reasons for their exclusion from the final analysis are provided in Appendix 1.

RESULTS

Of the 31 citations that were chosen for full manuscript review, nine were selected for this systematic review article because they fulfilled the inclusion criteria specified in the Methods section. The remaining 22 citations that did not fit the inclusion criteria are detailed in Appendix 1.[17-38] For each of these 22 citations, the primary objective of the study, the patient population, findings related to recruitment and age, and reasons for exclusion from the current systematic review are listed in Appendix 1. Some of these articles described reviews of institutional databases or trial data from large cooperative groups to identify factors that influenced patient participation in clinical trials.[25-27,29,32,37] None of these articles set a priori hypotheses about age being a barrier to recruitment, but most had found older age to be one of the significant negative predictors of trial participation.[25,26,32,37] A few of the articles were surveys of individuals with or without cancer or surveys of physicians, to understand their attitudes toward clinical trial participation.[18-21,23,30,34,36,38] Whereas some of these surveys reported that older individuals were less willing

than younger individuals to participate or to be recruited,[19-21,23,30,34] others did not find age to be a relevant factor.[18,36,38] None of these studies had primarily set out to determine if age is important for trial participation or recruitment, hence explaining their exclusion from the final analysis of this systematic review.

A brief description of the nine studies included in this systematic review is presented in Table 1.[39-47]

Table 1. Evidence Detailing the Nine Studies Used in the Systematic Review, by Year

Study	Year Published	Country	Description	Method	Phase	Age Cut-Off Used to Define Elderly (years)
Talarico et al[45]	2004	USA	Retrospective analysis of the accrual of elderly patients in trials for registration of new cancer drugs or new indications of marketed drugs approved by the FDA from 1995 to 2002, and compared with cancer demographic data from US Census and NCISEER	Retrospective review of trial data	II and III	65
Murthy et al[44]	2004	USA	Retrospective analysis of elderly patients enrolled onto NCICCG trials between 2000 and 2002, and compared with cancer demographic data from NCISEER	Retrospective review of trial data	II and III	65
Kemeny et al[47]	2003	USA	Interviews of 77 pairs of older and younger women matched by breast cancer stage and treating physician to determine reasons for participation *v* non-participation in an open cancer treatment trial for which all women were eligible; questionnaires were sent to treating physicians about reasons for offering or not offering trials to these patients	Retrospective case-control study	Not mentioned	65
Lewis et al[39]	2003	USA	Retrospective analysis of elderly patients enrolled onto NCI trials between 1997 and 2000, and compared with cancer demographic data from NCISEER	Retrospective review of trial data	II and III	65
Yee et al[40]	2003	Canada	Retrospective analysis of elderly patients enrolled onto NCIC CTG trials between 1993 and 1996, and compared with cancer demographic data from Statistics Canada and published rates by SWOG; a separate survey of selected Canadian physicians at a conference	Retrospective review of trial data physician survey	I, II, or III	65
Kornblith et al[46]	2002	USA	Mail survey of selected physicians treating breast cancer at 10 CALGB institutions regarding barriers to recruitment of elderly breast cancer patients	Physician survey	Not mentioned	65
Sateren et al[41]	2002	USA	Retrospective analysis of all patients enrolled onto NCI trials between 1998 and 1999, and compared with cancer demographic data from US Census and NCISEER	Retrospective review of trial data	I, II, or III	Divided as 60-69, 70-79, and 80+
Hutchins et al[42]	1999	USA	Retrospective analysis of elderly patients enrolled onto SWOG trials between 1993 and 1996, and compared with cancer demographic data from US Census and NCISEER	Retrospective review of trial data	Not mentioned	65
Trimble et al[43]	1994	USA	Retrospective analysis of elderly patients enrolled onto NCICCG trials in 1992, and compared with cancer demographic data from 1990 NCISEER	Retrospective review of trial data	II and III	65

Abbreviations: FDA, US Food and Drug Administration; NCISEER, National Cancer Institute's Surveillance, Epidemiology, and End Results Program; NCI CCG, National Cancer Institute Clinical Cooperative Group; NCI, National Cancer Institute; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; SWOG, Southwest Oncology Group; CALGB, Cancer and Leukemia Group B.

Population-Based Studies

Seven of the nine studies used a similar population-based design. Retrospective reviews of clinical oncology cooperative group trials over the last decade were conducted to determine actual accrual rates of older cancer patients.[39-45] These rates were compared with the corresponding proportions of the cancer population using available demographic data to demonstrate underrepresentation of the older patient population and assess barriers to recruitment.

Four of the studies analyzed trial recruitment data from the National Cancer Institute Clinical Cooperative Group (NCICCG), for the following time periods: 1992, 1998 to 1999, 1997 to 2000, and 2000 to 2002, and compared them with the cancer incidence data of similar time periods from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (NCISEER).[39,41,43,44] Whereas the outcomes of these analyses were reported differently, they consistently demonstrated the underrepresentation of older patients in cancer trials. Trimble et al[43] observed that in 1992, 39% of the males and 25% of the females with common cancers such as lung, prostate, colorectal, pancreas, and leukemia recruited to clinical trials were aged 65 years or older, compared with the incidences of 72% and 56% of these cancers accounted for by older men and women in the US population, respectively. Lewis et al[39] performed a similar analysis between 1997 and 2000, and noted that only 32% of the trial participants were aged 65 years or older, compared with 61% of patients with incident cancers from the same age bracket. Sateren et al[41] examined accrual by age, sex, residence, health insurance, and a number of other proxy measures of socioeconomic status during a 12-month period from 1998 to 1999. The authors found that the highest proportion of adults accrued to clinical trials was of patients between 40 and 55 years old; accrual rates steadily declined to less than 1% for patients 75 to 79 years old. Murthy et al[44] examined the enrollment fractions for NCICCG breast, colorectal, lung, and prostate cancer clinical trials between 2000 and 2002. The enrollment fraction was calculated by dividing the number of patients accrued by the estimated United States cancer cases at that time. This parameter was determined for three different age subgroups: 30 to 64 years, 65 to 74 years, and 75 years or older. A strong relationship was found between age and the enrollment fraction. Patients aged 30 to 64 years who were enrolled in clinical trials represented 3.0% of incident cancer patients in that age group. The enrollment fractions were even lower as age increased, with the respective values of 1.3% for patients aged 65 to 74 years, and 0.5% for those aged 75 years or older.[44]

Other United States groups have conducted similar studies to evaluate the accrual rates of older patients in clinical trials. Hutchins et al[42] analyzed data from the Southwest Oncology Group (SWOG) trials from 1993 to 1996, and compared them with United States national rates using US Census and NCISEER data. The authors also demonstrated that the proportion of patients over the age of 65 enrolled onto the SWOG trials was significantly lower than the corresponding incidence rate in the population (25% *v* 63%, respectively). Talarico et al[45] examined the accrual of older patients in trials for registration of new cancer drugs or new indications of marketed drugs, approved by the US Food and Drug Administration from 1995 to 2002. The accrual rates for each trial, separated by age groups, were compared with corresponding age-specific rates of each cancer in the general population obtained from US Census and NCISEER data. Patients aged 65 years or older were significantly underrepresented in almost all cancer trials, and this imbalance was even more notable for patients older than 75 years.

Outside of the United States, Yee et al[40] analyzed Canadian data from the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) from 1993 to 1996 and compared them with cancer incidence data from Statistics Canada and US SWOG data generated by Hutchins et al[42] over the same time period. Patients who were 65 years or older accounted for 22% of patients in the NCIC CTG trials compared with 58% of the Canadian population of cancer patients from that age bracket. This rate was also lower than the reported SWOG accrual rate of 25%.

Physician Surveys

Two of the included studies[40,46] were recent surveys of physicians participating in cancer cooperative groups in Canada and the United States. These studies were designed to address physician perceptions on potential barriers to older patients' enrollment in cancer trials. In the course of their study, Yee et al[40] also conducted a pilot survey of 40 physicians attending the NCIC CTG 2000 Spring Meeting of Participants (Toronto, Canada; April 2000) to address the perspective of Canadian physicians on the barriers to enrollment of older patients onto cancer trials. The second survey included 156 physicians (85% oncologists) who treated breast cancer patients at 10 Cancer and Leukemia Group B (CALGB) institutions and completed a questionnaire pertaining to the recruitment of older breast cancer patients.[46] These 10 institutions were selected based on the largest accrual of patients to breast cancer trials across all age groups.

Retrospective Studies

A retrospective case-control study[47] was also conducted in these same CALGB institutions, matching 77 pairs of patients (one younger than and one older than 65 years) by disease stage and treating physician, to control for confounding factors of individual differences between oncologists and disease stage. This study determined the extent to which patients were offered a trial, and examined the differences in participation rates between younger and older patients once the trial was offered. Both the physician's reasons for offering a trial, and the patient's reasons

for participating, were assessed. Table 2 presents a comparison of the results from the two CALGB studies.

The findings of all the studies listed in this section can be summarized into three major groupings: barriers as a result of the study design of cancer trials, barriers related to physician factors, and barriers related to patient factors.

Barriers Related to Cancer Trial Design

In general, underrepresentation of older patients seems to be a universal problem for all trials, and does not appear to be restricted to a specific sex or tumor site.[43] The majority of cancer trials prohibit participation of people with hematologic, hepatic, renal, or cardiac abnormalities. Exclusions on the basis of hypertension, cardiac disease, hematologic, or pulmonary function abnormalities resulted in 8.6%, 5.3%, 14.1%, and 9.3% lower enrollment of older patients, respectively, in National Cancer Institute (NCI) trials from 1997 to 2000.[39] Since protocols no longer specify an upper age limit for eligibility, the number of trials with age restrictions are small and chronologic age itself does not seem to be a significant barrier to enrollment.[39] However, more than 80% of the trials required participants to be either ambulatory and capable of work, or capable of carrying out their activities of daily living independently.[39] The proportion of older patients was 22% lower in trials that excluded patients with mild or moderate functional status impairment than in trials that did not exclude these patients.[39] Trials that did not specify any functional status exclusion also enrolled 29% lower numbers of older patients than trials that explicitly allowed older patients with impaired functional status.[39] Approximately 90% of trials, both phase II and phase III, excluded individuals with a previous cancer, which may favor recruitment of younger patients.[39] Enrollment of older patients was much higher in trials for late-stage cancers than early-stage cancers,[39,40] and slightly higher in trials that specified any life expectancy requirement.[39] In the Canadian NCIC CTG study,[40] participation of older patients was equally low in clinical trials evaluating investigational agents, like phase I trials, versus supportive care trials (24% and 21%, respectively).

Barriers Related to Physician Factors

When physicians were questioned about what they considered to be potential barriers to older patient recruitment, both United States and Canadian physicians most frequently cited comorbid conditions and toxicity of the treatment.[40,46] Other less common factors or perceived barriers included: lack of support for the older patient to manage side effects at home[40,46]; patient preference and influence of their families[40,46]; transportation needs of the older patient[46]; patient difficulty in understanding the trial[46]; excessive time required to enroll older patients[40]; patients not meeting study eligibility criteria[46]; lack of coverage for certain health care costs related to clinical trial participation[46]; physicians' personal bias that one arm of the trial was not effective or unacceptable[46]; perceptions that the best treatments for their patients were not included in the trial[40,46]; that life expectancy of some patients was too short to justify participation in clinical trials[46]; or that the likelihood of success was low in many trials.[46] Geographic inaccessibility, trials simply not being offered by physicians, physicians being unaware of trials, and concerns about additional investigations were infrequently cited as other possible barriers.[46]

In the case-control study conducted in parallel to the survey from the 10 top-accruing CALGB institutions, the reasons cited by physicians for trials not being offered to older breast cancer patients were obtained. Among these, increasing age, late-stage disease, and greater number of comorbidities were all significant predictors for patients not being offered a trial.[47] Sixty-eight percent of younger, stage II breast cancer patients were offered a trial, compared with

Table 2. Comparison of Two Studies Using Physicians' and Patients' Information From Breast Cancer Clinical Trials From CALGB Institutions

Study	Objective and Methods	Important Findings	Discussion Points
Barriers to clinical trial participation by older women with breast cancer; Kemeny et al,[47] 2003	Retrospective case-control study to examine whether older breast cancer patients, seen at a CALGB institution, were offered trials less often, and whether they were more likely to refuse participation; 77 matched patients interviewed; physicians given questionnaires	Younger patients were offered entry onto a trial more often (68%) than older patients (34%; $P = .0004$). Interestingly, of those patients offered a trial, there was no significant difference in participation rates between older and younger patients	It appeared that the greatest barrier to the accrual of older patients was physician perceptions about age and tolerability of treatment. For both younger and older patients, the main reason to decline trial participation was their desire to choose their own treatments
Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials; Kornblith et al,[46] 2002	Prospective physician survey of 156 physicians who had treated breast cancer patients at CALGB institutions	Surveyed physicians felt that the most important barriers to older patient accrual were significant comorbid conditions, poor compliance for the elderly patient, treatment toxicity, and difficulty meeting the eligibility requirements	It seemed that physicians perceived the barriers to be multidimensional with factors such as protocol requirements, treatment-specific issues, social support, logistic issues, and the medical and cognitive condition of older patients all playing a potential role

Abbreviation: CALGB, Cancer and Leukemia Group B.

34% of remaining patients ($P = .0004$). Older age remained significant as a predictor of not being offered a trial despite controlling for comorbidity and physical functioning. The finding that late-stage disease negatively influenced accrual of older patients in this case-control study contradicted the observations in retrospective studies.[39,40]

The most common reasons physicians reported on their questionnaires for not offering trials to patients were: treatment considered too toxic for the patient (33%), the best treatment was not included in the available clinical trials (27%), and unaware that a trial was available (21%). Physician characteristics such as specialty, age, sex, and percentage of caseload older than 65 years were not associated with their likelihood of offering clinical trial participation to older patients.[47] Recruitment of older patients to cancer trials from community-based oncology practices was comparable to recruitment in urban academic centers (27% *v* 22%; $P =$ not significant).[42]

Barriers Related to Patient Factors

Although comorbid conditions were more frequent in older breast cancer patients compared with their younger counterparts in the case-control study by Kemeny et al[47] (mean number of comorbid conditions, 3.2 *v* 1.9, respectively; $P < .0001$), there was no difference in the degree to which these interfered with their daily functioning (Revised Rand Functional Limitation Scale, 1.5 *v* 1.4, respectively; $P = .43$). There were similarities and differences observed between the younger and older patients when reasons for agreeing or declining to participate in clinical trials were discussed. When younger patients were asked their reasons for participating in a trial, the three most common reasons were: an improvement in their health, to find a cure for cancer, and a desire for the most updated treatment. For older patients, the most common reasons for participating were: it was the best treatment available, an improvement in their health, and to find a cure for cancer. The primary reason for not participating in a study for younger patients was that they wanted to choose their own treatment. The older patients also chose this reason most frequently for their refusal to take part in a study.

DISCUSSION

Although cancer clinical trials are essential in evaluating the safety and efficacy of novel anticancer agents, only 3% of newly diagnosed cancer patients participate in clinical trials annually.[48] Previous population-based studies in the United States, Europe, and Canada have consistently identified old age as a barrier to access for therapy, including surgery, radiotherapy, and chemotherapy, for cancer patients.[49,50] The clinical applicability of the results of a cancer treatment trial depends largely on whether the study participants are representative of the population of interest.[51] Hence, to ensure that clinical trial results are generalizable to older patients, trials should include them in numbers proportional to their distribution among the cancer population. In this report, we have performed a systematic review of the recent literature addressing barriers to recruitment of older patients with cancer in the hope that the information will help determine ways to overcome these barriers, and result in better care for this important and vulnerable population.

Although there is a paucity of recent data in this specific area, there are some recurring themes that are evident in many of the papers. These fall into four main categories on the pathway to accrual: protocol design barriers, physician barriers, patient barriers, and trial logistical barriers.

Protocol Design Barriers

There are many potential areas in the protocol design of cancer trials that may be targeted to optimize recruitment of a proportional number of older patients. Excluding older patients based on poor performance status occurs primarily because of safety concerns, as researchers do not want to cause undue harm to frail patients. However, the problem with this approach in the older patient is that "inadequate" performance status may be difficult to interpret, because it may be based on orthopedic conditions that limit mobility rather than systemic medical problems that may potentially be worsened by chemotherapy and radiation. Different methods of ascertaining performance status may be more appropriate in older patients so that an accurate picture of their overall health can be determined in relation to whatever may be affected by the cancer treatment. Removing performance status as an exclusion criterion altogether is another potential option. However, in the study by Lewis et al,[39] it was found that trials that did not specify any functional status exclusion enrolled significantly lower numbers of older patients than trials that explicitly allowed older patients with impaired functional status. This suggests an inherent reluctance on the part of physicians to enroll older patients with even mild functional impairment, unless specifically mandated by the protocol to consider these patients. The same group's finding of an association between life expectancy requirements and increased participation by older patients was somewhat unexpected.[39] The authors speculated that these trials may be actively targeting older patients, and investigators may have preferred to have this limitation specified to consider enrollment. Balducci[52] has evaluated the functional assessment of the geriatric patient in depth, and has found that the clinical evaluation of age should account for the diversity of the older population. He suggests that an appropriate evaluation of an older patient with cancer should be based on a comprehensive geriatric assessment, which is composed of the following seven domains: functional status, comorbidity, mental status,

emotional conditions, nutritional status, polypharmacy, and geriatric syndromes. This may enable clinicians to better determine the group of older patients who will be less likely to suffer adverse effects and more likely to benefit from cancer treatment.

Patients with a previous malignancy are often excluded from most cancer trials because of the difficulties in interpretation of patient outcomes as they relate to the current malignancy. This exclusion should be re-evaluated, since it will clearly exclude a larger proportion of older patients, as they would more likely have had a second malignancy. There are insufficient data to confirm that a previous cancer that is not currently active will affect study-related outcomes. Instead of a blanket statement excluding all patients with a previous malignancy, a modified criterion should be used to allow the inclusion of some of these patients, such as one with a reasonable time frame since their previous malignancy, for example 3 to 5 years. For phase I trials where the primary end point is toxicity, there is no justification for patients with prior malignancies to be excluded.

Physician Barriers

Potential toxicity from study treatment and comorbid conditions of patients were consistently stated by physicians as the most common reasons for excluding older cancer patients from clinical trials in our review. Other reasons cited by physicians included the lack of home and social support among older patients, patient preference and influence of their families, physicians' unawareness of trial availability, and physicians' own perceptions about the available trials. The exclusion of older patients from clinical trials based on potential toxicity or comorbidity was the primary factor affecting the management choice of physicians, regardless of their age, sex, specialty, or area of practice. Part of the reason for this exclusion stems from the fact that there is a relative paucity of primary research related to the biology of cancers, the effect of treatment on comorbid conditions, and treatment-related toxicities in the older patient. In the case of some tumors such as breast and lung cancers, older patients have no increased toxicity and similar survival rates when compared with younger patients given the same treatment regimen and dose intensity.[15,16] In contrast, older patients with hematologic malignancies, such as acute myeloid leukemia and non-Hodgkin's lymphoma, show increased toxicity with relatively poor overall survival compared with their younger counterparts.[53-55] Toxicity related to treatment is dependent on the type and dose intensity of the therapy, the type and stage of cancer, the underlying biology of the cancer, and differences in functional reserve of the different organ systems. Until data from primary research addressing the unique aspects of cancer biology and treatment in the older patient are available, it will be difficult to ease concerns of physicians about including older patients in studies where they fear toxicity would be intolerable. In-depth evaluation of dose-dependent toxicities in the older patient and the effects of dose modifications on comorbid conditions and outcomes will enable researchers to build dose-modification strategies into future protocols, thereby enhancing recruitment of older patients. Stratification of patients based on age and physiological impairment is another strategy to determine toxicity and maximum-tolerated dose in both older and younger patients.[43]

Patient Barriers

It is interesting to note that in contrast to physician concerns about treatment tolerance of older patients in clinical trials, older breast cancer patients did not cite this as an important factor for refusing studies.[47] The most important reason for nonparticipation was primarily related to the patients' desire to choose their own treatment and this view was common among both younger and older patient age groups.

Older patients, in general, have a lower level of education than their younger counterparts, and some may be illiterate.[56] The concept of a clinical trial may be foreign to older patients who are unfamiliar with the term. These patients may benefit from additional time and effort dedicated to explain to them the purpose of clinical trials in general, their risks and benefits, the details of a specific clinical trial, and the consent form. In the survey by Kornblith et al,[46] increasing the staffing of oncology clinics to allow for the extra time and resources was rated by oncologists as the most important method for improving older patient accrual. A study by Ellis et al[30] focused on increasing patients' knowledge about clinical trials so that they would be better able to understand the positive value of participation. Their results also suggested that increasing older patients' knowledge about trials might increase the frequency of their requesting a trial from their oncologists.

A recent study by Rose et al[57] examined the relationships between physician and patient perspectives, patient preferences for treatment, care practices, and outcomes in older and middle-aged (45 to 64 years) patients. This study illustrated the importance of educating patients about treatment goals and options, ensuring their understanding of these concepts, and encouraging their involvement in care decision-making. Interestingly, although the majority of patients in both age groups considered pain relief a priority treatment goal, the link between preference for this treatment and actual care practices was only found in the older patient group. This suggests that the wishes of older patients for less aggressive care may be more readily accepted than similar desires of a middle-aged population, whereas their wishes for aggressive interventions may require a greater effort to overcome stereotypic hurdles.

Older patients often live alone and have a smaller support network than younger patients, though these social

factors seemed to be less significant barriers to trial participation in actual practice.[56] It is likely that older patients who actually visited the cancer clinics are those who have sufficient support at home, whereas those who lack such a support network never made it to their appointments. Hence, support systems should be put in place to help older patients with issues such as transportation, management of treatment-related adverse effects, and maintenance of any central or peripheral intravenous lines required for the study.

Barriers Related to Trial Logistics

Lastly, logistic issues and problems with the clinical trial infrastructure must be addressed. Physicians need timely access to knowledge of available, ongoing studies so that they can refer their eligible patients to centers with appropriate trials. It has been shown that physicians whose practices were based in university settings or had help from a cooperative group had higher rates of patient accrual onto studies.[34] By improving the dissemination of information about available clinical trials to treating physicians, we could hopefully improve access to trials for all eligible patients. Before September 2000, Medicare provided reimbursement for costs incurred during standard care but not for those incurred during participation in clinical trials. Since then, all costs related to clinical trials are covered.[58] This issue may have posed a significant barrier to the recruitment of patients onto trials, as patients who were required to incur extra costs to be on study would be less likely to enroll, thus favoring entry of a higher proportion of patients from a higher socioeconomic background. With the change in reimbursement policy, this barrier should be minimized.

Limitations

Although this review may help to clarify the specific barriers to recruitment of older patients with cancer, there are limitations. There is, in general, a marked paucity of published data in this area as evidenced by the small number of complete papers we were able to include in this review. Until more cancer research in the older population is conducted, our conclusions about clinical care and barriers to recruitment among older patients are based on this limited number of studies. Also, the reviewed articles are all based on North American research, and therefore may not be generalizable to older populations outside of the United States and Canada. Issues pertaining to older patients may be very different in other countries where there may be more multigenerational homes, older patients may not have the same access to medical care compared with younger patients, financial coverage for clinical trials may not exist, and even the incidence and biology of certain tumors may be different.

Recommendations From This Review

First, the most significant barrier to proportionate recruitment of older patients in clinical trials is the lack of data on their tumor biology and treatment tolerance, resulting in reluctance on the part of the medical community to enroll these patients. Clinical trials designed specifically for the older patient, addressing questions related to these areas, are urgently needed.

Second, protocols for trials should be designed to either stratify for age at study entry and/or modify exclusion criteria related to comorbid conditions, functional status, and previous malignancies, so as to not discriminate against older patients. Also, better functional assessments would help to differentiate the "well" older patient from the "frail" older patient.

Third, improvements in clinical trial infrastructure such as easy access to central databases of currently active clinical trials to determine eligibility will improve enrollment for all patients, including older patients. In June 2004, the Centers for Medicare and Medicaid Services (CMS) and the NCI announced that they would work together to identifying high-priority clinical questions and address additional concerns, such as cancer health disparity issues and reducing unwarranted variation in treatment patterns.[59] This type of initiative is likely to help remove some of the trial barriers to older patients.

Fourth, clinical trial resources need to be properly allocated so that clinical trial personnel can spend the extra time and effort required to recruit older patients, by explaining the protocol and consent procedures adequately, assisting with support at home, addressing transportation needs, and ensuring that older patients on study are functioning well.

Lastly, increased effort should be put into educating physicians about the treatment of cancer in the older patient and determining which older patients are appropriate for clinical trials.

In conclusion, there exist multiple reasons to explain the considerably lower accrual of older patients compared with younger ones in cancer clinical trials. In addition to their underrepresentation in cancer therapy utilization, older patients with cancer are vulnerable to being inappropriately managed, due to continuing misconceptions about the tolerability and feasibility of treating them with cancer therapeutics, and the paucity of evidence-based medicine to guide management. Even small changes in one or more of the areas targeted in this review may be enough to break down some of these barriers. If we are able to increase the accrual rate of older patients to clinical trials, we will better understand how to treat older patients with cancer and may thereby impact cancer-related morbidity and mortality in this expanding segment of our population.

Acknowledgment

We thank J. Jackson for his help with the systematic search of appropriate databases.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Appendix 1. Summary of the 22 Studies Reviewed but Not Included in This Systematic Review, by Year

Study	Primary Objective	Population	Findings Relative to Recruitment and Age (years)	Reason for Exclusion
Why cancer patients enter randomized clinical trials: Exploring the factors that influence their decision; Wright et al,[18] 2004	To identify the independent predictors of cancer patients' decisions to enter a randomized, clinical trial, based on expressed attitudes of patients, physicians, and CRAs close to the time of an actual decision to enter a trial.	189 cancer patients, their physicians, and CRAs were asked to complete questionnaires.	Mean age of the 189 patients was 60, with a range of 38-93. The patient's perception of personal benefit was the most important variable, which correlated with the decision to enter a clinical trial. Sex of the patient, but not age, also correlated with the decision to take part.	Results and discussion of study concentrated primarily on attitude related findings. Study did not address age as a barrier to clinical trial enrollment.
Recruiting older African American men to a cancer screening trial: The AAMEN Project; Ford et al,[19] 2003	To describe the demographics of participants on the AAMEN project designed to recruit older (55+) African American men for cancer screening.	34,376 African American men were eligible and were contacted by telephone or mail to participate in the study.	The group that was the most difficult to contact was the youngest group (55-59 years). Participants in the eligible and interested group were younger than those in either the ineligible group or the group that refused to participate. Regardless of income status, older individuals were more likely to refuse to participate.	Results and discussion of study concentrated primarily on race related and income related findings. Did not discuss age-related findings.
Willingness to participate in clinical treatment research among older African Americans and Whites; Brown et al,[20] 2003	To examine racial differences in factors predictive of the behavioral intention of older persons to participate in a clinical trial should they have a diagnosis of cancer.	Community-based telephone survey of 216 African Americans and 222 whites, aged 50 years and older.	Willingness to participate was significantly higher among males, individuals of younger age, higher incomes and non-fatalistic cancer beliefs. When analyzed by race, the willingness to participant in a clinical cancer treatment trial declined significantly with increasing age among African Americans, but not for whites.	Results and discussion of study concentrated primarily on race related findings. Discussion speculated on reasons why older African Americans were less likely to participate than their white counterparts.
Public attitudes toward participation in cancer clinical trials; Comis et al,[21] 2003	To understand the attitudes of American adults toward participation in cancer clinical trials.	A national sample of 1,000 adults aged 18 years and older were interviewed by telephone.	Approximately 32% of American adults indicated that they would be very willing to participate in a cancer clinical trial if they were diagnosed with cancer. Younger adults were more likely to hold positive views about participating in a cancer clinical trial than older adults. Reasons for unwillingness to participate were not explored.	The determination of willingness to participate based on age was a secondary analysis and not the primary outcome of the study.
Perceptions of equipoise are crucial to trial participation: A qualitative study of men in the ProtecT study; Mills et al,[22] 2003	To explore patients' perceptions of randomization and reasons for consent or refusal to participate in the ProtecT study for localized prostate cancer.	In-depth interviews with 21 men who were invited to participate in the ProtecT trial.	Belief in clinical equipoise was key to participants' consent to randomization.	Study did not relate findings to patients' ages.
Barriers to participation of African-American patients with cancer in clinical trials: A pilot study; Advani et al,[23] 2003	To better understand barriers to African American participation in clinical trials and increase their recruitment.	218 cancer patients of mixed ethnicity were surveyed about their attitudes toward clinical trials.	Willingness to participate in a clinical trial depended on race. Demographic predictors that were correlated with increased willingness to participate in clinical trials included younger age (odds ratio, 0.79; 95% CI, 0.63 to 1.00; $P = .05$), in a multivariate analysis.	Results and discussion of study concentrated primarily on race related findings, and not on age-related findings.
Why patients don't take part in cancer clinical trials: An overview of the literature; Cox et al,[24] 2002	To explore the problem of attaining adequate recruitment to clinical trials and to provide possible explanations for non-participation in clinical trials.	Review of papers about clinical trial participation in cancer and in other fields.	The authors highlighted the necessity of understanding the issues surrounding the decision-making processes of potential trial participants in order to increase accrual. The possibility of using "participant advisors" was mentioned to help ethnic minorities deal with cultural considerations.	Review article. Discussion was broadly applicable to all age groups and not confined to an elderly population.

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Appendix 1. Summary of the 22 Studies Reviewed but Not Included in This Systematic Review, by Year (continued)

Study	Primary Objective	Population	Findings Relative to Recruitment and Age (years)	Reason for Exclusion
Clinical trial participation among patients enrolled in the Glioma Outcomes project; Chang et al,[25] 2002	To evaluate factors that influenced patient enrollment onto clinical trials using a prospective, large, observational, multi-institutional registry of patients with malignant glioma.	708 patients of any age who underwent surgery for malignant glioma, 151 (21%) participated in a clinical trial.	Multivariate logistic regression model showed that young age was a significant predictor of trial participation (odds ratio, 0.98; 95% CI, 0.967 to 0.996; $P = .038$). Functional parameters such as performance status or comorbidity were not captured, and may be confounding.	The difference in clinical trial participation based on age, was one of the findings and not the primary outcome of the study.
Therapy choices among older patients with lung carcinoma: An evaluation of two trials of the Cancer and Leukemia Group B; Rocha Lima et al,[26] 2002	To determine the participation, tolerance of treatment, and outcome and in two NCI-approved NSCLC trials.	515 patients with locally advanced or metastatic NSCLC from two trials: CALGB 8931 and 9130. Evaluated by 4 age groups.	No differences in response, survival, or continuation of treatment based on age. For the two trials, patients aged 70-79 accounted for 16% and 22% of all enrolled patients, respectively. No patients aged > 80 entered onto either study, even though there were no age restrictions.	Primary objective of study was to evaluate drug tolerability and outcomes in the elderly. Participation analyzed by age, was a secondary outcome.
Prospective evaluation of cancer clinical trial accrual patterns: Identifying potential barriers to enrollment; Lara et al,[27] 2001	To determine the overall accrual rate onto clinical trials, to evaluate factors that affect eligibility and to study characteristics of those who failed to enroll, at a single cancer center.	276 new oncology patients of any age seen at the University of California Davis Cancer Center.	Patient characteristics (ie, age, sex, race, referral source, and insurance) and odds of a physician considering a patient for trial participation were analyzed by a univariate analysis. None of the patient characteristics, including age, was significant in influencing physician triage decision-making. The main reason for physicians not considering a patient for study was a perception of protocol unavailability. The main reason for patients declining trial participation was a desire for other treatment.	The evaluation of the odds of a physician considering a patient for study, based on age, was a secondary analysis and not the primary outcome of the study. Specific barriers for elderly patients were not discussed.
Factors that influence the recruitment of patients to phase III studies in oncology: The perspective of the Clinical Research Associate (CRA); Wright et al,[28] 2001	To explore the factors that influence the decision of patients with cancer regarding clinical trial entry, specifically from the prospective of the CRA at a single cancer center.	Two focus groups of CRAs from the Hamilton Regional Cancer Centre.	CRAs identified information transfer within the informed consent process as a major aspect of their specialized role. CRAs believed that they have an important influence on recruitment success.	Results and discussion of study concentrated primarily on attitude related findings. Study did not address age as a barrier to clinical trial enrollment.
Sociodemographic and clinical predictors of participation in two randomized trials: Findings from the Collaborative Ocular Melanoma Study COMS report No. 7; The Collaborative Ocular Melanoma Study Group,[29] 2001	To evaluate factors predictive of participation in two multicenter randomized clinical trials (COMS) that compared effectiveness of radiotherapy *v* enucleation in patients with choroidal melanoma.	6,906 patients with choroidal melanoma were evaluated for the trials, 4,191 were eligible. Logistic regression used to identify factors predictive of participation.	Multivariate logistic regression model showed that older age (> 60) was a significant predictor of trial participation ($P < .05$).	The difference in clinical trial participation based on age was one of the findings, and not the primary outcome of the study.
Randomized clinical trials in oncology: Understanding and attitudes predict willingness to participate; Ellis et al,[30] 2001	To explore women's willingness to participate in randomized clinical trials at different time points in their breast cancer care.	Cross-sectional survey of 545 women, with or without breast cancer, attending a breast clinic to assess attitudes toward and willingness to participate in clinical trials.	Multivariate logistic regression model showed that younger age was a significant predictor of participation in a randomized clinical trial (odds ratio, 0.96, 95% CI, 0.93 to 0.99; $P = .01$).	The evaluation of the odds of a woman considering participation in a randomized clinical trial, based on age, was a secondary analysis and not the primary outcome of the study. Specific barriers for elderly patients were not discussed.

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Appendix 1. Summary of the 22 Studies Reviewed but Not Included in This Systematic Review, by Year (continued)

Study	Primary Objective	Population	Findings Relative to Recruitment and Age (years)	Reason for Exclusion
Originality, benefits, and difficulties of clinical research performed by cooperative groups: The experience of an Italian Lung Cancer Study Group; Gridelli et al,[31] 2000	To summarize the experience of an Italian Lung Cancer Study Group in coordinating, stimulating, and developing clinical research in the field of lung cancer.	Review of lung cancer studies conducted by an Italian Lung Cancer Study Group.	This group has been very successful in conducting large multicenter trials in lung cancer among the elderly, such as the ELVIS (Elderly Lung cancer Vinorelbine Italian Study) and the MILES (Multicenter Italian Lung cancer in the Elderly Study) trials.	Summary article. This Group did not encounter age as a barrier to clinical trial recruitment. Specific recruitment strategies were not discussed.
Representation of Asian Americans in clinical cancer trials; Alexander et al,[32] 2000	To analyze the accrual of Asian Americans to NCI-supported cancer clinical trials.	Data from all participants accrued to NCI-sponsored clinical trials from 1994-1998. Percentages of Asian Americans on trials were calculated and divided by age categories.	Asian American accrual in NCI-supported trials was representative of their cancer burden in the US. Younger Asian Americans participated significantly more in treatment trials than older Asian Americans.	Results and discussion of study concentrated primarily on race-related findings, and not on age-related findings.
Attitudes towards and participation in randomized clinical trials in oncology: A review of the literature; Ellis,[33] 2000	To provide a broad review of the issues pertinent to physician and patient participation in randomized clinical trials.	Search of computerized databases.	Patient education can improve understanding about clinical trials.	Review article. Discussion was broadly applicable to all age groups and not confined to an elderly population.
Factors that predict the referral of breast cancer patients onto clinical trials by their surgeons and medical oncologists; Siminoff et al [34] 2000	To investigate physicians' reluctance to refer patients to clinical trials.	147 physicians discussed 245 patient cases with respect to their own knowledge and attitudes toward clinical trials.	Older patients and those with a poorer prognosis were less likely to be referred.	The difference in referral based on age, was one of the findings and not the primary outcome of the study. Study did not address reasons why older patients were referred less often.
What influences participation in clinical trials in palliative care in a cancer centre? Ling et al,[35] 2000	To highlight the challenges of recruitment into clinical trials in palliative care.	Information about 1,206 patients of various ages referred for any of 23 studies in palliative care was collected prospectively.	The most common reasons for unwillingness to participate were a wish to defer to a later date, deterioration in condition, and distance to hospital.	Patients' reasons for declining trial participation were not evaluated by age. Discussion was broadly applicable to all age groups and not confined to an elderly population.
Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy; Jenkins et al,[36] 2000	To investigate reasons why patients agreed or declined to participate in randomized clinical trials, following discussions conducted by clinicians.	204 cancer patients in UK were surveyed about their reasons for accepting or declining trial entry.	The main reasons for participating in a trial were that "others will benefit" and "trust in the doctor". One main reason for declining trial entry was the concern about randomization.	Patients' reasons for accepting or declining trial entry were not evaluated by age. Discussion was broadly applicable to all age groups and not confined to an elderly population.
Entry into clinical trials in breast cancer: The importance of specialist teams; Twelves et al,[37] 1998	To identify factors influencing entry of women with invasive breast cancer onto clinical trials.	Retrospective chart review of 4,688 patients diagnosed with breast cancer in Scotland between 1987 and 1993.	Age was marginally significant in the multivariate analysis, with women over 65 less likely to enter a trial (odds ratio, 0.76; 95% CI, 0.57 to .99; $P = .05$). This effect was more pronounced for women over 80 (odds ratio, 0.43; 95% CI, 0.22 to 0.84; $P = .01$).	The difference in clinical trial participation based on age, was one of the findings and not the primary outcome of the study. Specific barriers for elderly patients were not discussed.
Psychosocial aspects of participation in early anticancer drug trials. Report of a pilot study; Cox et al,[38] 1996	To explore the psychosocial aspects of participation in early anticancer drug trials from the perspective of the patient.	The views of 7 patients were obtained as they progressed through an anticancer drug trial.	Findings identified information transfer and patient support as main aspects important to patients in an ongoing study.	Study did not relate findings to patients' ages.
Treatment tolerance of elderly cancer patients entered onto phase II clinical trials: An Illinois Cancer Center study; Giovanazzi-Bannon et al,[17] 1994	To determine treatment tolerance of elderly patients that had been entered onto any phase II study in the Illinois Cancer Center database.	672 cases of patients treated on phase II studies were evaluated.	No significant differences between elderly and non-elderly patients based on 7 treatment-toxicity–related variables: performance status, dose reductions, treatment interruptions, delays, best response, reason off-study, and number of grade 3 or greater toxicities.	Study did not examine accrual rates of elderly patients onto the phase II studies.

Abbreviations: CRA, clinical research associates; NCI, National Cancer Institute; NSCLC, non–small-cell lung cancer; CALGB, Cancer and Leukemia Group B.

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VOLUME 31 · NUMBER 29 · OCTOBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

End Points and Trial Design in Geriatric Oncology Research: A Joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology Position Article

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Published online ahead of print at www.jco.org on September 9, 2013.

Supported by a donation from the Fondation Contre le Cancer in Belgium through the European Organisation for Research and Treatment of Cancer Charitable Trust. H.W. is senior clinical investigator of the Fund for Scientific Research (FWO-Vlaanderen).

This article is endorsed by European Organisation for Research and Treatment of Cancer, Alliance for Clinical Trials in Oncology, and International Society of Geriatric Oncology.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/13/3129w-3711w/$20.00

DOI: 10.1200/JCO.2013.49.6125

ABSTRACT

Selecting the most appropriate end points for clinical trials is important to assess the value of new treatment strategies. Well-established end points for clinical research exist in oncology but may not be as relevant to the older cancer population because of competing risks of death and potentially increased impact of therapy on global functioning and quality of life. This article discusses specific clinical end points and their advantages and disadvantages for older individuals.

Randomized or single-arm phase II trials can provide insight into the range of efficacy and toxicity in older populations but ideally need to be confirmed in phase III trials, which are unfortunately often hindered by the severe heterogeneity of the older cancer population, difficulties with selection bias depending on inclusion criteria, physician perception, and barriers in willingness to participate. All clinical trials in oncology should be without an upper age limit to allow entry of eligible older adults. In settings where so-called standard therapy is not feasible, specific trials for older patients with cancer might be required, integrating meaningful measures of outcome. Not all questions can be answered in randomized clinical trials, and large observational cohort studies or registries within the community setting should be established (preferably in parallel to randomized trials) so that treatment patterns across different settings can be compared with impact on outcome. Obligatory integration of a comparable form of geriatric assessment is recommended in future studies, and regulatory organizations such as the European Medicines Agency and US Food and Drug Administration should require adequate collection of data on efficacy and toxicity of new drugs in fit and frail elderly subpopulations.

J Clin Oncol 31:3711-3718. © 2013 by American Society of Clinical Oncology

INTRODUCTION

The choice of appropriate end points is important to assess the benefit of therapy. In oncology, there are well-established clinical end points for clinical research in randomized clinical trials (RCTs); in the curative/adjuvant setting, disease-free survival (DFS) and overall survival (OS) are the most recognized and well accepted. For metastatic solid tumors, progression-free survival (PFS), time to tumor progression (TTP), time to treatment failure (TTF), response rate (RR), and OS are the most commonly used end points.

A caveat is that the definitions of these so-called standard outcomes have varied in different trials in the past, challenging the ability to compare across studies and provide evidence-based care. There are international efforts to streamline this, such as the DATECAN (Definition for the Assessment of Time-to-Event End Points in Cancer Trials) project.[1]

However, these standard end points may not be the most appropriate to balance the benefits with the risks of therapy in older patients with cancer, because older patients often die as a result of other diseases, and relapse will not always affect survival, whereas cancer-directed therapy can sometimes cause severe acute or chronic toxicities and decreased quality of life (QoL). For young patients with familial/social obligations (eg, toward young children), prolongation of life might be the most important end point; however, older adult patients with incurable disease may prefer QoL above quantity of life, especially if treatment also has an impact on their functional capacity and ability to carry out

daily tasks, their cognitive function, their social situation/capability to stay at home, or their caregiving abilities.[2] Therefore, there is a need for delineation of relevant clinical end points for older individuals, which can then be uniformly incorporated into future clinical trials.[3,4]

The best-established form of clinical trial design is the RCT. When designing RCTs for older patients with cancer, selection of what should be the standard arm may vary because this can be different for fit, vulnerable, and frail patients. As a result, it will often not be possible to have the same standard arm for all older patients, so other trial designs should be considered, especially for vulnerable and frail patients.

This article describes several potential outcome measures/end points and their advantages and disadvantages for elderly-specific clinical trials and discusses potential trial designs that could be used to greatly expand evidence-based treatment outcomes for the older population with cancer.

OUTCOME MEASURES/END POINTS FOR CLINICAL TRIALS IN OLDER INDIVIDUALS

OS

OS is considered the gold standard in clinical trials, especially when evaluating the superiority of new treatments; other end points such as PFS and DFS are commonly used to report on clinical benefit, but this has been subject to criticism (Table 1).[5] Surrogacy of these end points for OS has been demonstrated in some specific settings and is under investigation in others. Compared with younger patients, elderly patients with cancer often present with significant comorbidities and therefore die as a result of other, non–cancer-related diseases more frequently.[6,7] Elderly patients are more likely to experience severe toxicities from cancer-directed therapies, including treatment-related mortality.[8,9] Non–disease-related deaths and treatment discontinuation/reduced dosage because of toxicity might dilute treatment benefit, and larger sample sizes would be needed to demonstrate treatment effects. It should be emphasized that this diluted benefit is an accurate estimate of the true clinical benefit in the older population, and larger sample sizes are the price society has to pay if it wants to ensure that older patients are not subjected to toxic therapies that provide no tangible clinical benefit. The mentioned concerns have resulted in age limits and stringent inclusion criteria, leading to the exclusion of large numbers of older patients from clinical trials.[3,10,11] Although excluding older patients with comorbidities could help a trial determine whether a benefit from treatment exists (especially if the benefit is small), this approach limits generalizability of the treatment for the vast majority of cancers, where most of the patients are older. On average, the trial population in chemotherapy trials is 5 to 10 years younger than the general population with the disease. Because there are no regulatory requirements for establishing the efficacy or toxicity of new therapies in older adults, the limited data in this population ultimately lead to the risk of expensive treatments being used in the older, less studied population, resulting in higher toxicity and smaller benefit than in younger patients with cancer.

Disease-Specific Survival

Whereas primary end points such as OS or PFS would still be suitable to provide a realistic estimation of treatment benefit in the targeted population in the presence of competing risks, measuring cancer-specific end points such as disease-specific survival (DSS) and performing competing risks analyses could generate crucial data. Nout et al[12] nicely demonstrated that including or excluding non–breast cancer–related deaths and contralateral breast cancer significantly affected outcome reporting in early breast cancer. DSS better indicates how many patients die as a result of disease and how many die as a result of other causes. A precondition to using DSS as the primary end point is that the cause of death can be reliably ascertained, and other causes of death are not related to the treatment. In that case, DSS as the primary end point might help in requiring a smaller sample size.[13] However, a reduction in the risk of one type of event (eg, death resulting from cancer) can lead to an increase in the number of observed events for competing types, just because patients remain at risk for those events for a longer period. At any rate, information on cause of death should always be reported to distinguish cancer deaths from treatment-related deaths and deaths resulting from other causes. We recommend reporting DSS always in addition to OS.

Coprimary End Points

Coprimary end points should also be considered because this allows capturing more than efficacy alone. Multiple single end points can be chosen as coprimary end points of equal importance, and a statistical design can be built to test each separately. However, coprimary end points also have disadvantages; statistical design is difficult because the correlation between the different end points is rarely known. Moreover, if the trial objective is to have positive results for at least one or all coprimary end points, the type I or II error, respectively, must be adjusted for multiple testing, which necessitates in increase of sample size.[14]

Composite End Points

Composite end points are another way of integrating other aspects into the end point, such as QoL, treatment effects on disease-related symptoms, functional capacity, and ability to carry out daily tasks. As the International Conference on Harmonisation stated,[15] composite end points avoid the need for arbitrary choice and deal with multiplicity in an efficient manner when several outcome measures are of equal importance to the patient. A composite end point in an RCT consists of multiple single end points that are combined so that an event is indicated if any of the end points occurs. Composite end points have sometimes been used in oncology (eg, skeletal-related events in clinical trials with bisphosphonates or denosumab[16]) but have been more widely used and studied in other medical disciplines, mainly in cardiology.[17,18] Major advantages of a composite end point are the simplicity of the statistical design, which is based on a single end point (ie, the composite one), and the resultant increase in statistical efficiency. However, there are also risks, and caution must be applied. The major possible issues include: lack of a strong rationale given for the composite (ie, mixture of end points with different clinical importance; eg, death and hospital admission), difficulty in interpretation of the results in case of positive results on the composite but observed divergent effects on the components, and inadequate or incorrect reporting of the results (eg, declaring positive effects on the most important component when statistical significance is only reached for the composite, and when the more important component, such as death, accounts only for a minority of the events). Less frequent but important to consider is the situation in which negative results can be observed for the composite, while

Table 1. Relevant End Points in Clinical Trials in the Older Cancer Population

End Point	Definition	Current Situation	Pro	Con
OS: time or proportion	Time from diagnosis of treatment situation/study entry until death or rate of patients alive at specified time point	Considered gold standard in clinical trials, especially when evaluating superiority of new treatments	Remains hardest end point, also in elderly	Oncologic relevance in elderly can be hampered by increased number of non–cancer-related deaths (all life ends with death)
			Easy and distinct to measure, high impact for patients	Does not include QoL aspects
DSS: time or proportion	Time from diagnosis of treatment situation/study entry until death resulting from index disease or rate of patients without death related to index disease at specified time point	Important to collect in addition to OS because it gives better insight into contribution of non–cancer-related deaths	Cancer treatment primarily aims at decreasing cancer death	Some cancer treatments might also influence non–cancer-related deaths (eg, treatment-related mortality) May lead to overestimation of true benefit for patients in presence of competing risks (eg, treatment benefit in localized prostate cancer) Reason for death will be of no/minor meaning for patients Reason for death can remain unclear
Coprimary end points	Combination of ≥ two equal primary end points	Rarely used in oncology	Allows capturing more than efficacy alone	Difficult statistical design because correlation between different end points is rarely known
				Might increase sample size
Composite end points	Combination of different end points in one defined end point	Rarely used in oncology (one example: skeletal-related events) but should be encouraged more	Can take into account multiple dimensions in definition of treatment benefit, including efficacy and toxicity	Requires individual components of composite that are clinically meaningful and of similar relative importance
			Simple and efficient statistical design Allows separate reporting of different end points	Difficult interpretation if there are divergent results for each component separately
TFFS and TTF: time or proportion	TFFS is time elapsing between random assignment and early treatment discontinuation because of any reason (including disease progression, treatment toxicity, early death), disease progression, death (resulting from any cause), or any other event of interest; TTF is similar, but death resulting from other cause is not considered an event	Often used in addition to OS	Integrates efficacy and toxicity	Difficult to distinguish between efficacy and toxicity (eg, toxic but effective) Treatments might be stopped for other reasons (eg, chemotherapy holiday)
QoL-related end points: level at specified time point or time until deterioration compared with baseline	Evaluation of QoL through validated instruments at baseline and during course of disease/treatment/study	Often used as secondary end point in clinical trials but should be promoted as primary end point or part of composite end point	QoL may be more important than duration of life for many older individuals	Difficult to measure and identify clinically relevant cutoffs that determine whether therapy is worthwhile
Maintenance of functional capacity/dependence: level at specified time point or time until deterioration compared with baseline	Evaluation of evolution of functioning and (in)dependence through validated instruments during course of disease/treatment/study	Rarely measured in oncology trials but crucial to include	Main contributor to QoL in elderly patients with cancer	No general consensus on optimal measurement or clinically relevant cutoffs determining whether therapy is worthwhile

Abbreviations: DSS, disease-specific survival; OS, overall survival; QoL, quality of life; TFFS, treatment failure–free survival; TTF, time to treatment failure.

statistical significance can be reached for the most important component. The pros and cons of composite end points have been summarized by Kleist.[19] Use of this approach is usually justified under the following assumptions:

- The individual components of the composite are clinically meaningful and of similar relative importance to clinical care.
- The expected effects on each component are similar based on clinical/biologic plausibility (which is, in the end, the rationale for using a composite end point).
- For the study to be ultimately positive, the clinically more important components of a composite end point should at least not be affected negatively.

All components of a composite end point should also be analyzed separately and reported as such. The separate reporting of end points is also essential to facilitate cross-study comparisons (although there are also intrinsic limitations to this) or to generate assumptions for designing future trials. It is important to mention that for the US Food and Drug Administration, a regulatory end point should clearly distinguish the efficacy of the drug from toxicity, patient or physician withdrawal, or patient intolerance.[20]

An interesting example of a composite end point in older individuals is therapeutic success.[21] This end point combines efficacy, toxicity, and patient compliance with treatment and has been defined as a patient receiving at least three cycles of chemotherapy, at the planned dose (without dose reduction) and schedule (no treatment delay beyond 2 weeks), and having a response (either complete or partial) without experiencing grade 3 or 4 toxicity according to the Common Toxicity Criteria criteria.[22] Variations of this design are possible, such as defining therapeutic success as being progression free at a fixed time point without having grade 3 or 4 nonhematologic or grade 4 hematologic toxicity. This seems to be an attractive end point in settings where significant differences in toxicity between two treatments are expected and requires further exploration. Looking simultaneously at toxicity and efficacy can be a disadvantage as well as an advantage; therapies might be temporarily toxic, requiring dose reduction, but might be efficacious. Dose, toxicity, and response are related (eg, in patients with non–small-cell lung cancer, those with a higher rate of hematologic toxicity survive longer[23]).

Another example is the use of overall treatment utility (OTU) as an end point in the FOCUS (Fluorouracil, Oxaliplatin, and CPT11 [irinotecan]—Use and Sequencing) trial of older patients with metastatic colorectal cancer,[24] in which good OTU indicated no clinical or radiologic evidence of disease progression and no major negative treatment effects in terms of toxicity or patient acceptability. Intermediate OTU signified either clinical deterioration but no negative treatment effect or a significant negative treatment effect but no clinical deterioration. Poor OTU indicated both clinical deterioration and a major negative treatment effect or death.

Treatment Failure–Free Survival and TTF

Treatment failure–free survival (TFFS) and TTF are well-known examples of composite end points and could also be interesting end points to consider for clinical trials in the elderly. TFFS is defined as the time that elapses between random assignment and early treatment discontinuation because of any reason (including treatment toxicity and patient refusal of further treatment), disease progression, death resulting from any cause, or any other event of interest. TTF is similar, but only disease-specific and treatment-related deaths are considered events. Treatment-related toxicity is a major issue in elderly patients with cancer, especially those with advanced disease stages where the goal of treatment is palliation rather than cure. TFFS and TTF provide an opportunity to take into account the role of toxicity and not concentrate only on efficacy. This is important because older patients are less willing than younger patients to continue treatments with severe toxicities,[2,25] especially if these have functional consequences that limit independence. One limitation, however, is that in some situations, treatment breaks are introduced not because of toxicity or progression but to provide a period without chemotherapy (ie, chemotherapy holiday), although this can be handled by not considering these breaks as treatment failures. Another limitation is that early treatment discontinuations are still considered failures in situations where significant toxicity occurs, but patients have good disease outcomes (perhaps with improvement of toxicities) thereafter.

QoL-Related End Points

The main goal of cancer treatment, certainly in the palliative setting, should be to reduce discomfort related to or caused by cancer progression and its related consequences (eg, loss of functionality, inability to stay at home, deterioration of QoL). Health-related QoL (HRQoL) is a major concern for patients with cancer, and it can be affected by symptoms caused by cancer as well as by treatment-induced toxicity.[26] For many older patients, the goal of cancer-directed treatment is not just how much additional time they can gain but how valuable that time is. Elderly patients are less willing to compromise their HRQoL for the potential for increased survival.[27] Thus, HRQoL may be an appropriate outcome for elderly-specific trials, but it remains to be defined how to measure or quantify HRQoL optimally, how to quantify the different domains of HRQoL in one score, and which cutoffs are relevant as end points for clinical trials, although a 10-point decrease (on score of 100) is frequently used as relevant change.[28] The EORTC (European Organisation for Research and Treatment of Cancer) QoL Group recently developed an elderly-specific QoL module,[29] which adds specific QoL-related aspects in older individuals to the general EORTC Quality of Life Questionnaire C30. HRQoL should be captured in all trials of palliative chemotherapy in older patients regardless of the primary end point of the trial. The Q-TWIST (quality-adjusted time without symptoms of disease or toxicity of treatment) approach measuring quality-adjusted survival is another QoL-related end point, which partitions the survival time of the patient into three consecutive health states (ie, time with toxicity resulting from treatment, time without symptoms of disease or toxicity, and time from progression/relapse to death) and assigns utility weights to each state.[30] The Q-TWIST value is the sum of the weighted health state durations and is used for treatment comparisons. This approach quantitatively adjusts periods in which treatment toxicities or symptoms of disease progression are present to reflect the potentially reduced value for the patient. In principle, this is a valuable approach for older patients with cancer, but the great difficulty lies in determining or quantifying the weight factor for QoL during the different periods.

Preservation of Functional Capacity/Independence

In a similar way, maintenance of function and independence should be one of the major principles of cancer management in the elderly. A negative impact on a patient's functional capacity will have a negative impact on survival as well.[31] The prolongation of active life expectancy seems much more important than the prolongation of life expectancy as such. The GERICO (French Geriatric Oncology Group) trial[32] nicely showed that functionality measured by instrumental activities of daily living does not decrease significantly (by $\geq$ two points) in older patients with breast cancer receiving adjuvant chemotherapy. Using single or multiple domains of geriatric assessment as outcome events would also be of great value to clinicians.

Surgical Trial End Points

Several trials in the surgical field, including elderly-specific trials such as the PACE (Pre-operative Assessment of Cancer in the Elderly)

study,[33] have used (primary) end points such as 30-day morbidity, 30-day serious morbidity (grade 3 to 4), and 30-day mortality, which are relevant but should be accompanied by information on longer-term outcome end points, as we have discussed here.

TRIAL DESIGN IN OLDER PATIENTS WITH CANCER

Trials for Older Patients Versus Trials Without Upper Age Limit

Table 2 lists issues in clinical trial design in older patients with cancer. Clinical trials need to be representative of the whole population in whom the treatment will be used later, which is not the case at present. Several studies have shown that there is substantial underrepresentation of older patients in clinical trials.[10,34,35] The differential effects of aging on organ function and the variety of comorbidities that characterize the older population result in significant heterogeneity.[36] This variance could result in considerable differences in the efficacy and safety of cancer treatments. For studies using therapy regimens expected to be used in all age categories, patients should be enrolled across the entire age spectrum, and a minimum cohort of elderly patients should be required. If treatment regimens are expected to be tolerated by only fit older patients or younger patients, severe selection bias will be present, and conclusions from these kinds of trials will not be generalizable to the whole population, especially the frail elderly. It is important to capture the fitness status of the older patients enrolled onto a clinical trial to provide information about the generalizability of the results. Documentation of the nonincluded population is also important. One option for ensuring sufficient accrual of older patients could be to require registration trials to remain open after they have met their target accrual until a minimum cohort of elderly patients is enrolled. It should be noted that older fit patients are likely included in clinical trials and so should likely receive the standard treatments. However, it is clear that several standard treatments administered to younger patients are not suitable for unfit or frail elderly adults (and sometimes even fit elderly adults) because of expected higher or unacceptable risk of toxicity or other competitive risks determining the long-term prognosis. For example, allogenic bone marrow transplantation; high-dose cytarabine, anthracycline, or cisplatin; major surgery; and concurrent chemoradiotherapy are treatments generally reserved for younger or sometimes fit older patients. In this setting, elderly-specific trials are certainly needed, because there is no clear standard therapy in this group of patients, who are not likely to tolerate the standard therapy administered to fit patients. In frail older patients, separate clinical trials could be designed because these patients could be better served by trials comparing modified approaches (eg, adapted chemotherapy/biologic agents) with pure palliative/supportive care. For vulnerable patients, a possible trial design could include standard therapies versus less aggressive therapies or no therapy, depending on the setting.

Randomized phase III trials remain the gold standard for clinical research, in older as well as younger people. However, designing these trials that address heterogeneity in all elderly populations might be challenging for many reasons (insufficient interest from sponsors/investors, difficulty in finding sufficient numbers of patients, and so on). Often, phase III data exist only for younger populations. Randomized phase II trials can provide insight into the range of efficacy and toxicity in older populations. If the treatment is too toxic, this would be established in a phase II trial. If a phase II trial in an older (nonfit) population shows that the toxicity is acceptable and confirms efficacy in the same range as previous phase III trials in younger people, there might not be a need to repeat the phase III trial again in an older (nonfit) population. However, if the phase II results are indeterminate concerning toxicity and/or efficacy, then confirmation in a phase III trial is likely. Randomized phase II trials in specific subsets of older patients can thus potentially provide relevant information. In these cases, physical status (frailty and vulnerability) could be used as a stratification factor to explore the benefit of treatment in different older populations. Often, no real standards exist for this population (because standard therapy for that disease/indication is expected to be too intense for that person), and all treatments/study arms could actually be seen as experimental arms. Although it might be difficult to select a control arm in a randomized phase II trial, one possibility would be to make the control arm the physician's decision. Because of the methodologic difficulties of defining appropriate control arms for the reasons mentioned in this article, randomized phase II trials might sometimes turn out to be infeasible. A pragmatic option for frail patients could be to perform only single-arm phase II studies with toxicity as an end point, allowing indirect comparison of toxicity (and efficacy) with fit young/old populations from previous studies. This kind of study could provide relevant information if the appropriate end points (HRQoL, functionality, and so on) are included but would be scientifically much less robust than randomized phase II or III studies. Nevertheless, this type of study is sometimes the only feasible option, and regimens studied this way, such as the R-miniCHOP (rituximab plus low-dose cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen in patients age > 80 years with diffuse large B-cell lymphoma,[37] have been adopted in clinical care because higher-level data are lacking.

Table 2. Issues in Clinical Trial Design for Older Patients With Cancer

Issue
RCTs remain gold standard when possible
Clinical trials should preferably integrate whole age range, including fit and frail older individuals
Elderly-specific clinical trials in older patients with cancer are required if standard therapy is different from that for younger patients
Trials of treatment strategy comparing different strategies (eg, therapy *v* best supportive care) should be encouraged
Randomized phase II or even single-arm phase II trials in specific subsets of older patients can provide insight into range of efficacy and toxicity in older populations but ideally should be confirmed in large phase III trials, which might be hard to perform for various reasons (eg, insufficient interest from sponsors/investors, difficulty in finding sufficient numbers of patients)
Not all questions can be answered with randomized trials, and large observational cohort studies or registries in community can provide further insight for frail population with less selection bias (preferably in parallel with or linked to RCTs)
Comparable/uniform geriatric assessment should be integrated into future trials in geriatric oncology
Regulatory authorities should require evaluation of efficacy and safety of new drugs in older and frail patients as well as in younger patients

Abbreviation: RCT, randomized clinical trial.

Aging is a highly individualized process that results in several changes in organ function, affecting the pharmacokinetics of anticancer drugs.[38] These organ system changes may result in altered drug metabolism, with a major impact on treatment tolerability. For that reason, pharmacokinetic studies and phase I studies should be designed specifically for older patients. New drugs could, for instance, be studied in amended phase I studies in populations with higher levels of comorbidity or functional limitations in parallel with standard phase I trials or after the drugs have shown promising results in the general population. An approach in the same line is to design phase I/II–type trials with progressively increasing inclusion criteria. The regimen of interest is first administered to patients in good condition, then in cohorts with increasing levels of functional limitations or comorbidities. This would provide evidence-based thresholds for dose reductions or regimen changes. Risk indicators that could be used for this approach include the CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) score,[39] the CARG (Cancer and Aging Research Group) score,[40] or criteria such as those used in lymphoma studies.[41,42]

Although incorporating geriatric assessment into oncology trials is usually feasible,[43] the major obstacle to using this as a stratification or even randomization factor is the exact/optimal definition of frailty or vulnerability. Balducci and Extermann[44] formulated an operational definition of frail, fit, and vulnerable patients in 2000 that is commonly used in the oncology world but has significant shortcomings; unfortunately, 10 years later, it is still not clear which are the best criteria and tests to be used to make this stratification.

Trials of Treatment Regimens Versus Trials of Treatment Strategies Versus Observational Cohort Studies

Randomized trials of treatment regimens comparing treatment A versus treatment B can provide important information. The CALGB (Cancer and Leukemia Group B) 49907 adjuvant breast cancer trial, for instance, showed that classical adjuvant chemotherapy (AC [doxorubicin and cyclophosphamide] or CMF [cyclophosphamide, methotrexate, and fluorouracil]) was clearly superior to so-called soft chemotherapy with capecitabine.[45] New drugs also need to be tested specifically in the older population because specific adverse effects might occur that potentially change the toxicity/benefit ratio. The older population represents a huge potential market for the pharmaceutical industry, but the enhanced risk of toxicity as well as non–treatment-related adverse events that sometimes occur in older patients might lessen the enthusiasm of the industry to support such trials and might hamper drug development and registration.

Trials of treatment strategy comparing no treatment with treatment (eg, prostate cancer surgery or no surgery; breast cancer adjuvant chemotherapy or not) are some of the most important kind of trials that need to be performed. However, several challenges exist. Persuading a patient to participate in a trial of therapy versus no therapy is generally much more difficult than participation in a trial of treatment A versus B, and selection bias and crossover will occur. In the former situation, the impact of random assignment (eg, chemotherapy or not) on older patients is much bigger than in the latter situation (eg, chemotherapy A *v* B). There are possible trial designs that might make this more palatable to patients, such as a cluster randomization design or postrandomization (double) consent design (also called the Zelen design), but these designs are less rigorous because they rely on unverifiable assumptions (eg, patient referral patterns). For both of these approaches, patient consent is sought for the study after the patient already knows which treatment (if any) he or she would receive, removing the anxiety that impending random assignment may produce. Another aspect is that funding is much more difficult to obtain for treatment strategy studies, because there is generally no benefit for industry (on the contrary, the omission of treatment might be disadvantageous for industry). Several attempts at trials of treatment strategy have failed in the past because of these and other reasons, as was nicely demonstrated in the ACTION (Adjuvant Chemotherapy in Older Women) trial for early breast cancer.[46] It should be noted that problems of accrual to trials that compare different treatment modalities or the omission of treatment in one arm are the same for younger, fit populations. Although treatment strategy trials are difficult, it is important that work continue on developing and using alternative designs for these types of trials in the nonfit older population. There is no perfect solution for this, but one pragmatic strategy is to invest much more in large observational cohort studies in the nonfit older population[47] or even in registry studies in the community. If possible, they can be linked to randomized trials, allowing the capturing of the nonincluded population as well as the assessment of different treatments and strategies with regard to outcome. This integration of an RCT into a registry trial increases the quality of an RCT, because the patient selection is better described, and it is better known to which patient populations the results of the RCT can be generalized.

Incorporation of Geriatric Assessment Into Clinical Trials

Geriatric assessment has not been used often in previous clinical trials, but it should become more frequently required in the future. Without geriatric assessment information, it is impossible to evaluate which older individuals were included in a trial (eg, fit patients only or fit as well as frail patients), limiting extrapolation of the study data to the general older population. This should be mandatory in registration trials and elderly-specific trials and should be encouraged in all trials including older people. However, many different forms of geriatric assessment exist, which complicates comparisons across trials. It is important to agree on a (more or less) uniform or at least comparable evaluation of the older population. EORTC has made an attempt by providing a minimal data set for geriatric assessment to be included in clinical trials,[48] and CALGB has also demonstrated the feasibility of a mainly self-administered tool in its trials,[49] but there are other options,[41,42] and it is important to continue international discussion on this topic.

Eligibility Criteria

The generally long list of inclusion and exclusion criteria during the last decade has led to selection bias and exclusion of older patients. Exclusion criteria are not based on a high level of evidence. In clinical trials, especially those focusing on older patients with cancer, an attempt should be made to have as few inclusion and exclusion criteria as possible. A National Institutes of Health team concluded that decreasing function and comorbidity restrictions can dramatically increase elderly accrual to clinical trials.[34]

European Medicines Agency and US Food and Drug Administration Geriatric Investigation Plan

In the medical care of pediatric patients, the European Medicines Agency (EMA) has established a pediatric investigation plan to ensure that drugs are examined appropriately in the pediatric population. There is a need for a global strategy within the EMA/US Food and Drug Administration (FDA) to do the same in the older population. Compulsory use of uniform geriatric assessment and frailty tools in drug registration trials could be helpful in establishing a better view of the fitness of older patients included in clinical trials. The EMA/FDA could require adequate representation of older adults in registration trials if applicable (with information from geriatric assessment) or require postmarketing safety studies in the general older population. The EMA recently established a geriatric expert group for this purpose.[50] Longitudinal as well as baseline evaluation of geriatric parameters (eg, functionality, social situation, QoL) is crucial to better understanding the impact of new therapies on older individuals and to improving care for this important population.

DISCUSSION

Choosing end points for clinical trials in older patients with cancer requires careful reflection on the ultimate goals of therapies. OS is a crucial end point, but DSS should also be recorded in trials where older patients with cancer are included, because deaths resulting from other causes (eg, other diseases, treatment toxicity) occur much more frequently in the older population. Composite end points allow the integration of multiple dimensions in addition to efficacy (eg, QoL, evolution of functionality) into the definition of treatment benefit and have clear advantages in RCTs involving older patients with cancer, such as simplicity of statistical design and statistical efficiency. Composite end points are not feasible in all settings, but they are justified if the individual components of the composite are clinically meaningful and of similar relative importance to clinical care. QoL and preservation of functional capacity and independence are important for the older population and should be included more often as end points in clinical trials in this population.

Although clinical trials in principle should include the entire age range of the population, the heterogeneity of this population generally does not allow the capture of the whole older population, leading to selection bias and difficulty in drawing firm conclusions for the frailer elderly who are often not included. Specific trials for subgroups of older patients with cancer are needed, with additional pharmacokinetic studies if required, and with appropriate control arms depending on the setting. Randomized or single-arm phase II trials can provide insight into the range of efficacy and toxicity in older populations, but ideally they should be confirmed in large phase III trials that are unfortunately often hindered by insufficient interest from sponsors/investors or difficulty in finding sufficient numbers of patients. Large observational cohort studies in the nonfit older population should be considered, preferably linked to randomized trials, to capture the nonincluded population. Incorporation of a preferably uniform geriatric assessment in elderly-specific or registration trials is crucial to better understanding the effect of treatments in different elderly populations. Regulatory authorities including the EMA/FDA should require geriatric assessment information and adequate representation of older adults, including patients of different health statuses such as vulnerable and frail patients, in trials. Better clinical trial design is crucial to understanding the impact of new therapies on older individuals and to improving care for this important population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** Arti Hurria, GTx (C), Seattle Genetics (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Arti Hurria, Celgene, GlaxoSmithKline **Expert Testimony:** None **Patents:** None **Other Remuneration:** None

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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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VOLUME 32 · NUMBER 24 · AUGUST 20 2014

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Designing Therapeutic Clinical Trials for Older and Frail Adults With Cancer: U13 Conference Recommendations

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Published online ahead of print at www.jco.org on July 28, 2014.

Written on behalf of the Cancer and Aging Research Group.

Supported by Grant No. U13 AG038151 from the National Institute on Aging and National Cancer Institute (NCI; National Institutes of Health); by the Alliance for Clinical Trials in Oncology; and by City of Hope and in part by Grants No. CA31946 from the NCI to the Alliance for Clinical Trials in Oncology and No. CA33601 to the Alliance Statistics and Data Center.

Presented at the 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013, and 2013 American Geriatrics Society Annual Meeting, Dallas, TX, May 2-5, 2013.

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/14/3224w-2587w/$20.00

DOI: 10.1200/JCO.2013.55.0418

ABSTRACT

A majority of cancer diagnoses and deaths occur in patients age ≥ 65 years. With the aging of the US population, the number of older adults with cancer will grow. Although the coming wave of older patients with cancer was anticipated in the early 1980s, when the need for more research on the cancer-aging interface was recognized, many knowledge gaps remain when it comes to treating older and/or frailer patients with cancer. Relatively little is known about the best way to balance the risks and benefits of existing cancer therapies in older patients; however, these patients continue to be underrepresented in clinical trials. Furthermore, the available clinical trials often do not include end points pertinent to the older adult population, such as preservation of function, cognition, and independence. As part of its ongoing effort to advance research in the field of geriatric oncology, the Cancer and Aging Research Group held a conference in November 2012 in collaboration with the National Cancer Institute, the National Institute on Aging, and the Alliance for Clinical Trials in Oncology. The goal was to develop recommendations and establish research guidelines for the design and implementation of therapeutic clinical trials for older and/or frail adults. The conference sought to identify knowledge gaps in cancer clinical trials for older adults and propose clinical trial designs to fill these gaps. The ultimate goal of this conference series is to develop research that will lead to evidence-based care for older and/or frail adults with cancer.

J Clin Oncol 32:2587-2594. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Cancer is a disease of aging, with the majority of patients age > 65 years.[1] Cancer incidence is expected to increase by 67% among individuals age ≥ 65 years from 2010 to 2030.[2] Furthermore, because those diagnosed with cancer are also living longer, the proportion of cancer survivors age ≥ 65 years will increase by 42% between 2010 and 2020.[3] This demographic wave of older patients with cancer was anticipated as early as the 1980s, leading to calls for greater attention to geriatric oncology and for increasing the interface between cancer and aging. B.J. Kennedy, MD, then president of the American Society of Clinical Oncology, predicted that cancer and aging would become a major problem in the United States.[4] Yancik et al[5] described the changing age structure of the nation's population and the discrepancy between chronologic and physiologic age. They identified the pressing need for increased research on cancer and aging.

Although much has been learned about aging and cancer since then, few clinical trials focus on the therapeutic decisions most directly facing older adults. Historically, older adults have been underrepresented in cancer clinical trials, and recent updated data suggest that this remains a significant concern.[6-8] As a result, there is a significant lack of information on the safety and efficacy of cancer treatment for the growing numbers of older patients with cancer. This becomes even more important because the biology of certain cancers changes with aging, and therefore, specific studies of the efficacy of therapeutic approaches are needed across the age spectrum.[9-11] Despite the increased incidence and prevalence of cancer among older adults, the literature reports that age-related differences in treatment patterns persist, with older adults often receiving less aggressive therapy,[12-19] despite the fact that many older patients with cancer can tolerate and benefit from cancer-directed therapies. For example, patients age 70 to 79 years with acute myeloid leukemia fare better with chemotherapy than patients receiving palliative care.[20] Conversely, a subset of older adults may be at increased vulnerability to treatment-related toxicities. There is increased understanding that chronologic age is a weak marker of physiologic age and that factors captured in a geriatric assessment (GA) can identify older adults at risk for cancer treatment toxicities.[21-26]

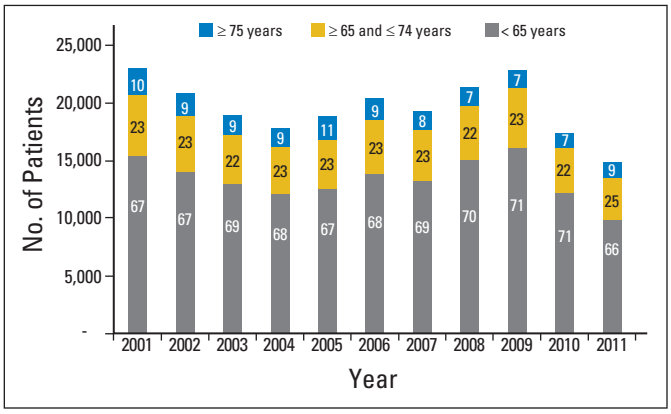

Fig 1. Age distribution for patients enrolled onto National Cancer Institute (NCI) adult cooperative group phase II and III treatment trials (all diseases) from 2001 to 2011. Percentage of patients enrolled in each age group is shown for each year, as reported by cooperative groups to the NCI Clinical Data Update System database (NCI Division of Cancer Treatment and Diagnosis) as of May 2012.

Compounding the overall problem is the underrepresentation of older adults in therapeutic clinical trials[6,7,27,28] (Fig 1). Twenty-eight percent of individuals diagnosed with cancer are age ≥ 75 years[1]; however, < 10% of patients enrolled onto National Cancer Institute (NCI) Cooperative Group clinical trials are age ≥ 75 years.[7] Although the overall number of patients enrolled onto clinical trials has declined over the past decade, the proportion of older adults in these trials remains the same. However, the portfolio of studies in the NCI Cooperative Group clinical trials was dominated by accrual from breast cancer trials, which were particularly slanted toward a group of patients younger than the general population of patients with the disease. In other disease types, such as prostate cancer, the age distribution of patients enrolled onto clinical trials was more reflective of the larger population with the disease.

It is crucial to find ways to improve the accrual of healthy older adults to existing clinical trials and to develop research studies that address the knowledge gaps regarding older and/or frail adults who would not typically be enrolled onto standard trials. Some vital knowledge gaps may not be addressed by the larger phase III cancer trials for all ages. Those gaps affect the care of patients with physiologic decline and/or those with comorbid conditions that exclude them from certain clinical trials, placing them at increased risk for toxicity. Specific studies targeting those knowledge gaps are needed.

GOALS OF THE CONFERENCE ON OLDER AND/OR FRAIL PATIENTS IN THERAPEUTIC CLINICAL TRIALS

The Cancer and Aging Research Group (CARG), in collaboration with the National Institute on Aging (NIA) and the NCI, has been holding a conference series funded by a U13 grant to examine the level of evidence and areas of highest research priority in geriatric oncology, identify strengths in existing research methods, and foster multidisciplinary collaboration. The first of these conferences, held in September 2010, found that few therapeutic data exist for patients with cancer who are age ≥ 75 years or who have chronic health conditions.[29-31] Conference participants further found that clinical, biologic, and physiologic markers of age are only rarely or inconsistently incorporated into clinical trials and that clinical trial infrastructure is often incompatible with the needs of older patients.

From November 17 to 18, 2012, CARG held the second conference in collaboration with the NIA, the NCI, and the Alliance of Clinical Trials in Oncology. The intent of this second conference was to focus on the design and implementation of therapeutic clinical trials for older and/or frail adults. The overall goal was to develop clinical trial designs specifically targeting questions that affect older and/or frailer adults with cancer, as well as to provide recommendations and create examples for others interested in geriatric oncology research. This article summarizes points raised at the conference and identifies common themes in geriatric oncology clinical trial design that emerged.

GERIATRICIZING TRIAL DESIGN

Defining the Study Population: Older and/or Frail Patients

The inclusion of older and/or frail patients in therapeutic clinical trials is hampered by difficulties in defining and recruiting this population. As one aspect of the research design considerations, an effort was made to define these groups for the purposes of cancer clinical trials.

Defining older. Typically included in cancer clinical trials are the healthiest and most robust of older patients, with ready access to specialized cancer centers or clinical oncology programs.[32] Those with second cancers or comorbidities including cognitive or functional impairments, cardiac disease, or organ dysfunction—all of which are more likely to occur among older patients— often are either explicitly excluded from or not actively enrolled onto clinical trials. Consequently, older patients typically seen by oncologists are less likely to be enrolled onto clinical trials, and those age > 75 years are especially unlikely to be included.[6,7,27,28] Considering age alone, those age > 75 years are defined as older for purposes of recruitment and design efforts.

Defining frail. Recognizing that a consensus has not yet been reached on a definition of frailty for oncology trials, one goal of this conference was to clarify the definition for older adults. A geriatric oncology definition of frailty is suggested: those older individuals who are at higher risk for cancer treatment toxicity because of age-associated conditions such as functional losses, cognitive impairment, or physiologic changes. This is distinct from, although may overlap with, the geriatrician's definition of frailty, which is a vulnerable health condition resulting in a decreased ability to respond to a stressor that is associated with a higher likelihood of functional decline, disability, hospitalization, and mortality.[33,34] Two well-established ways of measuring frailty have been developed by Fried et al[33] and Rockwood and Mitnitski.[35] However, there are limitations in applying these definitions to geriatric oncology, because the definitions were developed for the general geriatric population and not specifically for older adults with cancer, whose physiologic stressors may be different. Often the stressors for a patient with cancer are surgery and/or chemotherapy, and tools are needed to identify older adults at risk for serious toxicity or functional loss resulting from these stressors. A way to apply this concept of frailty to older patients with cancer is beginning to emerge, with tools being developed to identify patients at high risk for chemotherapy toxicity.[21,22]

Study End Points

Therapeutic phase III clinical trials focus primarily on efficacy as measured by tumor response or overall and progression-free survival. However, these standard trial end points do not capture a key concept in geriatric medicine, which is maintenance of active life expectancy (ie, number of years an individual lives independently without significant disability). The effects of cancer therapies on physical or cognitive function could be just as important, if not more important, to older patients than response or survival.[36] The inclusion of functional end points can aid in shared decision making by physicians and patients by identifying the most important areas for intervention.

Trial Designs: Opportunities, Strengths, and Weaknesses

Several study designs were proposed to help fill the gaps in knowledge regarding cancer therapy in older and/or frail adults. The advantages and limitations of these trial designs are summarized in Table 1.

Randomized controlled trial. The objective of this study design is to determine the gold standard of treatment using a randomized approach to ascertain the superiority (or lack of inferiority) of one treatment over another. Randomized controlled trials (RCTs) for older adults are particularly important if there are age-related changes in cancer biology that may affect treatment efficacy. Furthermore, they can include novel end points, such as composite measures of tolerability and treatment efficacy. However, RCTs can be costly and lengthy and require a large sample size.

Two approaches can be considered for the randomized design. First, the study could specifically focus on older adults and address questions that are most pertinent to the geriatric oncology population. An example is CALGB (Cancer and Leukemia Group B) 49907 (Alliance), which compared standard adjuvant polychemotherapy with monochemotherapy in adjuvant treatment for adults age $\geq$ 65 years with breast cancer. In this study, an adaptive Bayesian design was used,[37] which allows for interim analysis of the accumulated data at specified time points. At these time points, if the treatment effect in one of the treatment arms satisfies a predefined futility boundary, accrual to that arm can be terminated while accrual to the other treatment arm(s) 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.

The second approach is to accrue patients of all ages but purposefully stratify enrollment into age groups representative of the general population with the disease. An advantage of this approach is that the study results are more generalizable to the overall population with the disease. A disadvantage of this approach is that requiring enrollment of specific age strata may limit accrual speed. Furthermore, the study objectives and end points may not be tailored to the geriatric oncology population.

Prospective cohort study. In a prospective cohort study, the cohort can be defined by the host, tumor, or treatment characteristics, depending on the research question. This design can be used to answer commonly posed questions in geriatric oncology regarding the feasibility, dosing, and toxicity of a selected regimen, particularly among patients receiving treatment as standard of care. A significant limitation is that this design does not identify the best treatment (ie, most efficacious and least toxic), because there is no randomized component. Furthermore, as with an RCT, significant data management resources are required to accurately capture and enter the dosing and toxicity data.

Another type of prospective cohort study is exemplified by CALGB 369901, which prospectively observed older women with nonmetastatic breast cancer receiving adjuvant treatment to understand treatment decision-making, quality-of-life, and survivorship issues.[38] This study was open to accrual in parallel with CALGB 49907.[37] Those patients who did not enroll onto 49907 were eligible for this prospective cohort study.

Embedded study. An embedded study, also known as a correlative or ancillary study, is placed within the infrastructure of a parent study. An embedded study can be used to identify the characteristics of those patients at high risk for toxicity and to evaluate the toxicity profile of new drugs. An example is CALGB 361006, which embeds a comprehensive GA within the schema of CALGB 11001,[39] a trial evaluating the efficacy of adding sorafenib tosylate to induction and postremission chemotherapy in patients age $\geq$ 60 years with *FLT3*-mutated acute myeloid leukemia. The goal of the companion substudy is to identify specific comprehensive GA measures that may predict overall survival and treatment-related mortality for older adults receiving this treatment. Several considerations in this study design are important. First, if participation in the embedded study is optional, a skewed sample may be accrued, limiting generalizability. Furthermore, the sample size of the embedded study should be determined a priori to reach the target accrual necessary to identify a vulnerable subgroup. A limitation of this design is that the parent study may not be specifically targeted to older adults. In such a case, there may be limited accrual of older adults to the embedded study.

Single-arm trial. Single-arm trials can be used to assess the benefits and toxicities of specific drugs for which there are limited data in older adults. Additional advantages of a one-arm trial design are that novel end points such as the impact of therapy on function and quality of life can be assessed, and age-related changes in the pharmacology of cancer treatment can be evaluated. The addition of a younger cohort of patients can bolster the ability to identify age-related changes in pharmacokinetics across the age spectrum. The disadvantage of a single-arm trial is that it does not compare the study treatment with a gold standard.

An example of a single-arm trial is CALGB 9762,[40] a prospective evaluation of the relationship between patient age and paclitaxel clinical pharmacology. This study sought to prospectively evaluate the association between patient age and the pharmacokinetics and toxicity profile of paclitaxel, as well as to understand the relationship between paclitaxel pharmacokinetics and toxicity.

Extended trial. The extended trial design is a novel concept discussed at the conference, with no precedent to our knowledge. The goal of the extended trial design is to obtain data regarding a new gold standard within the older population. For example, once the results of a phase III study have been reported, the age distribution of the participants in the superior arm is examined. If the study failed to accrue an age distribution similar to the population of individuals at risk, the superior arm is reopened to accrue an adequate number of older adults. This study design aims to fill the knowledge gap regarding the tolerability of a new regimen in older cohorts. The limitation of this (hypothetic) design is that there is no precedent for reopening a study several years after the study has been closed. This would therefore require a shift in the present paradigm for the conduct of clinical

Table 1. Opportunities in Geriatric Oncology Clinical Trial Designs

Design	Description and Characteristics	Potential Objectives and Outcomes	Advantages	Limitations and Vital Considerations	Clinical Trial Examples
RCT	RCTs are gold standard of clinical trial design; study participants are randomly assigned among different treatment arms	Determination of gold standard of treatment by comparing efficacy and tolerability of different outcomes	Excellent for direct comparison of different treatment regimens	Requires large sample size because of randomized design	CALGB 49907[37]
	Eligibility criteria considerations: Method 1: accrue only older patients Method 2: accrue patients of all ages, then stratify into age groups representative of general population with disease Trial design consideration: Adaptive (Bayesian) design; trial design is modified as study proceeds based on interim data analysis; randomization ratio can be altered by shifting patients to more effective treatment arm and eliminating underperforming arms	Development of novel end points (including composite measures of tolerability and toxicity)	Method 1: Particularly important if there is age-related change in cancer biology Important for identifying treatment options among patients who are traditionally excluded from clinical trials because of chronic health conditions or concerns regarding toxicity and who would otherwise not enroll onto clinical trials for all age groups End points can be specifically tailored for geriatric oncology population Method 2: Allows for greater generalizability of results Would rectify current situation of older adults being under-represented on clinical trials	Can be costly and time intensive Method 2: Could result in slower accrual due to the enrollment of specific age strata Lack of end points tailored specifically for geriatric oncology population	PI, Hyman Muss; ClinicalTrials.gov ID, NCT00024102 Comparison of different adjuvant chemotherapy (standard treatment [AC or CMF] *v* new therapy [capecitabine]) treatments for older women with early-stage breast cancer
Prospective cohort study	Assessment of treatments currently on market to evaluate outcomes of interest in older patients	Identification of patterns of care	Enrollment of patients receiving standard-of-care treatment increases generalizability of findings	Treatment is not randomized; therefore, investigators unable to determine which treatment is most efficacious and least toxic for older patients	CALGB 369901[38]
	Cohort can be defined by host, tumor, or treatment factors	Understanding decision making	Can be used to understand patterns of care and decision making	Significant data management resources required to accurately capture drug dosing and toxicity data	PI, Jeanne Mandelblatt; ClinicalTrials.gov ID: NCT00068328
	Observational No randomization Hypothesis driven	Determination of toxicity and feasibility of delivering specific therapies			Patient preference as determinant of breast cancer adjuvant chemotherapy use in older women
Embedded study	Also known as correlative or ancillary study	Use of GA to describe cohort	Better baseline characterization of the geriatric oncology population that enters the study	The parent study may not be specifically targeted to older adults, thus limiting the sample size of older patients	CALGB 361006
	Additional measurements of interest to geriatric oncology research (such as GA measures) are placed within infrastructure of parent study	Use of GA in longitudinal follow-up to understand impact of therapy on function and other GA measures Identification of characteristics of specific group of patients who are at high risk for toxicity	Ability to identify baseline predictors of treatment tolerance and/or longitudinal declines in function	If participation in embedded study is optional, then characteristics of patients who choose to enroll may not be representative of entire cohort and/or adequate sample size of older patients may not be accrued	PI, Heidi Klepin GA embedded in CALGB 11001[39] PI, Geoffrey Uy; ClinicalTrials.gov ID for CALGB 11001, NCT01253070 Sorafenib tosylate and chemotherapy in treating older patients with AML

(continued on following page)

Table 1. Opportunities in Geriatric Oncology Clinical Trial Designs (continued)

Design	Description and Characteristics	Potential Objectives and Outcomes	Advantages	Limitations and Vital Considerations	Clinical Trial Examples
Single-arm trial	Current gold-standard design for phase II clinical trials	Evaluation of efficacy of drug for which there are limited data for older adults	Quantification of novel end points such as impact of therapy on functional status and QOL	No comparison of treatment under study with gold standard	CALGB 9762[40]
	No randomization	Identification of predictors of toxicity based on GA variables or biomarkers	Fills gap in knowledge regarding efficacy, feasibility, and toxicity of drugs that have been understudied in older adults		PI, Stuart Lichtman; ClinicalTrials.gov ID, NCT00003092
	All patients receive treatment under study	Understanding of age-related changes in pharmacokinetics and pharmacodynamics of cancer therapeutics			Prospective evaluation of relationship of patient age and paclitaxel clinical pharmacology
Extended trial	Addition of cohort of older patients to treatment arm from RCT that was shown to be superior	Determination of tolerability of treatment in older adults	Trial infrastructure is already in place	Currently no precedent exists for reopening study several years after closure	No precedent
			Accrual of older patients might be easier because efficacy of treatment has been previously demonstrated Additional data regarding tolerability in older patients will be obtained	Accrual is only to superior arm to bolster data about tolerability in older adults; however, data regarding efficacy of treatment (compared with inferior arm) in older population will not be obtained	

Abbreviations: AC, doxorubicin and cyclophosphamide; AML, acute myeloid leukemia; CALGB, Cancer and Leukemia Group B; CMF, cyclophosphamide, methotrexate, and fluorouracil; GA, geriatric assessment; PI, principal investigators; QOL, quality of life; RCT, randomized controlled trial.

trials. Furthermore, the extended trial design would not establish age-related differences in treatment efficacy between study arms included in the original randomized trial. Alternatively, if reopening a phase III study is considered too large a barrier to overcome, phase IV studies could potentially evaluate the tolerability of the new standard in populations with the disease that were underrepresented in the original study; however, there is no precedent for this approach either.

Considerations for Dosing Schema

The significant underrepresentation of older adults in US Food and Drug Administration registration trials[8,28] has led to a dearth of information regarding the optimum dose and schedule of cancer therapeutics for the geriatric population. Differences in treatment patterns between older and younger adults have been noted.[12-19] Concerns about the risk of toxicity may influence a health care provider's willingness to deliver the full chemotherapy dose with the first cycle of treatment, particularly if the treatment goal is palliation. In the geriatric literature, the adage "start low and go slow" may increase both the physician's and older patient's comfort with a new regimen, particularly when there are concerns about heightened toxicity risks. A way of applying this principle to geriatric oncology trials is to reduce the first dose, then escalate to standard dosage if the patient tolerates the treatment well. This approach was used in the FOCUS2 (Fluorouracil, Oxaliplatin, and CPT-11 [irinotecan]: Use and Sequencing 2) trial[41] for older and/or frail adults with metastatic colorectal cancer. A potential downside of this approach is that patients would not receive a standard dose upfront, which could compromise efficacy. However, if dose escalation is performed rapidly, this is unlikely to have a major impact. Furthermore, it is not clear that the dose-reduced approach is associated with decreased toxicity. If this approach is used, it is favored in patients who are receiving therapy for metastatic disease, not for adjuvant treatment, where standard dosing should be used in those undergoing treatment with curative intent.

Trial Designs to Predict Treatment Tolerability

The general goal of studies to predict treatment tolerability is to develop risk-adapted strategies for treatment by identifying the profile (by toxicity risk, life expectancy, and/or tumor biology) of individuals who can or cannot tolerate a specific treatment. This optimizes the benefit-to-risk ratio. The aging process is heterogeneous, making chronologic age a relatively poor marker of overall physiologic and health status. Inclusion of a GA can help to deconstruct this heterogeneity by providing information regarding independent predictors of morbidity and mortality, such as functional status, comorbidities, nutritional status, psychologic state, social support, and cognitive function.[42] These can be included as predictor and/or outcome variables. For example, the GA could be used at study entry as a predictor of treatment tolerability. Furthermore, the GA could be collected in longitudinal follow-up to understand the impact of treatment on GA variables (eg, function or cognition). Three potential trial designs were discussed.

All-comers design. A key question in geriatric oncology is whether there is a subgroup of older patients who are at higher risk for toxicity. This trial design enrolls all comers with the goal of identifying the specific characteristics of patients who derive benefit from the treatment without significant toxicity, typically defined as grade ≥ 3, according to the NCI Common Terminology Criteria for Adverse Events, or grade 2, determined a priori to be of relevance.

Enrichment design. If there is confidence that a specific group of individuals is at high risk for toxicity, an enrichment design allows the trial to accrue patients with those specific characteristics. To use an enrichment design, there must be agreement about risk factors for toxicity. However, a uniform definition of patients at high risk for toxicity has not yet been formally established within the geriatric oncology community. Recent research studies are starting to provide an evidence-based definition.[21,22]

Marker-by-treatment interaction design. A marker-by-treatment design compares the risks and benefits of two treatment strategies for two groups of older patients: those predicted to be at low risk for toxicity versus those predicted to be at high risk for toxicity, based on a prespecified definition. At entry, eligible patients are stratified based on this toxicity risk and are subsequently randomly assigned to the treatment arms. In oncology clinical trials, a typical paradigm has been to add treatments to the gold standard to see if the efficacy can be improved. However, the cumulative addition of therapeutic agents can increase the risk of toxicity. If the toxicity exceeds a threshold, efficacy may be compromised because of the inability to deliver the therapy. The marker-by-treatment design can help weigh the risks and benefits of novel therapies (in comparison with the standard) between patients with different predicted risks of toxicity. A disadvantage of this approach is the requirement of a large sample to accomplish the study objectives.

Facilitating Enrollment of Older Adults

Older age alone should not be a contraindication to clinical trial enrollment; however, older adults are underrepresented in cancer clinical trials.[6,7,27,28,43] One study found that older age was the sole reason why otherwise eligible patients were not offered clinical trial enrollment.[44] Often a combination of patient-, provider-, study-, and system-related barriers may keep older patients with cancer from participating in therapeutic clinical trials.[45-51] For example, patient nonparticipation has been attributed to wanting a different therapy,[52] living too far from the cancer center,[52,53] worrying about insurance reimbursements,[52,53] or being ruled ineligible because of poor performance status, need for emergent therapy, or number of comorbid conditions.[53] A lack of social support or a reluctance to travel to university centers where trials are most often conducted are additional deterrents to trial enrollment among older patients.[54-56]

Nevertheless, attitudes of older patients with cancer have not been shown to significantly result in lower enrollment. A majority of older patients report a positive attitude toward cancer clinical trials,[57] and a survey of patients age > 70 years found that three quarters of these patients are willing to participate in clinical trials.[58] Physician recommendations play an important role in patients' decisions regarding trials,[58] and physician bias can be one of the main barriers to the enrollment of older patients.[54]

Overly restrictive eligibility criteria are also commonly cited as a reason for accrual difficulties, particularly for older and/or frail patients. Criteria that are too stringent jeopardize the generalizability of a study; however, criteria that are overly broad can jeopardize patient safety and generate an overly heterogeneous study population, which interferes with detecting a treatment effect. The reduction or elimination of irrelevant criteria that hinder enrollment and the better use of instruments that assess prognosis and risks for toxicity can improve inclusion criteria.

Difficulties in identifying appropriate clinical trials, as well as the complexity of the trials themselves, can impede recruitment of older adults. Reducing the complexity of study schemas as well as the number of correlative studies may increase study participation. The experience itself may also be enhanced by simply providing supportive settings that include such things as soundproof curtains, bedside hearing and visual assistance devices, nonskid floor surfaces that help prevent falls, natural lighting conditions to counteract sensory losses, safety measures geared for individuals with comorbidities, and resources and support infrastructure for caregivers.[59,60] Culturally appropriate recruitment approaches and technology that allows remote data collection could also improve recruitment by eliminating the need for frequent travel to major medical centers. Collaboration between geriatricians and oncologists from the outset, as well as geriatric training for support staff, would facilitate the design and implementation of clinical trials to make them more amenable to the participation of older and/or frail patients.

CANCER SURVIVORS: TOPIC FOR THE NEXT U13 CONFERENCE

The number of cancer survivors increased from almost 4 million in 1977 to 13.7 million in 2012, and this number is expected to reach 18 million in the next 10 years.[61] Approximately 60% of today's cancer survivors are age $\geq$ 65 years,[3] and this number will steadily increase because of an overall rise in life expectancy and advances in early detection and cancer treatment. Approximately 16% of new diagnoses occur in individuals who already have a history of cancer, and this proportion is expected to increase.[62] There is much to learn about caring for cancer survivors, accounting for both the risks of subsequent cancers as well as the immediate and longer-term effects of treatment.

Therapeutic clinical trials can address these issues by gathering pretreatment and follow-up data such as that captured in a geriatric assessment, along with information on socioeconomic status and access to health resources, social support (or more importantly, among the aging population, social isolation), and modifiable factors such as smoking history, nutrition status, signs of depression, and level of physical activity. The next U13 conference (scheduled for May 2015) will address these questions.

DISCUSSION

Cancer is associated with aging, and although a majority of cancer diagnoses occur in individuals age $\geq$ 65 years, these patients continue to be underrepresented in cancer research and clinical trials. In addition, the standard clinical trial design rarely addresses end points of particular interest to older adults (such as preservation of function). To increase the enrollment of older adults onto clinical trials, clinical trials must be developed specifically for those individuals who do not meet the eligibility criteria or are not fit enough for enrollment onto clinical trials focused on individuals of all ages.

We have presented the results of a recent U13 conference held by CARG in collaboration with the NIA, the NCI, and the Alliance of Clinical Trials in Oncology, including proposals for improved clinical trial designs and their advantages and disadvantages for the geriatric oncology population. These proposals can serve as a blueprint for individuals who are entering or engaged in the field of geriatric oncology research and help in the consideration of trial designs that are best suited to answer the research questions they are posing. Ultimately, there is hope that this ongoing conference series will contribute to substantial enhancement of the evidence base so critical for the adequate treatment of older and/or frail individuals with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** Arti Hurria, GTx (C), Seattle Genetics (C); Hyman B. Muss, Pfizer (C), Eisai (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Arti Hurria, GlaxoSmithKline, Celgene; Martine Extermann, GTx **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

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Acknowledgment

We thank Basil Eldadah, MD, PhD (program officer, Geriatrics Branch, Division of Geriatrics and Clinical Gerontology, National Institute on Aging), for his participation in this U13 conference series. We thank Frances McFarland Horne and Carol Pearce for their assistance in preparing the manuscript.

Appendix

Attendees at the U13 Conference, Chicago, IL, November 17-18, 2012 (affiliation at time of conference): Andrew Artz (University of Chicago), Lodovico Balducci (H. Lee Moffitt Cancer Center), Karla Ballman (Mayo Clinic), Myra Barginear (Hofstra North Shore–LIJ School of Medicine), Beverly Canin (Breast Cancer Action, Breast Cancer Options), Ben Clark (American Society of Clinical Oncology), Harvey Cohen (U13 Oversight Board member; Duke University), William Dale (U13 Oversight Board member; University of Chicago), Efrat Dotan (Fox Chase Cancer Center), Basil Eldadah (U13 Oversight Board member; National Institutes of Health, National Institute on Aging), Susan Ellenberg (University of Pennsylvania), Martine Extermann (U13 Oversight Board member; H. Lee Moffitt Cancer Center), Betty Ferrell (U13 Oversight Board member; City of Hope National Medical Center), Gini Fleming (University of Chicago), David Flores (University of Texas), Ajeet Gajra (SUNY Upstate Medical University), Ilene Galinsky (Dana-Farber Cancer Institute), Richard Goldberg (North Carolina Cancer Hospital), Abdo Haddad (Cleveland Clinic), Paul Hamlin (Memorial Sloan-Kettering Cancer Center), Holly Holmes (MD Anderson Cancer Center), Joleen Hubbard (Mayo Clinic), Arti Hurria (U13 Oversight Board member; City of Hope National Medical Center), Aminah Jatoi (Mayo Clinic), Gretchen G. Kimmick (Duke University), Heidi Klepin (Wake Forest University), Marianna Koczywas (City of Hope National Medical Center), Ronald Maggiore (University of Chicago), Allison Magnuson (University of Rochester), Supriya Mohile (U13 Oversight Board member; University of Rochester), Margaret Mooney (National Institutes of Health, National Cancer Institute), Vicki A. Morrison (University of Minnesota), Ewa Mrozek (Ohio State University), Hyman Muss (U13 Oversight Board member; University of North Carolina Chapel Hill), Arash Naeim (University of California Los Angeles), Nitya Nathwani (City of Hope National Medical Center), Rebecca Olin (University of California San Francisco), Cynthia Owusu (Case Western Reserve University), Ira Parker (University of California San Diego), Carolyn Presley (Yale University), Erika Ramsdale (University of Chicago), Arati Rao (Duke University), Marilyn Raymond (American Society of Clinical Oncology), Ellen Ritchie (New York Presbyterian/Weill Cornell), Miriam Rodin (Saint Louis University), Julia Rowland (National Institutes of Health, National Cancer Institute), Saleha Sajid (University of Chicago), Richard Schilsky (U13 Oversight Board member; University of Chicago), Armin Shahrokni (University of California Los Angeles), Dale Shepard (Cleveland Clinic), Walter Stadler (University of Chicago), Richard Stone (Dana-Farber Cancer Institute), William Tew (Memorial Sloan-Kettering Cancer Center), Pamela Valera (Albert Einstein College of Medicine), Tanya Wildes (Washington University School of Medicine), and Elizabeth Won (Memorial Sloan-Kettering Cancer Center).

VOLUME 33 · NUMBER 32 · NOVEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement

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Published online ahead of print at www.jco.org on July 20, 2015.

American Society of Clinical Oncology Board of Directors approval: May 14, 2015.

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Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/15/3332w-3826w/$20.00

DOI: 10.1200/JCO.2015.63.0319

ABSTRACT

The American Society of Clinical Oncology (ASCO) convened a subcommittee to develop recommendations on improving the evidence base for treating older adults with cancer in response to a critical need identified by the Institute of Medicine. Older adults experience the majority of cancer diagnoses and deaths and make up the majority of cancer survivors. Older adults are also the fastest growing segment of the US population. However, the evidence base for treating this population is sparse, because older adults are underrepresented in clinical trials, and trials designed specifically for older adults are rare. The result is that clinicians have less evidence on how to treat older adults, who represent the majority of patients with cancer. Clinicians and patients are forced to extrapolate from trials conducted in younger, healthier populations when developing treatment plans. This has created a dearth of knowledge regarding the risk of toxicity in the average older patient and about key end points of importance to older adults. ASCO makes five recommendations to improve evidence generation in this population: (1) Use clinical trials to improve the evidence base for treating older adults with cancer, (2) leverage research designs and infrastructure for generating evidence on older adults with cancer, (3) increase US Food and Drug Administration authority to incentivize and require research involving older adults with cancer, (4) increase clinicians' recruitment of older adults with cancer to clinical trials, and (5) use journal policies to improve researchers' reporting on the age distribution and health risk profiles of research participants.

J Clin Oncol 33:3826-3833. © 2015 by American Society of Clinical Oncology

INTRODUCTION

The Institute of Medicine (IOM) report "Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis"[1] (hereinafter referred to as IOM quality report) highlights the need to improve the evidence base for treating older adults with cancer. Older adults experience the majority of cancer diagnoses and deaths and make up the majority of cancer survivors.[2-4] However, the evidence base for treating this population is sparse, because older adults are underrepresented in clinical trials, and trials designed specifically for older adults are rare.[5] The Cancer and Aging Research Group, in collaboration with the National Cancer Institute (NCI) and National Institute on Aging (NIA), received a U13 grant to conduct and disseminate a series of workshops on geriatric oncology research. However, there are few policy initiatives targeting the lack of evidence on older adults. In response to this problem, the American Society of Clinical Oncology (ASCO) convened a subcommittee of the Cancer Research Committee to develop an ASCO statement on improving the evidence base for treating older adults. ASCO presents a series of recommendations to improve evidence generation in this population.

PROBLEMS

The major drivers creating the need to generate more evidence on the treatment of older adults are: (1) the aging US population, (2) the underrepresentation of older adults in clinical research, and (3) the clinical implications of the lack of evidence in older adults on the quality of care.

Aging Population

The US population is aging at a dramatic rate; 13% of the population was age ≥ 65 years in 2010.[6] By 2030, nearly 20% of adults are expected to be in this age range, and the number of people age > 65

years is projected to double by 2050. The most rapidly increasing segment of the population is people age ≥ 85 years; they made up 14% of the population age ≥ 65 years in 2010 and are projected to make up > 21% of this population by 2050.

Underrepresentation in Research

Multiple studies have documented the underrepresentation of older adults in cancer research. Underrepresentation is occurring in trials conducted to achieve US Food and Drug Administration (FDA) approval of new drugs, biologics, and devices as well as in federally funded research.

The proportion of older adults participating in FDA registration trials is historically low, as Talarico and Pazdur[7] found in an analysis of 28,000 research participants from 55 trials conducted between 1995 and 2002. Specifically, only 36% of trial participants were age ≥ 65 years, compared with 60% of the overall patient population; 20% of trial participants were age ≥ 70 years, compared with 46% of the overall patient population; and 9% of trial participants were age ≥ 75 years, compared with 31% of the overall patient population.

A Government Accountability Office study reviewed 36 new drug applications from 2001 to 2004.[73] Of the 28 applications reporting the number of older adults participating in trials, only 33% of the participants were age > 65 years. More recently, Scher and Hurria[8] reviewed the geriatric use sections of drug package inserts for 24 drugs approved for cancer treatment between 2007 and 2010. Only 33% of the participants were age ≥ 65 years, compared with almost 60% of the cancer population in this age range.

Similarly, low numbers of older adults participate in trials sponsored by the NCI Cooperative Group Program (now called National Clinical Trials Network).[9-14] Hutchins et al,[10] for example, analyzed enrollment of > 16,000 older adults in Southwest Oncology Group trials between 1993 and 1996. Twenty-five percent of the trial participants were age ≥ 65 years, compared with 63% of the patient population with cancer. When the age cutoff was set at 70 years, older adults made up 13% of research participants, compared with 47% of the patient population.

Lewis et al[11] evaluated the participation of older adults in NCI-sponsored treatment trials from multiple cooperative groups from 1997 to 2000. Of the 59,000 research participants in 495 trials, 32% were older adults, compared with > 60% of patients with cancer. There is limited evidence that participation of older adults in NCI-sponsored trials is improving over time. Data from the NCI show that the percentage of older adults enrolled onto cooperative group trials has remained flat at just > 20% between 2001 and 2011.[15]

Clinical Implications

Older adults respond differently to cancer treatments than younger people. This is partly attributable to age-associated physiologic changes, such as alterations in organ function. It is also influenced by the higher incidence of comorbidities and use of concomitant medications in older adults, which may interact with cancer treatments. According to the Centers for Disease Control and Prevention, approximately 80% of older adults have one chronic condition, and 50% have ≥ two.[16] These factors make older adults more sensitive to toxicity and adverse effects resulting from treatment. In addition, the treatment of older adults is complicated by the fact that there is great heterogeneity in their health. Chronologic age is an inadequate characterization of older adults' health status. Consideration of patients' functional age more accurately accounts for the genetic, lifestyle, and environmental factors that contribute to overall health status.

The underrepresentation of older adults in clinical trials means that clinicians have less evidence on how to treat the majority of patients with cancer. Clinicians and patients are forced to extrapolate from trials conducted in younger, healthier populations when developing treatment plans.[17-19] This has created a dearth of knowledge regarding the risk of toxicity in the average older patient. In addition, key end points of importance to older adults (eg, functional independence) are often not captured or reported.[20,21]

The lack of evidence on how to treat older adults is contributing to systematic differences in their treatment. Clinicians are uncertain whether all older adults are able to tolerate and benefit from cancer therapy.[22-25] Older patients receive chemotherapy less frequently than recommended by clinical practice guidelines, which could contribute to suboptimal health outcomes.[26-35]

RECOMMENDATIONS

ASCO makes five overarching recommendations for improving the evidence base for treating older adults with cancer, which build and expand on the recommendations in the IOM quality report. Table 1 summarizes these recommendations.

Recommendation 1

Use clinical trials to improve the evidence base for treating older adults. There are opportunities in clinical trials to improve the evidence base for treating older adults. Overly restrictive eligibility criteria in many trials limit the accrual of older adults.[11,19,36-39] For example, Bellera et al[39] reviewed clinical trial participation of older adults with non-Hodgkin lymphoma in 87 trials published in Medline between 2005 and 2011; > 25% of the trials directly excluded patients age > 65 years, and 54% indirectly excluded older adults through selective eligibility criteria. Common eligibility criteria in trials that lead to the exclusion of older adults include performance status, comorbid conditions, concomitant medication usage, and delayed diagnoses.

There is growing recognition that eligibility criteria in clinical trials could be relaxed without compromising scientific rigor.[19,40] From 1999 to 2005, the median number of eligibility criteria per trial increased from 31 to 49.[41] In addition, it is estimated that only 20% to

Table 1. Recommendation Goals

Recommendation
To improve the conduct of research
Use clinical trials to improve evidence for treating older adults with cancer
Leverage research designs and infrastructure for generating evidence on older adults with cancer
To improve the research environment
Increase FDA authority to incentivize and require research involving older adults with cancer
Increase clinicians' recruitment of older adults with cancer to clinical trials
Use journal policies to improve researchers' reporting of age distribution and health risk profiles of research participants

Abbreviation: FDA, US Food and Drug Administration.

40% of patients treated at cancer centers are eligible to participate in clinical trials, primarily as a result of stringent eligibility criteria.[42] A 2010 IOM report recommended the development of eligibility criteria that allow the broadest participation possible.[43] Members of the ASCO Cancer Research Committee have also urged researchers and funders to carefully consider the necessity of individual eligibility criteria.[43a] Making eligibility criteria less stringent would speed up accrual, lead to more generalizable research, and improve identification of toxicities.[43,44]

Gathering additional data elements in clinical trials would also help improve the evidence base.[45] The health of older adults is heterogeneous[21]; however, little information is routinely captured about older adults who enroll onto trials aside from their chronologic age and performance status. The IOM quality report recommended that the NCI work with other stakeholders, like ASCO, to develop a common set of data elements to be collected by researchers in all trials.[1] Including elements from the geriatric assessment domains (eg, functional status, comorbid medical conditions, psychological state, cognitive function, nutritional status, social support) in these common data sets would help identify which older adults are most likely to benefit or not from treatment, because factors other than age are crucial to making these assessments.[46-53] Clinical trials conducted by the cooperative groups have documented that it is feasible to collect geriatric assessment data in a timely and efficient manner using existing tools.[54]

Similarly, there is substantial information to be gained from tumor specimens collected during clinical trials.[5] Tumors in older adults can be biologically different from those in younger populations.[31,55-59] For example, older adults are more likely to have hormone receptor–positive breast tumors than younger adults.[59] Requiring researchers to report the age distribution of samples studied in trials in which tumor specimens are collected would improve clinicians' understanding of how aging affects cancer biology.

Finally, the NCI should take a leadership role in ensuring that funders of cancer research, including the NIA and National Institutes of Health (NIH), encourage and incentivize increased involvement of older adults in clinical trials. Various approaches to fulfilling this role include creating targeted funding opportunities to support research involving older adults and including experts in geriatrics and geriatric oncology on review panels.

Action Items

- Regulatory agencies, funders of cancer clinical research, and researchers should carefully consider whether there is evidence supporting limitations to eligibility criteria based on age, performance status, or comorbid conditions. Researchers should provide a rationale, informed by input from experts in aging and geriatric oncology, when trials include eligibility criteria that are restricted based on these factors.
- The NCI, FDA, and other organizations developing common sets of data elements for researchers to collect in clinical trials should include measures from the geriatric assessment domains.
- Funders of cancer clinical trials in which tumor specimens are studied should require researchers to report on the age distribution of samples studied and whether this is reflective of the age distribution of the population enrolled onto the trial or the population with the disease overall.
- The NCI should collaborate with the NIA, NIH, and other funders of cancer clinical research to encourage and incentivize research including older adults.

Recommendation 2

Leverage research designs and infrastructure to improve the evidence base for treating older adults. Different study designs are appropriate for answering various types of questions, and researchers should choose the design most appropriate for the question of interest.[60-62] A recent U13 conference reviewed the benefits and limitations of various study designs for improving the evidence base for older adults, including randomized clinical trials, prospective cohort studies, embedded studies, and single-arm trials (Table 2).[15]

There are also several innovative trial designs, such as extended design trials and adaptive trials, which could improve the generation of evidence on older adults.[15] Extended design trials, for example, allow researchers to examine the age distribution of patients in the superior arm of a trial after the results have been reported. If the superior arm fails to accrue a sufficient number of older adults to draw conclusions, researchers reopen it to accrue a sufficient number.[15] Appropriately using the full range of trial designs to fill knowledge gaps could improve the evidence base guiding the treatment of older adults.

Comparative-effectiveness research (CER) is another effective method for developing the evidence base for treating older adults. CER is defined as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods, to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care."[60(p13)] To leverage CER to improve the evidence base for treating older adults, the IOM quality report recommends that funders require researchers "to include a plan to study a population that mirrors the age distribution and health risk profile of patients with the disease."[1(p12)] This would further the central goal of CER: gathering data to inform real-world clinical decisions.

CER often depends on database research to answer important clinical questions. There are multiple databases with information on patients with cancer, including learning health care systems that merge data from large numbers of electronic health records, such as the ASCO CancerLinQ, as well databases that rigorously collect data, such as the SEER-Medicare database and cancer registries. A major advantage of research using these information sources is that researchers have access to data from large, diverse populations, including older adults, individuals with comorbidities, people using concomitant medications, and those who are in the oldest age ranges. Database research also produces results quickly and inexpensively. However, the data are not always collected systematically, creating the potential for bias or erroneous conclusions. To leverage databases to inform the treatment of older adults, it will be important that databases collect and store relevant information (eg, measures from geriatric assessment domains) and that they support appropriate analyses.

Coverage with evidence development (CED) is also a strategy for collecting clinical evidence on older adults.[63,64] Sponsors of new medical products currently have few incentives to conduct additional research after achieving insurance coverage for their products.[65] Under CED, payers cover the cost of a treatment while additional research is conducted.[66] This is unlike the more traditional research paradigm,

Table 2. Opportunities in Geriatric Oncology Clinical Trial Designs

Design	Description and Characteristics	Potential Objectives and Outcomes	Advantages	Limitations and Vital Considerations
RCT	Gold standard of clinical trial design; participants randomly assigned to treatment arms Study design for generating evidence in older adults: accrue only older adults or accrue patients of all ages but stratify enrollment into age groups representative of distribution of individuals with disease Adaptive (Bayesian) design: trial design is modified as study proceeds based on interim data analysis; randomization ratio can be altered by shifting patients to more effective treatment arm and eliminating underperforming arm	Compare efficacy and tolerability of different treatments; develop novel end points	Excellent for direct comparison of different regimens	Requires large sample sizes; is costly and time intensive; lack of end points tailored to geriatric population In trials stratified by age: slow accrual because of enrollment of specific age strata
Prospective cohort study	Assesses treatments already approved by FDA Cohort can be defined by host, tumor, or treatment factors Observational (no randomization) Hypothesis driven	Identify patterns of care; understand decision making; determine toxicity and feasibility of delivering specific therapies	Generalizable findings; provides insight into patterns of care and decision making	Lack of randomization; significant data management resources required to capture drug-dosing and toxicity data
Embedded study (correlative or ancillary study)	Measures of interest to geriatric oncology research are included within infrastructure of parent study (eg, GA domains)	Use GA to describe cohort; use GA in longitudinal follow-up to understand impact of therapy; identify characteristics of patients at high risk for toxicity	Baseline characterization of geriatric population in study; ability to identify baseline predictors of treatment tolerance and/or longitudinal declines in function	Parent study may not be targeted to older adults, thus limiting sample size of older patients If participation in embedded study is optional, patients may not be representative of entire cohort and/or adequate sample size of older adults may not accrue
Single-arm trial	Gold standard for phase II trials No randomization All patients receive treatment under study	Evaluation of efficacy of drug for which there are limited data for older adults Identification of predictors of toxicity based on GA variables or biomarkers Understanding of age-related changes in pharmacokinetics and pharmacodynamics of therapeutics	Qualification of novel end points Fills gaps in knowledge regarding efficacy, feasibility, and toxicity of drugs that have been understudied in older adults	No comparison arm
Extended trial	Addition of cohort of older patients to superior treatment arm or RCT	Determination of tolerability of treatment in older adults	Trial infrastructure in place Easier accrual of older patients because efficacy of treatment has been demonstrated Provides additional data on tolerability of treatment in older patients	No precedent exists for reopening study several years after closure No data regarding efficacy of treatment from inferior arm in older adults

NOTE. Data adapted.[15]
Abbreviations: FDA, US Food and Drug Administration; GA, geriatric assessment; RCT, randomized controlled trial.

where industry covers treatment costs in trials. Clinical trials conducted under CED programs are likely to be more generalizable, given that payers are interested in supporting research that will inform coverage decisions for their insured populations.

The Centers for Medicare and Medicaid Services (CMS), the major insurer of older adults, employed CED in oncology in 2005 by covering the off-label use of several chemotherapy treatments for colorectal cancer in specific NCI-sponsored trials.[67] Medicare should be highly motivated to participate in additional CED programs in oncology, given the difference between the average trial participant and the average Medicare beneficiary, who is older and less healthy.[18] Moreover, previous additions to the coverage of clinical trials by Medicare have increased the number of older adults participating in research.[68]

Action Items

- Researchers and funders of cancer clinical research should use the full range of research designs, including innovative trial designs, to fill knowledge gaps in the treatment of older adults with cancer.
- Funders of CER should require researchers evaluating the role of a standard or novel cancer treatment to include a plan to study a population that mirrors the age distribution and health risk profile of patients with the disease.
- Developers of research and clinical databases should ensure that their systems collect geriatric assessment data and have the functionality to support studies designed to improve the evidence base supporting the treatment of older adults with cancer.
- The CMS should use its coverage with evidence development authority to cover the off-label use of marketed drugs in select cancer clinical trials. The CMS should work with the NIH, patients, and researchers to prioritize trials for this additional coverage.

Recommendation 3

Increase the authority of the FDA to incentivize and require research including older adults. The FDA has limited authority to require sponsors of new treatments to test their products in older adults. Manufacturers are required to report their clinical trial results by age and include a geriatric use subsection on their product labels.[69,70] The FDA has also issued guidance that encourages, but does not require, sponsors to generate evidence on the effectiveness of their products in older adults.[71,72]

Despite these policies, older adults are rarely included in registration trials.[7,8,73] Moreover, the lack of information included in the geriatric use section of product labels has limited impact on the ability of manufacturers to market and sell their products to older adults. Only approximately half of drugs commonly prescribed to older adults contain precautionary information in the geriatric use section of their labels.[74] Manufacturers typically comply with this labeling requirement by noting that their products were tested in insufficient numbers of older adults to determine whether the products are likely to produce higher risks for older adults.

Given that the current regulatory approach of the FDA does not generate actionable information on the therapeutic effect of new treatments in older adults, changing the requirements and incentive structure for new treatments is required. Specifically, the FDA should have authority to require a sponsor to outline a plan to test its products in older populations. The FDA could issue a waiver if a product is unlikely to benefit older adults. Companies could meet this requirement through postmarketing trials, so products that are ready for approval in the general population are not kept off the market.

The FDA should also have the authority to create incentives for manufacturers to test their products in older adults. This incentive-based approach could be extended to drugs for other diseases that also occur frequently in older adults. The IOM quality report recommends rewarding companies for conducting clinical trials of new cancer treatments in older adults by providing them with 6 months of patent extensions, as modeled after the pediatric market exclusivity incentive.[1] There is substantial evidence of the success of the pediatric market exclusivity program at incentivizing research in children.[75,76]

There are also other examples of incentives that successfully encourage manufacturers to conduct research on specific topics or in specific populations, which could serve as models for a new incentive program for research in older adults: (1) the FDA Amendments Act of 2008 includes transferable vouchers for expedited review for companies developing new drugs to treat tropical diseases, (2) the Affordable Care Act includes multiple incentives to encourage manufacturers to develop biologic drugs, (3) the Orphan Drug Act provides market exclusivity for drugs treating rare diseases, and (4) the Hatch-Waxman Act includes incentives for both brand-name and generic drug manufacturers.[76] Although market exclusivity is the core approach to motivating manufacturers to conduct research, other types of incentives, such as prizes and government research and development contracts, can also be effective.[77]

The FDA should have flexibility in designing an appropriate incentive program to encourage research involving older adults. The program should be informed by previous incentive programs and narrowly tailored to achieve the desired outcome of generating the needed evidence. The authorizing law should also require an evaluation of the impact of the program on public health, include a mechanism that allows the FDA to modify the incentive based on the evaluation, and place limits on the compensation available to manufacturers. Moreover, it will be important that both the incentive program and any new requirements be harmonized with the European Medicines Agency (EMA) procedures.

In addition, the FDA should enhance the aging expertise on its advisory boards as it implements these new programs. Part of the EMA geriatric strategy included forming a geriatric expert group to advise the EMA and its scientific committees on relevant issues.[78] In the United States, the FDA Oncology Drug Advisory Committee is the most logical place to increase geriatric expertise. This committee is charged with reviewing and evaluating data concerning the safety and effectiveness of cancer treatments. It consists of 13 voting members from various fields but currently does not require a member with geriatric or aging expertise.[79] Including geriatric expertise would better ensure that manufacturers are submitting the appropriate data on the safety, efficacy, and dosing of their products in older adults.

Action Items

- Congress should provide the FDA authority to require that a drug or biologic marketing application contain a plan to gather data and develop recommendations on safety, efficacy, and dosing in older adults.
- Congress should grant the FDA authority to create incentives for companies that conduct clinical trials of new cancer treatments in older adults.
- The FDA should include experts in aging and geriatric oncology on its advisory boards to provide scientific advice on the development and assessment of novel agents and emerging federal policies.

Recommendation 4

Increase clinician recruitment of older adults to clinical trials. The biggest predictor of whether a patient decides to enroll onto a clinical

trial is whether a clinician has discussed and recommended participation. Thus, clinicians can be a major barrier to older adults' participation in research.[7,9,36,37,80] Although there is no evidence that enrollment of older adults onto clinical trials is associated with increased risk of harm over standard therapy,[11,14] clinicians regularly cite concerns about drug toxicity and the impact of treatment as reasons not to enroll older adults onto trials.[7,9,36,37] Clinicians' decision to offer trial participation to patients is often influenced by patients' chronologic rather than functional age.[81-86]

Nevertheless, multiple studies have found that older adults are as willing to participate in trials as younger adults when given the opportunity.[84,86,87] Older adults also generally have positive attitudes toward clinical trials.[88] Given these data, educational programs will be necessary to reduce clinicians' reluctance to enroll older adults onto trials. In addition, trial sponsors should avoid distributing educational materials that may discourage clinicians from enrolling older patients onto trials.

Increasing reimbursement for clinicians who enroll patients onto clinical trials would also improve recruitment. An IOM report concluded that the current reimbursement system fails to recognize the extra time and effort it takes to enroll patients onto trials, such as the time required to find applicable trials, explain trials to patients, and obtain informed consent.[43] There are also extra data collection and documentation and regulatory requirements for clinicians whose patients participate in research.[88] One study found that clinicians spend, on average, 4 hours enrolling patients onto trials, and some of these patients ultimately decide not to participate.[89] The additional uncompensated time and effort required for trial enrollment is particularly burdensome for clinicians enrolling older adults, given the increased challenge of identifying appropriate trials for this population, some older adults' heightened toxicity risks, and older adults' potential for cognitive impairments, which must be assessed to determine whether patients can provide informed consent.

Action Items

- Professional societies should develop and promote educational materials for clinicians and researchers to encourage greater recruitment of older adults to clinical trials.
- The American Medical Association should establish new current procedural terminology (CPT) codes to reimburse clinicians who offer older patients the opportunity to participate in clinical trials, enroll them onto these trials, and conduct management and follow-up of these patients for the additional time and effort involved. These CPT codes should be reimbursed by Medicare, Medicaid, and third-party payers.

Recommendation 5

Use journal policies to incentivize researchers to consistently report on the age distribution and health risk profiles of research participants. Researchers are currently collecting substantial data about older adults that are not being analyzed or reported. Thus, information that could inform clinical practice at little additional cost is not being reported. Kumar et al,[14] for example, reviewed 345 completed phase III clinical trials conducted by five cooperative groups for participation of older adults. They found that 57% of the trials did not stratify the results by age, and only 12% of trials stratified by age $\geq$ 65 years. This represents an easily addressed, missed opportunity to identify differences in safety, efficacy, and dosing associated with age. Using journal policies could improve researchers' reporting of data relevant to the treatment of older adults.

Action Items

- Require authors to submit and report the detailed age distribution (by decade) of the population included in the study, not just the age ranges of population, and data analyses that could potentially yield valuable age-related information, including age-based analyses of response, benefit, and toxicity.
- Include geriatric oncology experts in the pool of editorial board members who serve as peer reviewers of manuscripts.
- Instruct peer reviewers to consider whether the authors have adequately reported the age distribution of the population included in the study, the generalizability of the results to the population with the disease, and data analyses that could potentially yield valuable age-related information.

DISCUSSION

This article lays out a multipronged approach to improving the evidence base for treating older adults with cancer. Some of the recommendations are achievable in a short timeframe. Others will require longer-term commitments and the collaboration of multiple stakeholders involved in clinical research. Given the rapidly aging population, this is a crucial time to act to ensure all patients with cancer receive high-quality, evidence-based care.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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Consulting or Advisory Role: GTx, Seattle Genetics, Boehringer Ingelheim
Research Funding: GlaxoSmithKline (Inst), Celgene (Inst)

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No relationship to disclose

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Research Funding: Bristol-Myers Squibb (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb

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Appendix

American Society of Clinical Oncology Recommendations: Improving the Evidence Base for Treating Older Adults With Cancer

Recommendation 1

Use clinical trials to improve the evidence base for treating older adults with cancer.

Action Items

- Regulatory agencies, funders of cancer clinical research, and researchers should carefully consider whether there is evidence supporting limitations to eligibility criteria based on age, performance status, or comorbid conditions. Researchers should provide a rationale, informed by input from experts in aging and geriatric oncology, when trials include eligibility criteria that are restricted based on these factors.
- The National Cancer Institute (NCI), US Food and Drug Administration (FDA), and other organizations that are developing common sets of data elements for researchers to collect in clinical trials should include measures from the geriatric assessment domains.
- Funders of cancer clinical trials in which tumor specimens are studied should require researchers to report the age distribution of samples studied and whether this is reflective of the age distribution of the population enrolled onto the trial and the population with the disease overall.
- The NCI should collaborate with the National Institute on Aging, National Institutes of Health, and other funders of cancer clinical research to encourage and incentivize research involving older adults.

Recommendation 2

Leverage research designs and infrastructure to improve the evidence base for treating older adults with cancer.

Action Items

- Researchers and funders of cancer clinical research should use the full range of research designs, including innovative trial designs, to fill knowledge gaps in the treatment of older adults with cancer.
- Funders of comparative-effectiveness research should require researchers evaluating the role of a standard or novel cancer treatment to include a plan to study a population that mirrors the age distribution and health risk profile of patients with the disease.
- Developers of research and clinical databases should ensure that their systems collect geriatric assessment data and have the functionality to support studies designed to improve the evidence base supporting the treatment of older adults with cancer.
- The Centers for Medicare and Medicaid Services should use its coverage with evidence development authority to cover the off-label use of marketed drugs in select cancer clinical trials. The Centers for Medicare and Medicaid Services should work with the National Institutes of Health, patients, and researchers to prioritize trials for this additional coverage.

Recommendation 3

Increase the authority of the FDA to incentivize and require research involving older adults with cancer.

Action Items

- Congress should provide the FDA authority to require a drug or biologic marketing application to contain a plan to gather data and develop recommendations on safety, efficacy, and dosing in older adults.
- Congress should grant the FDA authority to create incentives for companies that conduct clinical trials of new cancer treatments in older adults.
- The FDA should include experts in aging and geriatric oncology on its advisory boards to provide scientific advice on the development and assessment of novel agents and emerging federal policies.

Recommendation 4

Increase clinician recruitment of older adults with cancer to clinical trials.

Action Items

- Professional societies should develop and promote educational materials for clinicians and researchers to encourage greater recruitment of older adults to clinical trials.
- The American Medical Association should establish new common procedural terminology codes to reimburse clinicians who offer older patients the opportunity to participate in clinical trials, enroll them onto these trials, and conduct

management and follow-up of these patients for the additional time and effort involved. These codes should be reimbursed by Medicare, Medicaid, and third-party payers.

Recommendation 5

Use journal policies to incentivize researchers to consistently report the age distribution and health risk profiles of research participants.

Action Items

- Require authors to submit and report the detailed age distribution (by decade) of the population included in the study, not just the age ranges of population, and data analyses that could potentially yield valuable age-related information, including age-based analyses of response, benefit, and toxicity.
- Include geriatric oncology experts in the pool of editorial board members who serve as peer reviewers of manuscripts.
- Instruct peer reviewers to consider whether the authors have adequately reported the age distribution of the population included in the study, the generalizability of the results to the population with the disease, and data analyses that could potentially yield valuable age-related information.

JNCI J Natl Cancer Inst (2018) 110(11): djy169

doi: 10.1093/jnci/djy169
First published online October 17, 2018
Commentary

COMMENTARY

Expanding the Evidence Base in Geriatric Oncology: Action Items From an FDA-ASCO Workshop

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Abstract

As part of the ongoing efforts to address the lack of clinical research on older adults with cancer, the American Society of Clinical Oncology (ASCO) and the US Food and Drug Administration cosponsored a public workshop on geriatric oncology in November 2017. The goals were to review progress, build collaborations across stakeholders, and generate new action items for increasing the evidence base for treating older adults with cancer. It built on previous work of the Institute of Medicine, ASCO, and the U13 Conferences convened by the Cancer and Aging Research Group, the National Cancer Institute, and the National Institute of Aging between 2010 and 2015. The workshop drew a diverse group of presenters, panelists, and attendees, including academic and clinical oncologists, regulators, other government officials, representatives from industry, and patient advocacy groups. Attendees at the workshop were tasked with proposing next steps to address the lack of evidence on treating older adults with cancer. Based on the workshop discussions, four new action items to move the field forward were developed: 1) increase enrollment of older adults in clinical trials, 2) collect more information on older adults enrolled on clinical trials, 3) expand the use of real-world data in research on older adults, and 4) strengthen collaboration between stakeholders to develop advocacy and policy solutions. These action items, alongside the previous ASCO, Institute of Medicine, and U13 recommendations, provide a strategy for improving the evidence base for treating older adults with cancer and ensuring all patients with cancer receive high-quality, evidence-based care.

Although adults age 65 years and older represent the largest group of patients diagnosed with cancer and suffer the most cancer deaths, older adults are underrepresented in cancer clinical trials and are rarely the focus of clinical research (1–3). The result is a critical lack of evidence for delivering high-quality cancer care to older patients. Lack of evidence affects cancer care on multiple levels. It impedes the ability of oncologists to deliver optimal treatment to older patients by forcing them to extrapolate from data collected in younger, healthier patients; places older adults at serious risk of negative health consequences; and uses sparse healthcare resources to pay for potentially ineffective or harmful care (2,3). With the number of cancer cases projected to multiply due to rapid aging of the US population (4,5), there is a growing consensus on the need for new research, policies, and strategies to improve the evidence base for treating older adults.

As part of the ongoing effort to address these concerns, the American Society of Clinical Oncology (ASCO) and the US Food and Drug Administration (FDA) cosponsored a public workshop on geriatric oncology in November 2017 (6). The goals were to review progress, build collaborations across stakeholders, and generate new action items for increasing the evidence base for treating older adults with cancer. The workshop drew a diverse group of presenters, panelists, and attendees, including academic and clinical oncologists, regulators, other government officials, industry, and patient advocates. This paper summarizes the workshop content on the status of the problem and presents action items generated by workshop discussions.

Evidence Gap in Geriatric Oncology

In 2013, the Institute of Medicine (IOM) report "Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis" presented a conceptual framework for improving the quality of care for Americans with cancer (3). Among other

Received: June 15, 2018; **Revised:** August 8, 2018; **Accepted:** August 27, 2018

findings, the report highlighted the complex treatment needs of older adults and expressed concern that the lack of research in this population is undermining the quality of care. IOM identified four problems contributing to the evidence gap: 1) underrepresentation of older adults and patients with comorbid health conditions in trials; 2) lack of research directed toward treating older and frail patients who are rarely enrolled on trials; 3) limited information regarding the characteristics of older adults who enroll on trials (such as functional status, comorbidities, and other items captured in geriatric assessments [GAs]); and 4) failure to collect endpoints that are important to older adults (eg, impact of treatment on function or cognition) or information on patient characteristics, health behaviors, and patient-reported outcomes (PROs). To address these gaps, IOM recommended expanding the breadth of research on cancer interventions to include older adults and patients with comorbid health conditions and increasing the depth of evidence by requiring researchers to capture GA and additional endpoints.

Following the publication of the IOM report, ASCO convened a working group to develop recommendations for improving the evidence base for treating cancer in older adults. In 2015, ASCO published a statement with five recommendations (Box 1) (2). ASCO's recommendations targeted increasing enrollment of older adults in trials, greater use of alternate research designs to generate more evidence on older adults, improvements to clinician recruitment, and journal policies. Additionally, the recommendations charged Congress to provide the FDA with new authority to require sponsors to include plans for gathering data on safety, efficacy, and dosing in older adults in all applications for investigational new drugs (INDs) and to provide incentives to sponsors to test new treatments in older adults, especially those who are frail or have comorbidities.

Despite the IOM and ASCO's efforts to increase research on older adults, sponsors have little incentive to meet these goals. The FDA has issued several guidance documents encouraging sponsors to study the effects of drugs on older adults (particularly if they represent the majority of people who are likely to be prescribed the drug) and to modify trial design and eligibility criteria to increase enrollment of older patients (7,8). However, the FDA lacks authority to require or incentivize trials of new drugs among older adults. Therefore, trials are typically conducted with a select group of healthier, younger patients and are focused on bringing new treatments quickly to market (9–11). Once drugs are approved, sponsors seldom conduct additional studies to test the effectiveness of treatments on older adults who were underrepresented in the initial approval process (12). This means that drug approvals are based on data from younger, healthier participants, and trials do not provide adequate information about drug efficacy, safety, and dosing for use with older adults (2,3).

Workshop Action Items

Attendees at the workshop were tasked with proposing next steps to address the lack of evidence on treating older adults with cancer. Based on the workshop discussions, this section presents four new action items to move the field forward (Box 2). Previous recommendations from ASCO and IOM continue to be relevant and should inform ongoing and future efforts to improve the evidence base in this population, including those related to physician education, research methodology, advocacy, and journal policies.

Increase Enrollment of Older Adults in Clinical Trials

Clinical trials represent the gold standard for evidence development and are used to establish the standard of care, so enrolling a representative sample of older adults in trials remains critical to improving the evidence base in geriatric oncology. Despite numerous efforts to increase enrollment of older adults, however, there have been only small changes in accrual (9–11,13–18). The action items in this section focus on increasing incentives and removing barriers to trial enrollment for older adults, including modifying eligibility criteria, expanding trial locations, and addressing patient concerns.

FDA Could Work With Sponsors to Outline Development Plans for New Drugs to Enroll Representative Numbers of Older Adults

FDA guidance documents state that sponsors should enroll patients in trials who are representative of the population who will receive the drugs after approval and encourages enrollment of people over age 75 years and those with comorbid health conditions (7,8). Although this guidance functions as a recommendation, not requirement, the FDA could work with sponsors to facilitate enrollment of older adults during the planning process for IND applications. Discussion of development plans for new drugs to enroll representative numbers of older adults could become a routine part of pre-IND and End of Phase 2 meetings. The FDA could highlight incentives for companies to enroll older adults in registration trials during these meetings, including the potential for broader label indications and the possibility that clinicians may use treatments in larger patient populations if this evidence is collected. The FDA could also consider postmarketing commitments for companies that fail to follow these plans or achieve adequate numbers of older adults in their registration trials.

Sponsors Should Implement the ASCO-FDA-Friends of Cancer Research Eligibility Criteria Recommendations for Organ Disfunction, Concurrent Malignancy, and Comorbidities

Trials routinely include eligibility criteria that have little relevance to the drugs being tested and that effectively exclude older adults. These eligibility criteria are used to create homogeneous patient samples, protect patient safety, and quickly establish efficacy, but stringent eligibility criteria can limit the generalizability of results and may not always be medically necessary (19). An analysis of clinical data from Kaiser Permanente Northern California demonstrated that eligibility criteria based on organ dysfunction, concurrent malignancy, and comorbidity exclude many older adults from trials (20). Based on these results, an ASCO-FDA-Friends project recommended rationalizing eligibility criteria across these domains and others (19–23). The FDA is now working on guidance documents for implementing these recommendations and is prepared to work with sponsors to ensure that eligibility criteria do not exclude patients who could safely enroll and are willing to participate in trials, such as older adults. Sponsors should implement these recommendations, and when they retain more restrictive eligibility criteria, they should provide a rationale for why the recommended criteria cannot safely be adopted.

Box 1. ASCO Recommendations: Improving the Evidence Base for Treating Older Adults with Cancer. The text in this box is reprinted from Hurria et al. 2015 (2).

Recommendation 1: Use clinical trials to improve the evidence base for treating older adults with cancer.

Action Items

- Regulatory agencies, funders of cancer clinical research, and researchers should carefully consider whether there is evidence supporting limitations to eligibility criteria based on age, performance status, or comorbid conditions. Researchers should provide a rationale, informed by input from experts in aging and geriatric oncology, when trials include eligibility criteria that are restricted based on these factors.
- The NCI, US FDA, and other organizations that are developing common sets of data elements for researchers to collect in clinical trials should include measures of the geriatric assessment domains.
- Funders of cancer clinical trials in which tumor specimens are studied should require researchers to report the age distribution of samples studied and whether this is reflective of the age distribution of the population enrolled onto the trial and the population with the disease overall.
- The NCI should collaborate with the National Institute on Aging, National Institutes of Health (NIH), and other funders of cancer clinical research to encourage and incentivize research involving older adults.

Recommendation 2: Leverage research designs and infrastructure to improve the evidence base for treating older adults with cancer.

Action Items

- Researchers and funders of cancer clinical research should use the full range of research designs, including innovative trial designs, to fill knowledge gaps in the treatment of older adults with cancer.
- Funders of comparative-effectiveness research should require researchers evaluating the role of a standard or novel cancer treatment to include a plan to study a population that mirrors the age distribution and health risk profile of patients with the disease.
- Developers of research and clinical databases should ensure that their systems collect geriatric assessment data and have the functionality to support studies designed to improve the evidence base supporting the treatment of older adults with cancer.
- The Centers for Medicare and Medicaid Services (CMS) should use its coverage with evidence development authority to cover the off-label use of marketed drugs in select cancer clinical trials. CMS should work with the NIH, patients, and researchers to prioritize trials for this additional coverage.

Recommendation 3: Increase the authority of the FDA to incentivize and require research involving older adults with cancer.

Action Items

- Congress should provide the FDA authority to require a drug or biologic marketing application to contain a plan to gather data and develop recommendations on safety, efficacy, and dosing in older adults.
- Congress should grant the FDA authority to create incentives for companies that conduct clinical trials of new cancer treatments in older adults.
- The FDA should include experts in aging and geriatric oncology on its advisory boards to provide scientific advice on the development and assessment of novel agents and emerging federal policies.

Recommendation 4: Increase clinician recruitment of older adults with cancer to clinical trials.

Action Items

- Professional societies should develop and promote educational materials for clinicians and researchers to encourage greater recruitment of older adults to clinical trials.
- The American Medical Association should establish new common procedural terminology codes to reimburse clinicians who offer older patients the opportunity to participate in clinical trials, enroll them on these trials, and conduct management and follow-up of these patients for the additional time and effort involved. These codes should be reimbursed by Medicare, Medicaid, and third-party payers.

Recommendation 5: Use journal policies to incentivize researchers to report age distribution and health risk profiles of research participants.

Action Items

- Require authors to submit and report the detailed age distribution of the study population, not just the age ranges of population, and data analyses that could potentially yield valuable age-related information, including age-based analyses of response, benefit, and toxicity.
- Include geriatric oncology experts in the pool of editorial board members who serve as peer reviewers of manuscripts.
- Instruct peer reviewers to consider whether the authors have adequately reported the age distribution of the population included in the study, the generalizability of the results to the population with the disease, and data analyses that could potentially yield valuable age-related information.

Box 2. ASCO-FDA Workshop Action Items.

Action Item 1: Increase enrollment of older adults in clinical trials.

1.a. FDA could work with sponsors to outline development plans for new drugs to enroll representative numbers of older adults.
1.b. Sponsors should implement ASCO-FDA-Friends criteria recommendations for organ dysfunction, concurrent malignancy, and comorbidities.
1.c. Sponsors should open more trials in community settings.
1.d. Sponsors should work with social and behavioral scientists, patient advocates, geriatricians, and geriatric oncologists to consider the needs of older adults when designing clinical trials.
1.e. NCI should take the following steps to implement the NIH Inclusion Across the Lifespan Policy:
- NCI-Designated Cancer Center applications and NCTN Award applications should require reporting on the recruitment of older adults to trials compared with the distribution of those with the disease.
- Investigator-initiated grant applications should require enrollment reports to capture the recruitment of older adults (planned and actual) compared with the distribution of those with the disease.
- NCI's Division of Cancer Prevention and Cancer Therapy Evaluation Program should increase accrual credit for enrollment of older adults.
- NCI Scientific Steering Committees should include experts in aging and geriatric oncology to ensure that the recruitment of older adults is considered before finalization of research protocols.

Action Item 2: Collect more information on treating older adults from clinical trials.

2.a. Sponsors and researchers should work with statisticians to design more trials with coprimary or composite endpoints, including elements of GA and end points that are important to older adults.
2.b. FDA and NCI should work with sponsors to design trials that collect more information on treating older/frail adults.

Action Item 3: Expand the use of RWD in research on older adults.

3.a. Geriatric oncology researchers should work with ASCO, FDA and other stakeholders to develop a framework for using RWD in clinical research. As part of this process, researchers should submit demonstration project proposals to CancerLinQ and other databases to establish the benefits and limitations of these data sources.
3.b. Clinicians should incorporate GAs into clinical care and record this information in EHRs, payers should reimburse for this time, and quality metrics programs should assess clinicians' performance of GAs.
3.c. Developers of large EHR databases should partner with EHR vendors to ensure GA elements can be entered EHRs as standard data elements.

Action Item 4: Strengthen collaboration between stakeholders to develop advocacy and policy solutions.

4.a. The geriatric oncology community should strengthen its advocacy efforts to be more cohesive and propose specific policy solutions.
4.b. Geriatric oncologists should discuss with developers of value frameworks how their definitions of "value" could be updated to consider the representativeness of the evidence to the population with the disease.

ASCO = American Society of Clinical Oncology; EHR = electronic health record; FDA = U.S. Food and Drug Administration; Friends = Friends of Cancer Research; GA = geriatric assessment; NCI = National Cancer Institute; NCTN = National Clinical Trial Network; NIH = National Institutes of Health; RWD = real-world data; RWE = real-world evidence

COMMENTARY

Sponsors Should Open More Trials in Community Settings

Although most patients are treated in community settings, trials are typically located in academic or large urban medical centers that may not be easily accessible to older patients living in suburban or rural locations. The National Cancer Institute (NCI) Community Oncology Research Program (NCORP) is a national network designed to open participation to NCI-approved studies at community sites, allowing patients to participate in trials while receiving treatment locally (24). Accrual of older patients is facilitated when trials are opened in NCORP because older adults may face more challenges than younger patients with travel, caregiver support, and other logistics associated with trial participation (25). Industry sponsors should make similar efforts to open registration trials in community settings to support increased enrollment of older adults in their trials.

Sponsors Should Work With Social and Behavioral Scientist, Patient Advocates, Geriatricians, and Geriatric Oncologists to Consider the Needs of Older Adults When Designing Clinical Trials

Older adults generally have positive attitudes toward trials and are willing to participate when given the opportunity (26–30). However, many older patients do not enroll in trials, and little is known about who is likely to enroll and the reasons behind their decisions. Both pragmatic concerns and personal preferences were raised at the workshop as influencing patient decision-making. Pragmatic barriers include restricted trial

availability, travel costs, and increasing caregiver burden. Trial sponsors could address these concerns through changes to trial design, such as limiting the number of in-person study visits, using telehealth to supplement in-person visits as is feasible and safe, making treatment locations more accessible within patients' communities, or providing travel support. Patients may also choose not to enroll because of concerns about effects of treatment on independence, functional status, and quality of life; negative opinions about the value of experimental treatments; or failure to understand the contributions that their participation may make for future patients. Further study is needed to determine how these factors influence enrollment in trials and to identify the characteristics of trials that successfully accrue older adults. Social and behavioral scientists will be crucial to conducting this research and to translating results into practice. Input from patient advocates, geriatricians, and geriatric oncologists during the study design process would also make trial participation more accessible and culturally sensitive for older adults by bringing the needs of these patients to the attention of sponsors early (31).

NCI Should Take the Following Steps to Implement the National Institutes of Health Inclusion Across the Lifespan Policy

- NCI-Designated Cancer Center applications and National Clinical Trial Network (NCTN) Award applications should require reporting on the recruitment of older adults to trials compared with the distribution of those with the disease in the catchment area.
- Investigator-initiated grant applications should require enrollment reports to capture the recruitment of older adults (planned and actual) compared with the distribution of those with the disease.
- NCI's Division of Cancer Prevention and Cancer Therapy Evaluation Program should increase accrual credit for enrollment of older adults.
- NCI Scientific Steering Committees should include experts in aging and geriatric oncology to ensure that the recruitment of older adults is considered before finalizing research protocols.

The National Institutes of Health (NIH) Inclusions Across the Lifespan policy requires NIH-funded research to include participants of all ages, including older adults, unless there is an ethical or scientific reason to not include them. The details of how NCI will implement this policy across its programs are unknown. However, implementation should include adding age reporting requirements to NCI-Designated Cancer Center applications, NCTN award applications, and investigator-initiated grant applications. The reporting should be stratified by age 65 years and older and 75 years and older and should build on the reporting requirements for racial/ethnic minorities and women (32,33). The NCI should also enhance the expertise in aging on its Scientific Steering Committees. Additionally, the NCI should develop an accrual credit for the enrollment of older adults on NCTN trials as well as for other underrepresented age groups.

Collect More Information on Older Adults Enrolled on Clinical Trials

Increasing the enrollment of older adults in trials will not solve the evidence gap because many older adults have health conditions or other limitations that preclude enrollment in standard trials (12). IOM and ASCO recommended that researchers expand the types of evidence that are collected in trials and utilize innovative trial designs to collect more evidence on older patients, but research adopting these recommendations is rare (2,3). The action items in this section reiterate the importance of expanding elderly-specific research by using broader endpoints and innovative trial designs.

Sponsors and Researchers Should Work With Statisticians to Design More Trials with Coprimary or Composite Endpoints, Including PROs, Elements of GAs, and Endpoints Important to Older Adults

Trials of new drugs typically analyze a narrow set of endpoints (eg, tumor growth, survival, toxicity) that demonstrate drug safety and efficacy but do not provide all the information needed by clinicians and patients to make informed treatment decisions (34). Therefore, an important part of expanding the evidence base in geriatric oncology is collecting broader endpoints in trials, such as the impact of treatment on function and congition (35,36). Given the heterogeneity in health status of older adults, there is widespread agreement that chronological age alone does not adequately characterize health status or predict response to treatment. GAs provide a structured way to measure psychological, social, and functional changes associated with aging, make predictions about the potential benefits and risks of different treatment options, and understand the unique needs and vulnerabilities of older adults to inform the development of intervention studies (37).

The FDA has used PRO data collected directly from patients, such as the impact of treatment on quality of life, independent function, and cognition, in its product labeling and has supported the reporting of PROs in published reports of trial results (38). As core sets of PROs are developed for trials, elements of GAs and other measures relevant to older adults could be incorporated. This may require working with statisticians to create composite or coprimary endpoints that focus on both efficacy, safety, and GA/PRO endpoints. Lessons from the European Medicines Agency suggest that building consensus around these measures is possible and will facilitate their inclusion in research and practice (39).

FDA and NCI Should Work With Sponsors to Design Trials That Collect More Information on Treating Older/Frail Adults

Trials designed specifically for older patients are critical to addressing the evidence gap surrounding the treatment of older adults with frailty or comorbidities who cannot enroll in standard trials. These studies may address questions about the risks/benefits of standard treatments in older patients, determine optimal dosing and drug selection, and examine the effects of standard treatments on quality of life, functional independence, and other factors that are critical to older adults. The U13 Conferences convened by the Cancer and Aging Research Group, NCI, and the National Institute of Aging between 2010 and 2015 defined research designs for studying older adults (12). They included two general approaches: 1) design "elderly-specific studies" that enroll only older patients, and 2) adapt standard trials to enroll cohorts of older adults. For example, researchers could use single arm trials, prospective cohort studies, or clinical trials that enroll only older adults to augment the evidence base in cancer care. Alternatively, standard phase III trials could be adapted to collect more evidence on older adults, such as through an extended trial design where an additional cohort of older adults is added to the superior arm of an existing trial once treatment utility has been demonstrated. This leverages existing trial

infrastructure to determine tolerability in older and/or frail patients who are not adequately represented in the general trial population. Standard trials could also include a treatment arm of older adults to measure efficacy and toxicity concurrently alongside the other trial arms.

At the workshop, FDA staff noted they are open to discussing alternative trial designs to obtain more information on older adults from industry trials. Additionally, they noted that in certain circumstances, results may lead to expanded indications on the labels. Increasing evidence collection in older adults is also supported by the NIH Inclusion Across the Lifespan Policy (40). The FDA and NCI should communicate these policies and positions to sponsors and encourage them to design trials that collect more information on older/frail adults.

Expand the Use of Real-World Data in Research on Older Adults

Real-world data (RWD) are data about patient health status and delivery of care that are collected at the point of care and are intended to document care received, record treatment outcomes, and justify billing. Real-world evidence (RWE) is derived from analyses of RWD and is intended to answer clinical questions about treatment outcomes for patients treated in routine clinical settings. The primary sources of RWD are electronic health records (EHRs), tumor registries, and claims data. Large oncology databases, such as ASCO's CancerLinQ and Flatiron, also hold RWD that can be used to generate RWE about the treatment of older adults with cancer. The action items in this section address the need to design RWD studies that complement trials in geriatric oncology and to incorporate GA items into EHRs.

Geriatric Oncology Researchers Should Work with ASCO, FDA, and Other Stakeholders to Develop a Framework for Using RWD in Clinical Research. As Part of This Process, Researchers Should Submit Demonstration Project Proposals to CancerLinQ and Other Databases to Establish the Benefits and Limitations of These Data Sources

While the amount of RWD continues to grow, methodology for using these data in research is still developing. The FDA was charged under the 21st Century Cures Act to develop a regulatory framework for using RWE to improve understanding of cancer therapeutics and is partnering with CancerLinQ, Flatiron Health, and other stakeholders to explore research uses of RWD (41,42). In contrast to the data from trials, RWD are more likely to include representative samples of older adults (43). They may also capture information about patterns of care and treatment responses in patients who are older, frail, and have comorbidities or previous cancers. Thus, RWE can address some of the limitations of evidence derived from trials by providing insight into treatment outcomes and side effects in patients not studied in trials. A recent multicenter study by Khozin and colleagues, for example, illustrated how RWD can be used to study treatment outcomes in more representative patient populations (44). However, there are limitations to RWD, including the lack of GA information that is critical to understanding both treatment choice and toxicity. Geriatric oncologists should be at the forefront of using RWD to conduct research regarding older adults to establish the benefits and limitations of these new data to inform treatment decisions.

Clinicians Should Incorporate GAs Into Clinical Care and Record This Information in EHRs, Payers Should Reimburse for This Time, and Quality Metrics Programs Should Assess Clinicians' Performance of GAs

Although EHRs are a rich repository of clinical information, the data available for research are limited to what is entered into the record. Because GA elements, such as cognition, functional independence, and social support are predictive of both morbidity and mortality in older adults with cancer, geriatric oncologists believe that assessing these elements is medically necessary to guide clinical decision-making for these patients (37). Although numerous reports have recommended GA be incorporated into routine cancer care for older adults, this is not standard practice, and there is no mechanism for oncologists to bill for the time and resources necessary to collect this information (35,36). The result is that GAs are not routinely conducted or recorded in EHRs and are not available for clinical decision-making or research. Ensuring that clinicians get reimbursed for this time and are assessed on their performance of GAs in quality metrics programs would facilitate making GAs a routine part of cancer care that is captured in EHRs. For example, ASCO could develop Quality Oncology Practice Initiative measures based on its recent guideline for assessing and managing vulnerabilities in older patients receiving chemotherapy (36).

Developers of Large EHR Databases Should Partner With EHR Vendors to Ensure GA Elements Can Be Entered Into EHRs as Standard Data Elements

Data elements captured in EHRs currently vary across vendors and oncology providers (43,45). To address this problem, developers of large EHR databases, such as CancerLinQ and Flatiron, should partner with EHR vendors to find ways to accommodate structured GA elements in EHRs. Because some GA elements can be collected as PROs, part of improving the quality of data available in EHRs may involve enabling patients to directly enter data into their EHRs.

Strengthen Collaboration Between Stakeholders to Develop Advocacy and Policy Solutions

The problems underlying the lack of evidence in geriatric oncology are complex, and change will require coordination from multiple stakeholders. Strategic use of advocacy is a powerful tool for advancing policy goals. This section presents action items for advocacy and policy, with the goal of increasing public awareness and building consensus on the solutions to the evidence gap.

The Geriatric Oncology Community Should Strengthen Its Advocacy Efforts to Be More Cohesive and Propose Specific Policy Solutions

Workshop discussion identified a common list of policy priorities for improving the evidence base in geriatric oncology, including requiring the age representation in clinical research to reflect the disease population, creating incentives for sponsors to conduct trials in older adults, promoting alternate research designs that focus on older adults, and incorporating GAs and other endpoints that are important to older adults into research studies. The strategies implemented by the pediatric oncology community to improve the evidence base in children, as described at the workshop, may provide a useful framework for organizing advocacy efforts in geriatric oncology. In their drive to expand drug development to pediatric patients, parents and families collaborated with oncologists to build consensus on the

solutions, lobby members of congress and their staff with new ideas, and increase public discussion and awareness of the problem and the reasons for proposed changes. Similarly, the geriatric oncology community should create an Older Adults Cause for Cancer to raise awareness regarding the need to improve evidence for geriatric oncology, highlight the negative consequences of the current situation, and promote strategies to collect evidence in this population. This might include forming partnerships to lobby congress and industry between ASCO, patient advocacy organizations, and other groups representing diseases predominantly occurring in older adults.

Geriatric Oncologists Should Discuss With Developers of Value Frameworks How the Definitions of "Value" Could be Updated to Consider the Representativeness of the Evidence to the Population With the Diseases

The US healthcare system has started moving away from traditional fee-for-service reimbursement towards value-based reimbursement (45). Value-based systems attempt to control the costs of healthcare by matching reimbursement to evidence-based care. ASCO and others have developed oncology-specific value frameworks to promote this evolution, which rely on evidence from trials to define value (45,46). However, existing value frameworks do not consider the representativeness of the study population to those with the disease. Thus, when older adults are not included in trials, the "value" of drugs for treating older adults (the majority of patients with cancer) cannot be determined. Developers of value frameworks should assess the representativeness of the evidence to the population with the diseases when determining value and should down-grade the level of evidence when the studies do not include an adequate sample of older patients. This may incentivize developers of new drugs to ensure that their treatments are tested in older adults and receive high value scores.

Conclusions

There have been promising steps to improving the evidence base for treating older adults with cancer. However, the evidence gap persists and continues to negatively affect the care of older patients. This manuscript presents four new action items to address this problem. Three items focus on improving the evidence base by increasing older adults' enrollment in trials, expanding the use of elderly-specific research studies and endpoints, and developing research uses for RWD. The fourth calls for developing new policies and using advocacy to promote change. Systemic barriers within the health care delivery system have been the primary obstacle to expanding geriatric oncology knowledge. The FDA-ASCO workshop raised awareness of the problem, and these new action items, alongside the previous ASCO, IOM, and U13 recommendations (2,3,12), outline the systemic, large-scale changes necessary for improving the evidence base for treating older adults with cancer and ensuring all patients with cancer receive high-quality, evidence-based care.

Notes

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The authors thank Kathryn Levit, science writer, who developed a written summary of the ASCO-FDA Workshop on Geriatric Oncology. They also thank everyone who participated in and attended the workshop. These individuals provided invaluable insights and comments, which led to the content and actions items described in this article. Finally, the authors thank Nicole Jenkins and Caroline Schenkel, ASCO staff, and Sonia C. Swayze and Dianne Spillman, FDA staff, for their contributions to the workshop panning and logistics. The opinions expressed in the article are those of the individual contributors and not necessarily those of ASCO or FDA.

Conflicts of Interest: Laura Levit, none; Harpreet Singh, none; Heidi D. Klepin, Unpaid scientific consultant Genentech, Contributor to Up-to-date; Arti Hurria, Consulting or Advisory Role: GTx, Boehringer Ingelheim, On Q Health, Sanofi, OptumHealth Care Solutions, Pierian Biosciences, MJH Healthcare Holdings, and Research Funding: GlaxoSmithKline, Celgene, Novartis.

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Geriatric Oncology

Promoting Accrual of Older Patients with Cancer to Clinical Trials: An Alliance for Clinical Trials in Oncology Member Survey (A171602)

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Older adults • Cancer • Clinical trials • Accrual

Abstract

Background. There are multiple known individual- and practice-level barriers to enrollment of older patients with cancer to clinical trials, but little is known about how the clinical research workforce feels about potential higher-level strategy changes aimed to promote increased enrollment of older patients.

Subjects, Materials, and Methods. We invited all 11,351 Alliance for Clinical Trials in Oncology ("Alliance") members to participate in an anonymous, web-based survey to examine awareness of current accrual patterns for older patients to clinical trials, to ascertain consensus on how to tackle enrollment challenges, and to provide the impetus for high-level changes to improve clinical trial accrual of older patients with cancer.

Results. During the period from February 28, 2017, to June 16, 2017, 1,146 Alliance members participated (response rate = 10%), including a national diverse sample of physicians, nurses, administrative/clinical research staff, and patient advocates with representation from community, academic, and rural sites. Overall, one third felt that >50% of clinical trial enrollees should be age ≥65, and 64.9% felt the Alliance could improve upon enrollment of older patients. The four most commonly ranked strategies to improve enrollment of older patients were creating more dedicated trials for this population (36.3%), minimizing exclusion criteria focused on comorbidity (35.5%), developing independent strategies for those aged ≥65 and for those aged ≥70 (33.2%), and requiring that most/all Alliance trials have a specific expansion cohort of older patients (30.0%).

Conclusion. We anticipate that the recommendations from >1,000 Alliance members will continue to propel important strategy changes aimed to improve accrual of older patients with cancer to clinical trials. ***The Oncologist*** 2018;23:1016–1023

Implications for Practice: This survey of the Alliance for Clinical Trials membership sought opinions on potential, large-scale, national strategies to improve accrual of older adults with cancer. Consensus was found around multiple strategies, including creating more dedicated trials for older patients, developing less stringent eligibility criteria, and mandating expansion cohorts of older patients within broader Alliance trials. It is anticipated that the recommendations from >1,000 Alliance members will continue to propel important strategy changes aimed to improve accrual of older patients with cancer to clinical trials.

Introduction

Cancer is a disease of aging, and the current median age at cancer diagnosis in the U.S. is 66 years, with 53.3% of all new cancer cases diagnosed in those aged ≥65 [1]. With an anticipated increase in U.S. life expectancy over time [2], there will be a concomitant increasing number of older adults who will develop cancer [3], yet accrual of older patients to cancer clinical trials remains challenging and stagnant [4, 5]. Approximately 25% of all trial participants for National Cancer Institute trials during 2000–2011 were aged ≥65 years, and 10% were aged ≥75 [4, 6].

Although older patients have been shown to enroll on research protocols as frequently as younger patients if a cancer clinical trial is offered [7], multiple individual- and practice-level barriers to accrual have been identified; these include comorbidity and toxicity concerns, physician/patient preferences, socioeconomic factors, access to care, concerns about losing continuity with primary oncologists, distance and time considerations, caregiver and transportation factors, and age itself [7–19]. Thus far, specific efforts to improve enrollment of under-represented subgroups with cancer to clinical trials have

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included educational interventions [20], improved processes for consenting [21–24], conferences and policy statements to promote change [4, 25–28], and the development of trials dedicated to older adults [29–31]. None of these strategies, however, has had a major impact on accrual of older patients. In addition, previous studies have examined the impact of doctor communication skills training [32], oncology nurse navigation [33], and improved tracking systems [34] with mixed success.

Although multiple studies have described potential barriers to accrual of patients in practice, there are limited data on how providers feel about potential strategies to effect change in accrual. In one relevant survey of 156 oncologists from 10 high-accruing cancer centers within the Cancer and Leukemia Group B (CALGB) [8], providers were asked about barriers to accrual of older patients with breast cancer in practice, how they would rank their importance, and their opinions about seven possible interventions to improve accrual, including education of staff and patients and personnel issues. In this survey, 25% of providers endorsed making personnel available in the clinic to explain clinical trials to elderly breast cancer patients and their families as the most important intervention. Additionally, 13% felt that providing patients with better educational materials concerning clinical trials was most important, and 14% felt that providing transportation was most important [8]. Although this survey was informative on a provider and practice level, it only surveyed physicians and did not provide clear direction regarding what larger-scale intervention changes might facilitate accrual of elderly patients. In addition, none of the above-mentioned intervention studies has led to clear improvements in accrual or policy changes around accrual of older adults to clinical trials.

In this study, to gain perspective on potential changes in strategies that would effect change in accrual for older patients with cancer, we conducted a web-based survey of the entire Alliance for Clinical Trials in Oncology ("Alliance") membership, including physicians, nurses, patient advocates, project managers, statisticians, leadership, and administrative staff. CALGB is now part of the Alliance for Clinical Trials in Oncology, a network group in the NIH National Clinical Trials Network. Our goal was to further propel implementation of new strategies by eliciting the opinions of a national sample of the oncology clinical research workforce and patient advocates who participate in high-impact cancer clinical research.

Subjects, Materials, and Methods

Survey Content

Through our survey, we aimed to assess the awareness of the current accrual of older patients with cancer to clinical trials, to ascertain whether there is consensus on how to tackle enrollment challenges on a national level, and to provide an impetus to apply new, large-scale strategy changes to improve clinical trial accrual of older patients within the National Clinical Trials Network. We developed a 26-question survey (full survey provided in supplemental online data) after obtaining input on questions from the Alliance Cancer in the Elderly Committee. The survey asked participants to report their opinions on the current state of accrual of older patients with cancer to clinical trials in the Alliance, at what age(s) they consider a person to be "elderly," and whether they think we can impact accrual of older patients within the Alliance, as well as demographics about their practice setting, gender, what Alliance committee(s) they participate in, their professional position, and years in practice (when relevant). We also asked about individual- and practice-level barriers to enrolling older patients in clinical practice, and we asked participants to rank up to four of these barriers, with number 1 identifying the most common/important barrier to accrual. Similarly, we asked participants to select and rank up to four large-scale interventions that they felt would promote enrollment of older patients with cancer. At the end of the survey, participants were asked if they would like to enter a drawing for a chance to win a $100 Amazon gift card as a token of their appreciation. Five of these gift cards were distributed randomly to survey participants. The survey was delivered in a web-based link using Qualtrics (www.qualtrics.com), allowing for sophisticated survey design and analysis. Because of the nature of our study, we received exemption from review by the Dana-Farber Cancer Institute Office for Human Research Studies.

Survey Administration

We invited all rostered Alliance members to participate in this survey using a blast e-mail invitation sent centrally from the Alliance Central Protocol Operations Office in Chicago, IL. This e-mail was sent four times, asking members to complete a brief online, one-time, anonymous, and confidential survey. We provided a direct link to the survey in the invitation with the ability to complete it on a computer or a mobile device. The initial e-mail invitation was sent twice to 11,351 members on February 28, 2017, with e-mail reminders sent on March 9, 2017, and March 16, 2017. We also provided a one-page paper survey invitation/reminder with the registration materials at the in-person Alliance meeting in Chicago, IL, in May 2017. All answers were automatically tabulated by the Qualtrics program software and aggregated for analyses; analyses were conducted by the Alliance Statistics and Data Center.

Statistical Analysis

Responses for the questions and demographics were analyzed descriptively. Due to the high frequency and variety of Alliance member type and disease specialty, we collapsed some of these categories for ease of analyses (see Table 1 for how these were defined). We compared the frequencies of responses by demographic factors (supplemental online Table 1) for the following questions using a chi-square test or Fisher's exact test: (a) At what age do you consider a patient to be "elderly"? (select all that apply). (b) What do you think should be the "right" or appropriate proportion of trial enrollees who are age 65 or older? (c) Do you think accrual of older patients to clinical trials in the Alliance is something we need to improve upon? (d) Do you feel that the geriatric assessment should be incorporated into all Alliance trials?

The frequencies of rankings for the perceived barriers to accrual in practice and the potential strategies for improved accrual of older adults were summarized and differences in rankings were also compared by demographic factors utilizing a chi-square test or Fisher's exact test (supplemental online Table 1). Demographic factors used for these analyses included the following: gender (male vs. female), participant role within the Alliance (clinician vs. nonclinician), age group ($\leq$50 vs. $>$50 years of age), years of clinical/research experience ($\leq$10 vs. $>$10 years of experience), and practice/research setting (rural vs. suburban vs. urban).

Table 1. Participant demographics ($n = 1,146$)

Characteristic	*n* (%)[a]
Gender	
Female	772 (67.4)
Male	198 (17.3)
Other	1 (0.0)
Not reported	175 (15.3)
Age, years	
<30	108 (9.4)
30–40	233 (20.3)
41–50	227 (19.8)
51–60	269 (23.5)
61–70	123 (12.7)
>70	11 (10.7)
Not reported	175 (15.3)
Practice/research setting	
Rural	142 (12.4)
Suburban	243 (21.2)
Urban	481 (42.0)
Not reported	214 (18.7)
Not applicable	46 (4.0)
Other and/or combined settings	20 (1.7)
Years in practice/research	
<5	273 (23.8)
5–10	197 (17.2)
11–15	127 (11.1)
>15	299 (26.1)
Not applicable	36 (3.1)
Not reported	214 (18.7)
Committee(s) served on within Alliance[a,b]	
Executive	15 (1.3)
Administrative	89 (7.8)
Translational	19 (1.7)
Disease	211 (18.4)
American College of Surgeons Clinical Research Staff	44 (3.8)
Cancer Control	146 (12.7)
Modality	240 (20.9)
Patient	4 (0.4)
Other	6 (0.5)
Committee not specified	581 (50.7)
Role(s) in the Alliance[a]	
Administrator	52 (4.5)
Basic research scientist	5 (0.4)
Clinical research professional/assistant	341 (29.8)
Clinical researcher	157 (13.7)
Data manager	129 (11.3)
Government representative	0 (0)
IT/Systems management support staff	3 (0.3)
Medical oncologist	132 (11.5)
Nurse or nurse practitioner	224 (19.6)
Office support staff	30 (2.6)
Pathologist	1 (0.1)
Patient or patient advocate	16 (1.4)
Pharmacist	8 (0.7)
Pharmaceutical representative	0 (0)
Physician assistant	2 (0.2)
Project manager	31 (2.7)
Protocol support staff	52 (4.5)
Radiation oncologist	22 (1.9)
Radiologist	1 (0.1)
Statistician (Ph.D., M.S., S.P.A.)	15 (1.3)
Surgeon	49 (4.3)
Other	43 (3.8)
Membership type not specified	207 (18.1)
Disease/System of expertise[a]	
Breast	567 (49.5)
Hematologic malignancies	371 (32.4)
Gastrointestinal	451 (39.4)
Genitourinary	349 (30.5)
Geriatric oncology	150 (13.1)
Gynecologic malignancy	247 (21.6)
Head and neck	348 (30.4)
Lung	430 (37.5)
Lymphoma	346 (30.2)
Melanoma and other skin cancers	291 (25.4)
Multiple myeloma	319 (27.8)
Neuro-oncology	232 (20.2)
Sarcoma and bone	181 (15.8)
I am a patient	8 (0.7)
Other	5 (0.4)
No disease/system specified	288 (25.1)
Work setting[a]	
Private practice (office or hospital-based)	321 (28.0)
Staff Model HMO	16 (1.4)
Academic medical center/university	481 (42.0)
Government agency	14 (1.2)
Pharmaceutical/biotech industry	2 (0.2)
Administration	38 (3.3)
Training program (i.e., student, resident, fellow, etc.)	14 (1.2)
Lab research	5 (0.4)
Community practice	44 (3.8)
Hospital-based practice	22 (1.9)
Clinical research	15 (1.3)
Not applicable (I am a patient or nonclinical researcher, etc.)	19 (1.7)
Other	6 (0.5)
No work setting specified	223 (19.5)

[a]Percentages are provided out of the total number of respondents ($n = 1,146$) and do not add to 100% as respondents could choose multiple categories.

[b]Alliance committees were categorized as the following: Executive = Alliance Executive, Board of Directors; Administrative = Audit, Conflict of Interest, Constitution and Bylaws, Data and Safety Monitoring Board, Ethics, Institutional Performance Evaluation, Membership, Pharmacy, Publications, Young Investigators, Clinical Trials Office, Administration/Safety, Not applicable/Support staff, Data manager, Regulatory, Forms Consistency Working Group; Translational = Biorepository, Imaging, Karyotype Review, Leukemia Correlative Sciences, Pathology, Pharmacogenomics and Population Pharmacology, Sequencing, Translational Research Executive; Disease = Breast, Gastrointestinal, Genitourinary, Leukemia, Lymphoma, Myeloma, Neuro-oncology, Respiratory, Melanoma, Sarcoma; American College of Surgeons Clinical Research Staff = Cancer Care Delivery Research, Cancer Care Standards Development, Dissemination and Implementation, Education; Cancer Control = Cancer in the Elderly, Community Oncology, Health Disparities, Health Outcomes, Prevention, Symptom Intervention; Modality = Clinical Research Professionals, Oncology Nursing, Transplant, Radiation Oncology, Experimental Therapeutics; Patient = patient, patient advocate (may still identify on a committee); Other = could not be categorized; Committee not specified = none provided.

Table 2. Opinions on current state of accrual for older patients with cancer ($n = 1,146$)

Question	*n* (%)[a]
As best as you can estimate, what percentage of all patients with cancer in the U.S. are age ≥65?	
<25%	32 (2.8)
25%–50%	198 (17.3)
51%–75%	664 (57.9)
>75%	138 (12.0)
I can't estimate, I don't know	69 (6.0)
Not answered	45 (3.9)
At what age do you consider a patient to be "elderly"?[a]	
60 and older	43 (3.8)
65 and older	179 (15.6)
70 and older	308 (26.9)
75 and older	254 (22.2)
80 and older	146 (12.7)
85 and older	50 (4.4)
I do not have a preferred cutoff	74 (6.5)
Poor functional status, regardless of age	298 (26.0)
Other	6 (0.5)
I don't know	10 (0.9)
Not answered	78 (6.8)
As best as you can, please estimate the percent of Alliance clinical trial enrollees (across disease sites, and over the last decade) who are age ≥65	
<25%	347 (30.3)
25%–50%	325 (28.4)
51%–75%	224 (19.5)
>75%	41 (3.6)
I can't estimate, I don't know	144 (12.6)
Not answered	65 (5.7)
Can you approximate what percentage of your own patients age ≥65 are treated on a clinical trial?	
<25%	411 (35.9)
25%–50%	209 (18.2)
51%–75%	112 (9.8)
>75%	22 (1.9)
I don't know	30 (2.6)
Not applicable, I don't enroll patients to clinical trials	264 (23.0)
Not answered	98 (8.6)
What do you think should be the "right" or appropriate proportion of trial enrollees who are age ≥65?	
<25%	37 (3.2)
25%–50%	323 (28.2)
51%–75%	325 (28.4)
>75%	56 (4.9)
I don't think there is a target number	265 (23.1)
Other	33 (2.9)
Do you think accrual of older patients to clinical trials in the Alliance is something we need to improve upon?	
Yes	600 (52.4)
No	70 (6.1)
Not sure	367 (32.0)
Not answered	109 (9.5)
Do you think the Alliance has the ability to improve upon the numbers of older patients enrolled to its clinical trials?	
Yes	744 (64.9)
No	25 (2.2)
Not sure	267 (23.3)
Not answered	110 (9.6)
Do you think the Alliance has the ability to impact the accrual of older patients enrolled even beyond the Alliance?	
Yes	607 (53.0)
No	59 (5.1)
Not sure	369 (32.2)
Not answered	111 (9.7)
Do you feel that the geriatric assessment should be incorporated into all Alliance trials?	
Yes	210 (18.3)
Maybe some but not all trials	596 (52.0)
No	29 (2.5)
Not sure	53 (4.6)
I don't know what the geriatric assessment is	127 (11.1)
Other opinion	17 (1.5)
Not answered	114 (9.9)

[a]Percentages may not add up to 100% for some categories, when multiple responses were allowed.

Results

Survey Participants (Table 1)

Among the 11,351 Alliance members initially contacted, 1,146 participated in the survey (response rate = 10%) during the period from February 28, 2017, to June 16, 2017. Respondents (Table 1) were mostly female (67.4%); 29.7% were aged ≤40 years, and 23.4% were aged ≥61. Overall, 42.0% reported practicing in an urban setting and 12.4% in a rural setting, with 17.2% and 26.1% of all participants reporting being in practice or research for 5–10 years and >15 years, respectively. Overall, 581 participants did not report that they served on a specific committee within the Alliance, and there were many who reported membership on multiple committees. With regard to their roles, the most common responses were the following: 29.8% were clinical research professionals, 19.6% were nurses or nurse practitioners, 13.7% were clinical researchers, and 11.5% were medical oncologists (overlap of responses allowed). Most worked in academic (42.0%) or private practice (28.0%) settings, and the most commonly reported disease areas of expertise included breast (49.5%), gastrointestinal (39.4%), lung (37.5%), and hematologic malignancies (32.4%).

Table 3. Barriers to accrual of older patients to clinical trials in practice in order of frequency ranked

Barrier	Frequency ranked (%)	Rankings (n, %)[a,b]
Older patients often don't meet eligibility of clinical trials due to comorbidities, tumor characteristics, etc.	773 (67.5)	1 = 397 (51.4); 2 = 165 (21.3); 3 = 134 (17.3) 4 = 77 (10.0)
Regimens are too toxic for older patients	509 (44.4)	1 = 129 (25.3); 2 = 195 (38.3); 3 = 119 (23.4); 4 = 66 (13.0)
Long distance to treating center, transportation issues, time considerations	506 (44.2)	1 = 116 (22.9); 2 = 142 (28.1); 3 = 148 (29.3); 4 = 100 (19.8)
Patient and/or family preferences to not enroll on clinical trials	405 (35.3)	1 = 88 (21.7); 2 = 91 (22.5); 3 = 126 (31.1); 4 = 100 (24.7)
Concern for limited life expectancy in older patients	320 (27.9)	1 = 69 (21.6); 2 = 105 (32.8); 3 = 93 (29.1); 4 = 53 (16.6)
Lack of trials relevant for older patients	286 (25.0)	1 = 60 (21.0); 2 = 82 (28.7); 3 = 70 (24.5); 4 = 74 (25.9)
Lack of patient/family education about clinical trials	281 (24.5)	1 = 63 (22.4); 2 = 66 (23.5); 3 = 81 (28.8); 4 = 71 (25.3)
Insurance issues with covering clinical trials	206 (18.0)	1 = 37 (18.0); 2 = 58 (28.2); 3 = 61 (29.6); 4 = 50 (24.3)
Lack of prioritization by the practice	59 (5.2)	1 = 9 (15.3); 2 = 16 (27.1); 3 = 17 (28.8); 4 = 17 (28.8)
Lack of institutional or clinic commitment to enroll patients	59 (5.2)/1,146	1 = 11 (18.6); 2 = 18 (30.5); 3 = 13 (22.0); 4 = 17 (28.8)
Not enough personnel or staff to help older patients enroll	54 (4.7)	1 = 12 (22.2); 2 = 11 (20.4); 3 = 14 (25.9); 4 = 17 (31.5)
Limited resources at my clinical site	51 (4.5)	1 = 8 (15.7); 2 = 10 (19.6); 3 = 10 (19.6); 4 = 23 (45.1)

[a]Percentages here are based out of the number who ranked this choice, not out of the total respondents.
[b]Rankings are from 1 = most common/important to 4 = least common/important.

Current State of Clinical Trial Accrual for Older Patients with Cancer (Table 2)

Participants acknowledged that most cancers occur in older patients, with 57.9% responding correctly that 51%–75% of U.S. cancer diagnoses occur in individuals age 65 and older. There was variability in responses for the age cutoffs for when participants consider a patient to be "elderly" (categories were not mutually exclusive), with 179 (15.6%) and 308 (26.9%) participants reporting that this should include patients age $\geq$65 and $\geq$70 and older, respectively. In addition, 298 (26.0%) felt that "elderly" should be defined by functional age rather than chronological age. Approximately 35.9% of participants reported that $<$25% of their own patients ages $\geq$65 participate in cancer clinical trials, whereas 1.9% reported that $>$75% of their older patients participate; 28.4% felt that 51%–75% of cancer clinical trials enrollees should be age $\geq$65. Overall, 64.9% felt that accrual of older patients to cancer clinical trials in the Alliance is something we can improve upon, and 18.3% felt that the geriatric assessment [35] should be included in all Alliance trials. However, 11.1% of respondents reported that they did not know what a geriatric assessment is.

Barriers to Accrual (Table 3)

The most commonly reported barriers to accrual of older patients in practice included "older patients often don't meet eligibly requirements due to comorbidities or tumor characteristics" (n = 773 [67.5%], with 397 ranking this as the number 1 barrier); "regimens are too toxic for older patients" (n = 509 [44.4%], with 129 ranking this as the number 1 barrier); "long distance to treating center, transportation issues, time considerations" (n = 506 [44.2%], with 116 participants ranking this as the number 1 barrier); and "patient and/or family preferences to not enroll on clinical trials" (n = 405 [35.3%], with 88 ranking this as the number 1 barrier).

In a separate question, we asked participants to expand on barriers in their practice and within the Alliance beyond the options provided, and we received 158 written-in responses (data not shown). Recurrent themes from these responses include the following concerns/suggestions: cost and insurance, exclusions with regard to past history of cancer and other medical conditions, complex and lengthy protocol consents, the intensity of schedules and visits, education gaps for patients and their families, fear or anxiety related to clinical trials, discrimination within the health care system, the feeling that trials are not publicized enough and should be offered in partnership with relevant organizations such as the American Association of Retired Persons to increase publicity of trials, and the need for more supportive care trials and trials aimed at quality of life and function.

Strategies to Improve Older Patient Accrual (Table 4)

The most commonly ranked strategies for improvement of enrollment of older patients included the following: "create more dedicated trials for older patients" (n = 416 [36.3%], with 173 ranking it as the number 1 strategy); "minimize exclusion criteria focused on comorbidities in clinical trials" (n = 407 [35.5%], with 189 ranking it as the number 1 strategy); "consider distinct strategies to increase enrollment for those aged 65 and older and 70 and older" (n = 380 [33.2%], with 79 ranking it as number 1); and "require that most/all Alliance trials have a specific 'expansion cohort' of older patients, with embedded statistics for outcomes/toxicity/quality of life for older patients" (n = 344 [30.0%], with 97 ranking it as number 1).

Table 4. Strategies to improve older patient accrual in order of frequency ranked

Strategy	Frequency ranked (%)	Rankings (n, %)[a,b]
Create more dedicated trials for older patients	416 (36.3)	1 = 173 (41.6); 2 = 139 (33.4); 3 = 66 (15.9); 4 = 38 (9.1)
Minimize exclusion criteria focused on comorbidities in clinical trials	407 (35.5)	1 = 189 (46.4); 2 = 79 (19.4); 3 = 78 (19.2); 4 = 61 (15.0)
Consider distinct strategies to increase enrollment for those aged 65 and older and 70 and older	380 (33.2)	1 = 79 (20.8); 2 = 112 (29.5); 3 = 106 (27.9); 4 = 83 (21.8)
Require that most/all Alliance trials have a specific "expansion cohort" of older patients, with embedded statistics for outcomes/toxicity/quality of life for older patients	344 (30.0)	1 = 97 (28.2); 2 = 113 (32.9); 3 = 84 (24.4); 4 = 50 (14.5)
Create a standardized educational intervention for the family members/caregivers of older patients treated at Alliance sites	256 (22.3)	1 = 41 (16.0); 2 = 69 (27.0); 3 = 83 (32.4); 4 = 63 (24.6)
Provide extra "credits" to sites when they enroll an older patient to any clinical trial	252 (22.0)	1 = 63 (25.0); 2 = 77 (30.6); 3 = 60 (23.8); 4 = 52 (20.6)
Create a standardized educational intervention for older patients at Alliance sites	235 (20.5)	1 = 57 (24.3); 2 = 66 (28.1); 3 = 71 (30.2); 4 = 41 (17.5)
Ensure inclusion of academic/community sites who treat high proportions of older patients in the Alliance	205 (17.9)	1 = 36 (17.6); 2 = 54 (26.3); 3 = 58 (28.3); 4 = 57 (27.8)
Require sites to capture why a patient declines enrollment	195 (17.0)	1 = 61 (31.3); 2 = 44 (22.6); 3 = 44 (22.6); 4 = 46 (23.6)
Create a standardized educational intervention for community and academic providers within the Alliance	157 (13.7)	1 = 30 (19.1); 2 = 43 (27.4); 3 = 44 (28.0); 4 = 40 (25.5)
Require that all clinical trial concepts be discussed and approved by the Cancer and Elderly Committee as part of the approval process	151 (13.2)	1 = 76 (50.3); 2 = 32 (21.2); 3 = 29 (19.2); 4 = 14 (9.3)
Require sites to screen (and record) all older patients they see with cancer, who is approached for studies, and if they decline/accept enrollment	128 (11.2)	1 = 21 (16.4); 2 = 40 (31.3); 3 = 35 (27.3); 4 = 32 (25.0)
Require that most/all trials have a specific target number of older patients for enrollment	116 (10.1)	1 = 27 (23.3); 2 = 28 (24.1); 3 = 40 (34.5); 4 = 21 (18.1)
I have other ideas, or I don't like these options	48 (4.2)	1 = 21 (43.8); 2 = 12 (25.0); 3 = 3 (6.3); 4 = 12 (25.0)

[a]Percentages here are based out of the number who ranked this choice, not out of the total respondents.
[b]Rankings are from 1 = most promising to 4 = least promising.

Associations of Responses with Participant Demographics (Supplemental Online Table 1)

Regarding responses by participants' gender, we observed significant differences in the responses for the appropriate percentage of clinical trial enrollees who should be aged ≥65 ($p = .015$; e.g., 27.2% of women vs. 16.2% of men felt there was no target proportion of older patients who should enroll). In addition, most men (68.2%) and women (56.5%) responded that we need to improve upon accrual of older patients. Men more frequently (23.2% vs. 19.8% in women) responded that the geriatric assessment should be included in all clinical trials, although it is of note that <25% of either gender responded this way. Differences between men and women for reported barriers to clinical trial enrollment in practice included "not enough trials relevant for older patients" (38.4% of men vs. 26.3% of women, $p = .0008$) and "not enough personnel to help patients enroll" (10.1% of men vs. 4.3% of women, $p = .001$; data not shown). There were no gender differences in opinions on strategies to improve accrual except the suggestion of providing extra credits to sites when they enroll older patients (37.4% of men vs. 23.1% of women, $p < .0001$; data not shown).

With regard to clinicians versus nonclinicians, clinicians more frequently responded that we need to improve upon accrual of older patients (73.0% vs. 48.9%, $p < .0001$) and were more likely to respond that we should include geriatric assessment in all trials (23.5% vs. 18.2%, $p = .026$). Nonclinicians more frequently reported that "elderly" are those aged ≥65 and less frequently stated that "elderly" is determined by poor functional status. There were also significant differences in preferred strategies to improve accrual, with 48.3% of clinicians selecting the option to "create more dedicated trials for older patients" versus 39.2% of nonclinicians ($p = .005$). Additional findings for differences in responses by participants' age, years of experience, and practice setting are summarized in supplemental online Table 1.

Discussion

In this study of 1,146 participants representing a national and diverse sample of clinical researchers, including providers, nurses, scientists, patient advocates, clinical and administrative support staff, and leadership who treat multiple cancers in a wide array of practice settings, we observed that most felt that the Alliance has the power to effect change with regard to

clinical trial enrollment of older patients with cancer and agreed that older patients should be enrolled on cancer trials more frequently. Similar to what has been suggested in prior calls to action [26], participants felt that the ideal large-scale strategies to improve accrual include a specific focus on this older cancer population: creating more dedicated trials for older patients, relaxing eligibility criteria so that older patients are not excluded from trials as frequently (reported as the limiting barrier to accrual in practice for over two thirds of survey participants), and recommending that clinical trials include expansion cohorts to specifically accrue older patients. Providing a standardized education tool for patients and family members/caregivers was also appealing for many survey participants. Participants also differed in their opinions based on demographic characteristics, with some differences noted by gender, position/role, age, and years of experience.

Our survey addressed important knowledge gaps and is the first-of-its-kind in its execution of a "needs assessment" for high-level strategies by those in the trenches of clinical research, protocol design, and patient care. Although Kornblith and colleagues asked providers about their preferences for potential interventions within their own breast cancer clinical setting [8], to our knowledge, no prior study has examined the opinions of all Alliance members, including patient advocates and nonclinicians, about potential structured high-level changes that could more globally promote enrollment of older patients with cancer to clinical trials across multiple disease sites. Through this survey, we harnessed the opinions of over 1,000 Alliance leaders, patient advocates, statisticians, clinicians, and clinical trials support staff providing a wealth of information on how the Alliance can effect change, further reinforcing ongoing initiatives and prior pleas for action [4, 36]. For example, the American Society of Clinical Oncology (ASCO) assembled a working group [27, 28] to address the issues surrounding stringent eligibility criteria for older patients, and we anticipate that their recommendations to relax criteria for organ dysfunction in particular will be widely adopted, disseminated, and implemented across the National Clinical Trials Network. Further, the U.S. Food and Drug Administration and ASCO recently led a Geriatric Oncology Workshop focused on these issues, which we hope will move the needle on accrual issues for older adults with cancer.

Aside from the efforts to relax eligibility described above and despite multiple calls to action to improve the evidence base for older patients with cancer [4, 5, 17, 25, 26, 37], little has been accomplished on a policy level to effect change. As a next step, a multipronged strategy will be required if we want to make increased accrual a reality for older patients with cancer on a national level. This will include earnest cooperation, commitment, and prioritization from funding agencies, industry, the U.S. Food and Drug Administration, the National Cancer Institute, the National Clinical Trials Network, and clinical and research leadership, particularly because of the high anticipated costs of implementing large-scale strategies to improve accrual. Our survey results promote the implementation of a more standardized process for protocol development by which each clinical trial undergoes a specific review by a geriatric-focused committee, including relevant statisticians. With this, eligibility criteria can be scrutinized to promote optimal inclusion of older patients with cancer and endpoints can be assured to be relevant to older adults. In addition, recommendations can be made to create an expansion cohort of older patients if a cancer treatment is found to be efficacious with broad implementation expected. Creating more education tools for this patient population and their caregivers is also warranted based on our results.

We acknowledge study limitations. First, although we obtained responses from a large sample of participants, we recognize that our member response rate was only 10% and that some subgroups were small and had potential for nonresponse bias. Because the survey was anonymous, we could not compare the demographics of those who participated to those who did not. However, participants came from a wide array of research backgrounds, ages, practice sites, and positions, all strengthening our findings and providing important data for clinical trial leadership and policy makers in the U.S. Further, we surveyed Alliance members only, although we had representation and inclusion of both academic and community sites as well as rural and urban centers. It is reassuring that the opinions of Alliance membership mirror those of the current national conversations to improve accrual of older patients.

Conclusion

The results from our survey of national stakeholders should catalyze change, with concrete strategies provided by the Alliance membership that can, we hope, translate into significant improvements in the evidence base for treatments of this growing subgroup of patients who are in urgent need of level I evidence to inform their care.

Acknowledgments

We thank all the study participants as well as Jamilah Owens and the Alliance for Clinical Trials Central Protocol Operations Office for their assistance with survey administration. We also thank the Alliance Cancer in the Elderly Committee for their assistance in survey development and for their support for this study. This study was supported by the National Cancer Institute of the National Institutes of Health under the Award Number UG1CA189823 (Alliance for Clinical Trials in Oncology NCORP Grant). R.A.F. is supported by the American Cancer Society (125912-MRSG-14-240-01-CPPB) and Susan G. Komen (CCR CCR14298143).

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Disclosures

Arti Hurria: Pierian Biosciences, MJH Healthcare Holdings, LLC, Boehringer Ingelheim Pharmaceuticals (C/A), Celgene, Novartis (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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

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

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DISCLOSURES: This work was supported by the National Institute on Aging (NIA R03AG064377), the National Cancer Institute (NCI K12CA001727), the Waisman Innovation Fund, and Circle 1500. Mina S. Sedrak reports grants from Seattle Genetics, Eli Lilly, Novartis, and Pfizer Foundation, outside the submitted work. Tanya M. Wildes reports research funding from Janssen and personal fees from Carevive Systems and Seattle Genetics, outside the submitted work. Gretchen G. Kimmick reports personal fees and nonfinancial support from Eisai, Boehringer Ingelheim, and Genomic Health; personal fees from Agendia; nonfinancial support from Seattle Genetics, Novartis, and Pfizer; and grants from Bionovo, PUMA, and Roche, outside the submitted work. All remaining authors report no conflicts of interest.

The funders had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; preparation, review, or approval of the article; or the decision to submit the article for publication.

doi: 10.3322/caac.21638. Available online at cacancerjournal.com

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.**

Keywords: clinical trials, older adults, oncology, patient participation, patient selection, practice patterns

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

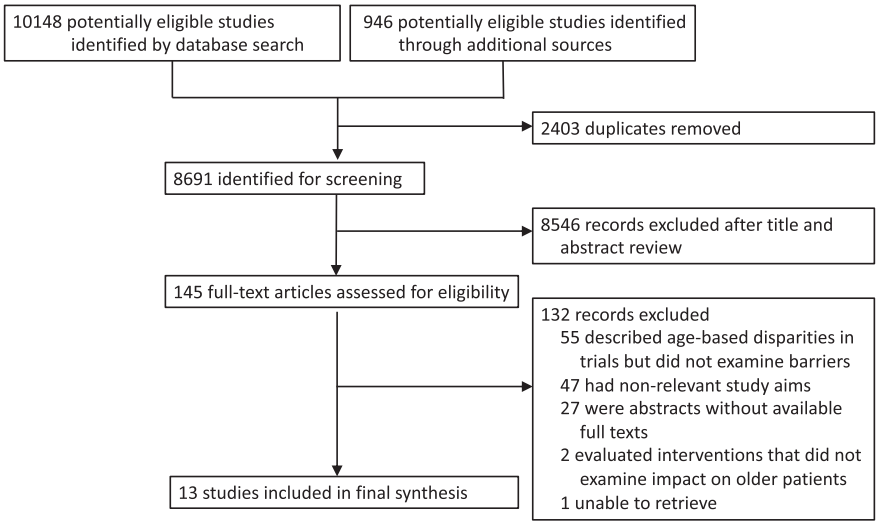

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

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. ■

Acknowledgments: We dedicate this work in honor of Dr. Arti Hurria, founder of the Cancer and Aging Research Group, who tragically died before the drafting of this article. Arti's dream was to improve outcomes for older adults—the current study exemplifies her vision, and we believe these results will bring us one step closer to realizing her dream and will positively impact future efforts to address the evidence gap in geriatric oncology. We also acknowledge Ms. Joy Eskander and Ms. Noel Vargas for their assistance with the data analysis and Dr. Kerin K. Higa for editorial assistance.

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Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3852

Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO–Friends of Cancer Research Joint Research Statement

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ABSTRACT

Purpose: Restrictive clinical trial eligibility criteria (EC) limit the number of patients who can enroll and potentially benefit from protocol-driven, investigational treatment plans and reduce the generalizability of trial results to the broader population. Following publication of expert stakeholder recommendations for broadening EC in 2017, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) convened working groups to produce additional recommendations and analyze the potential impact on clinical trials using real-world data.

Experimental Design: Multistakeholder working groups were appointed by an ASCO-*Friends* leadership group to propose recommendations for more inclusive EC related to: washout periods, concomitant medications, prior therapies, laboratory reference ranges and test intervals, and performance status.

Results: The four working groups, ASCO Board of Directors, and *Friends* leadership support the recommendations included in this statement to modernize EC related to washout periods, concomitant medications, prior therapies, laboratory references ranges and test intervals, and performance status to make trial populations more inclusive and representative of cancer patient populations.

Conclusions: Implementation of the recommendations is intended to result in greater ease of determining patient eligibility. Increased opportunities for patient participation in research will help address longstanding underrepresentation of certain groups in clinical trials and produce evidence that is more informative for a broader patient population. More patients eligible will also likely speed clinical trial accrual.

Introduction

Accelerating advances in cancer treatment requires efficient clinical trials that produce clinically meaningful outcomes and generalizable knowledge. Clinical trials are not possible without patients, whose eligibility to participate is determined by inclusion and exclusion criteria. Trial eligibility criteria (EC) are designed to protect participant safety and define an appropriate study population. Following approval, patient safety may be compromised if a trial generates insufficient evidence to inform care for specific patient groups, for example, those underrepresented among trial participants. Furthermore, restrictive EC limit clinical treatment options for patients who weigh the potential risks, benefits, and alternatives of a protocol-driven investigational treatment plan and opt to participate in studies.

Exclusion of certain patient populations or disease characteristics is common in oncology clinical trials and is often not founded on current evidence-based scientific justification. This leads to underrepresentation of older adults (1), racial/ethnic (2–4) and sexual/gender minorities (5–7), and patients with well-managed comorbidities (8). An estimated 17%–21% of patients are not able to enroll on clinical trials due to restrictive EC, among other reasons (9, 10). In the era of biomarker-driven therapies where the pool of potential study participants may be very low due to low biomarker prevalence, the negative impact of excessively restrictive EC is magnified (11).

The desire to mitigate safety concerns and ensure trial integrity is paramount, but EC are often replicated from earlier trials and may date back to concerns about cytotoxic chemotherapy. A 2017 review by the FDA concluded that clinical trial EC can be expanded without compromising patient safety (12). To ensure that only criteria relevant to safety concerns about the specific agent are included and extraneous EC are excluded, scientific rationale should be included to justify any exclusion criteria.

ASCO-*Friends* Eligibility Criteria Initiative

Eliminating overly restrictive EC is a priority for the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*), as well as many other patient groups (such as the American Cancer Society Cancer Action Network), researchers, sponsors, regulators, and the National Academy of Medicine (9, 13–18). Enacting

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Clin Cancer Res 2021;XX:XX–XX

doi: 10.1158/1078-0432.CCR-20-3852

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3852

Translational Relevance

Cancer clinical trials are critical for developing safety and efficacy evidence to advance cancer care. Narrow clinical trial eligibility criteria can compromise the relevance of results to the broader population of patients with the disease. Studies should employ the principles of distributive justice to help ensure appropriate inclusion of underrepresented groups in research, where safety permits. Equitable access to research will also help ensure external validity of results. ASCO and Friends of Cancer Research worked with stakeholders throughout the cancer research community to develop evidence-based, consensus recommendations that are focused on expanding eligibility criteria to make trial populations more reflective of the general cancer population. Implementation of the recommendations is intended to result in greater efficiency of trial conduct and quicker clinical trial accrual, and will provide increased opportunities for patient participation and more informative evidence to guide appropriate uses of new therapies.

changes will optimize trial enrollment and ensure that benefits to patients and the broader scientific community are maximized. In addition, broadening EC is desirable to improve accrual and prevent trial delays and failures, which are a significant strain on human and financial resources during development of new therapies (19–21).

Through this work, ASCO and *Friends* propose a new cancer clinical trial paradigm, in which:

(i) Patients are eligible for a trial by default and excluded only when there is scientific rationale and/or evidence demonstrating that enrollment would compromise the patient's safety.
(ii) In all cases, protocol development begins with informed consent as the only eligibility criteria. Any inclusion/exclusion criteria are tailored to the scientific objectives of the study, based on the investigational treatment and study population, and address only substantiated participant risks.
(iii) Trial participants more closely resemble the population intended to receive the therapy and no group is excluded without scientific justification based on current evidence.

ASCO, *Friends*, and FDA first formed a collaboration to address overly restrictive cancer clinical trial EC in 2016, which led to publication of recommendations for more inclusive EC for brain metastases, minimum age for enrollment, human immunodeficiency virus (HIV) status, organ dysfunction, and prior or concurrent malignancies (13–17).

In 2019, project leadership consulted with stakeholder experts, including ASCO's Cancer Research and Health Equity Committees, to select additional categories of common EC that pose significant barriers to clinical trial enrollment. These topics were selected with an eye for how many patients they impact and how they affect special populations, as well as their potential impact on evaluation of safety and efficacy if relaxed.

Representatives from academic and community research sites, regulatory agencies (FDA and NCI), patient advocacy groups, NCI Network Groups, and the pharma-biotech industry were invited to join the project work groups. The work groups finalized their consensus recommendations after convening with additional patient and industry representatives to discuss their draft recommendations. ASCO and *Friends* herein recommend broadening approaches to clinical trial enrollment related to the following five EC:

(i) Washout periods
(ii) Concomitant medications
(iii) Prior therapies
(iv) Laboratory reference ranges and test intervals
(v) Performance status (PS)

ASCO-*Friends* Recommendations

This statement provides a high-level summary of additional ASCO-*Friends* recommendations for more inclusive clinical trial EC (**Table 1**). Detailed discussion of each recommendation and supporting rationale is presented in separate manuscripts.

There are three common themes across these recommendations. First, clinical trial designers should launch every trial with a goal of inclusion and should add exclusions only where safety concerns warrant exclusion of patients with certain characteristics. Protocols should be living documents; that is, over the course of new agent development from first-in-human through phase III studies, EC should be examined critically and revised to allow for the enrollment of patients who may have previously been excluded because of safety concerns, but for whom new information provides sufficient evidence to support their inclusion.

Second, inclusion of all populations who are anticipated to benefit from the therapy based on the mechanism of action early in clinical development is both equitable and necessary. This will ensure that patients who may ultimately benefit from the treatment being studied are not excluded because of lack of safety data for that population. If representative populations are not included, dose, tolerance, risk of adverse events, and therapeutic benefit remain unknown. The inclusion of exploratory cohorts with broader eligibility in early-phase trials will help to inform and enable revisions to the protocol EC based on these earlier risk-benefit analyses. These exploratory cohorts should help sponsors strike a balance between more rapid patient accrual with broader criteria, time associated with enacting protocol amendments later in development, and number of postmarketing requirements and commitments to expedite trial completion and submission of more complete study findings to regulatory agencies, ultimately leading to broader knowledge in clinical use. At minimum, participants in trials leading to marketing authorization should be inclusive of the patients in the intended use population.

Finally, study design should consider both internal and external validation. In phase I studies, safety is paramount and EC are based on existing knowledge. More stringent EC may also be appropriate in early-phase studies conducted to establish principles of management or to explore a biological question. Including an exploratory cohort in early-phase trials through broadened EC will provide safety information to expand participation in the next phase of study. Registration trials can include participants that resemble the entire population of patients who may use the therapy after approval more closely, that is, improving external validity. Including broader populations also helps fulfill the principle of distributive justice, ensuring appropriate representation of groups who are underrepresented in research, where safety permits.

Washout periods

A washout period is a time between most recent treatment and trial enrollment that is intended to prevent confounding the interpretation of the effect of a new treatment by a persistent effect of an immediately prior

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3852

Table 1. Summary of Work Group Recommendations.

Eligibility criteria category	Recommendation
Washout periods	1. Time-based washout periods should be removed from protocol eligibility criteria in most cases. Any inclusion of time-based washout periods should be scientifically justified and clearly specified. 2. Relevant clinical and laboratory parameters should be used in place of time-based washout periods to address safety considerations. 3. Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.
Concomitant medications	1. Concomitant medications use should only exclude patients from trial participation when clinically relevant known or predicted drug–drug interactions or potential overlapping toxicities will impact safety or efficacy.
Prior therapies	1. Patients are eligible for clinical trials regardless of the number or type of prior therapies and without a requirement to have received a specific therapy prior to enrollment unless a scientific or clinically based rationale is provided as justification. 2. Prior therapy (either limits on the number and type of prior therapies or requirements for specific therapies before enrollment) could be used to determine eligibility in the following cases: a. If the agents being studied target a specific mechanism or pathway that could potentially interact with a prior therapy. b. If the study design requires that all patients begin protocol-specified treatment at the same point in the disease trajectory. c. In randomized clinical studies, if the therapy in the control arm is not appropriate for the patient due to previous therapies received. 3. Trial designers should consider conducting evaluation separately from the primary endpoint analysis for participants who have received prior therapies.
Laboratory reference ranges and test intervals	1. Laboratory test results should only be used as exclusion criteria when scientifically justified and when abnormal test results confer safety concerns. 2. Laboratory reference values should account for potential normal variations due to race, ethnicity, age, sex, and gender identity (i.e., due to surgical and/or hormonal changes). 3. Routine reassessment of laboratory test-based exclusion criteria should be conducted during the course of clinical research and drug development as investigational agents progress from earlier- to later-phase clinical trials. 4. Increasing the intervals between protocol-specified tests should be considered to help reduce patient burden and increase ability to rely on routine clinical testing, especially in later cycles of treatment and over the evolution of the protocol from earlier- to later-phase clinical trials.
Performance status	1. Patients with reduced PS (e.g., ECOG PS 2) should be included unless there is a scientific and/or clinical rationale for exclusion justified by established safety considerations. a. ECOG PS eligibility criteria should be based on the patient population in which the intervention is expected to be used in clinical practice. b. PS eligibility criteria should be continually reevaluated and modified throughout the clinical development process to reflect accumulated safety data of the investigational treatment. Decisions about PS eligibility criteria should be based on early clinical safety and efficacy data about the specific investigational agent or based on known data from other drugs in the same class with similar mechanism of action. Later-phase trials (e.g., phase II/III) should generally mirror the intended use population and ECOG PS 2 patients should be included, unless safety concerns have manifested in earlier-phase trials. The rationale for exclusion should be justified and stated explicitly. c. Incorporating the rationale for inclusion of a broader population into the protocol could help encourage investigators to enroll these patients. d. Performance status data should still be collected for use as a stratification factor, regardless of how it is incorporated into eligibility criteria. 2. Consider alternate trial designs, such as prespecified cohorts with lower PS that are exempt from the primary analysis, to encourage inclusion of these patients. These cohorts would generally be small in size and exploratory in nature and could be enrolled in an incremental way to enable an early stopping rule based upon safety data. Consideration of the data analysis approach for the broader eligibility cohort and subgroup analysis should be determined during the study design phase. Early discussion with FDA about enrollment of a broader population may have implications for marketing and post-marketing research requirements. 3. Additional assessments of functional status should be considered to better characterize the functional status of ECOG PS 2 patients and patients ages ≥65, such as activities of daily living (ADLs) and instrumental ADLs.

treatment. Washout/waiting time periods prior to enrollment are common for all modalities of cancer treatment. In many cases, washout periods are associated with theoretical concerns (e.g., prevention of untoward adverse events, drug interactions, and incorrect adverse event attribution) that lack scientific rationale and/or are clinically irrelevant.

Concomitant medications

On average, patients with cancer take five chronic noncancer medications, in addition to drugs that manage adverse effects of their cancer treatment (22). Exclusion of concomitant medications during trials is intended to prevent adverse drug interactions that may affect pharmacokinetic assessment or patient safety, reduce the risk of drug-related adverse events, and, rarely, prevent the use of drugs that are known or predicted to antagonize the anticancer efficacy of investigational therapies. While some medications may be necessarily prohibited early in the development of an investigational agent while knowledge is gained, persistent prohibition reduces the applicability of a therapy to a broader population of patients both in trials and following approval.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3852

Prior therapies

Many cancer trial protocols disallow patients based upon receipt of previous cancer-directed therapies. This may take the form of blanket EC (e.g., any history of prior therapy excluded) or conditional criteria (e.g., specific treatments or a specified number or type of prior treatment lines excluded). In other situations, particularly earlier in drug development, clinical trials commonly exclude patients if they have not received a specific therapy prior to enrollment. Improved molecularly driven therapies and immunotherapies may alter the risk-benefit consideration of study participation in relation to treatment with standard therapies with low efficacy or high toxicity, and in some cases participation in a clinical trial without a requisite receipt of prior standard-of-care therapy may be warranted with appropriate informed consent. As with any other EC, clinical trial designers and sponsors should rigorously justify any restrictions based on prior therapies.

Laboratory reference ranges and test intervals

Laboratory tests that predict and assess toxicity are critical for determining whether a patient can safely enroll on a clinical trial. However, some laboratory reference ranges and test intervals that are included as trial EC are arbitrary, with minimal justification for their use, particularly for investigations of targeted therapies and immunotherapies that may have more favorable or unique toxicity profiles. Reference ranges or intervals that lack scientific rationale and/or differ from routine clinical care often result in biased clinical trial outcomes (as healthier, more homogeneous trial participants may not represent the patients actually treated with a drug once it is approved) and may hinder clinical trial accrual. In addition, nonroutine testing, requirements for central testing, and/or strict adherence to time intervals often increase trial expenses for participants, sponsors, and research sites, and may increase risks associated with certain tests and biopsies (23). Because each clinical trial has distinct therapies with differing toxicity and pharmacokinetic considerations, it is not feasible to provide specific laboratory test value thresholds for broad applicability. Nevertheless, incorporation of principles in **Table 2** may help ensure safety, while minimizing unnecessary participant exclusions.

PS

PS is one of the most common EC utilized in oncology, with many trials limited to patients with good PS [i.e., Eastern Cooperative Oncology Group (ECOG) PS 0 or 1; ref. 13]. This practice restricts therapeutic options for a significant proportion of patients (12), contributes to the pervasive age disparity observed in oncology clinical trials (24), and limits the generalizability of research results in clinical practice. PS as an eligibility criterion should be reconsidered to be more inclusive while maintaining patient safety and study integrity.

Discussion

ASCO and *Friends* are engaged in additional activities to maximize the likelihood that these recommendations are implemented and representative participant populations are accrued to trials.

Our strategies involve four primary elements:

(i) Dissemination—Stakeholders are aware of the EC recommendations and endorse the new cancer clinical trial paradigm outlined above.
(ii) Implementation—More inclusive EC are incorporated into cancer clinical trial protocols.
(iii) Equity—Investigators discuss clinical trial participation with all patients who would qualify and seek to enroll all eligible participants.
(iv) Evaluation—Clinical trial sponsors and investigators monitor the impact of implementing the recommendations, continuously assess accrual during clinical trial conduct to address any challenges that may delay efficient enrollment and completion, and identify additional opportunities to broaden EC to ensure that cancer clinical trial populations mirror the entire population who will be prescribed the treatment.

In efforts to broaden EC, ASCO and *Friends* gathered feedback, reviewed evidence, and conducted analysis of the most common and restrictive criteria. An analysis of 21 Southwest Oncology Group studies showed that 60% of EC are related to comorbidities (including prior treatment exclusions, prior malignancy exclusions, PS, organ function status, HIV status, and brain metastases, among other criteria; ref. 25). Recommendations in this statement and the previous ASCO-*Friends* statement address all of these EC (13).

Research suggests that adoption of the 2017 ASCO-*Friends* recommendations could lead to more inclusive protocols. Data presented at the 2019 ASCO annual meeting demonstrated in a cohort of 10,500 patients with advanced non–small cell lung cancer that implementation of ASCO-*Friends* recommendations could avoid exclusion of nearly half the cohort due to broadened inclusion criteria for brain metastases, prior/concurrent malignancies, and/or reduced kidney function (26).

Publication of these recommendations and analysis of their potential impact will accomplish little if protocols are not updated and investigators do not enroll representative participant populations. Support from trial sponsors, physician investigators, institutional review boards, contract research organizations, and research staff is essential to ensuring that broadened EC are applied appropriately. Eligibility for clinical trials should be recognized as a distributive justice issue for individual patients and for vulnerable populations (27). To the fullest extent possible, FDA, NCI, NIH, and other regulatory bodies, and sponsors should leverage the incentives for broader enrollment that they can offer.

ASCO and *Friends* have partnered with various stakeholders to disseminate and encourage implementation, including working closely with FDA, NCI, and NCI Network Groups. FDA finalized four guidance documents in July 2020 to encourage sponsors to apply the 2017 ASCO-*Friends* recommendations (28–31). NCI revised its protocol template to incorporate the recommendations, including implementation in active protocols and future NCI-funded trials (32).

The general EC in ASCO's TAPUR (Targeted Agent and Profiling Utilization Registry) study mirrors ASCO-*Friends* recommendations by not excluding patients who: are 12 years and older; have new or progressive brain metastases or previously treated or untreated brain metastases, if they are clinically stable; have a prior malignancy; are HIV+; and/or are ECOG PS 0–2. For biomarker-selected therapies, the biomarker driving the cancer should be the primary inclusion criteria, as these therapies often do not pose the same risks as cytotoxic chemotherapy.

Conclusions

EC for washout periods, concomitant medications, prior therapies, laboratory references ranges and test intervals, and PS can and should be modernized to be inclusive of broader, more representative patient populations. These considerations, along with previously proposed

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3852

Table 2. Benefits and risks/challenges of expanded eligibility criteria (Adapted from Kim and colleagues, 2017).

Benefit and risk/challenge	Patients	Physicians	Sponsors and investigators
Benefits	Earlier access to investigational agents and expanded trial and treatment options	More complete safety data, which can inform clinical use and enable safe delivery if investigational agent becomes commercially available	Ability to generalize to real-world patients and potentially reduce postmarketing requirements; efficacy in traditionally understudied population(s) could potentially result in expanded marketing claims and provide a differentiating factor between drugs of same class
	Increased confidence in treatment decision-making due to availability of efficacy and safety (i.e., side effect) data from a representative group of trial participants	Availability of efficacy and safety data informs weighing of available treatment options across a broader array of patients and increases confidence in therapy selection	Quicker accrual, fewer trial delays and failures, and more patients may be eligible at each site. All these factors may also reduce cost and time of clinical trial conduct.
	If early trial data in expanded populations demonstrates concerns with efficacy or safety, future patients will have better information to avoid more toxic or less efficacious therapies or know how to modify therapy delivery to avoid toxicities.	Earlier identification of drugs that may not be efficacious in a specific patient population or that may cause more harm than good or earlier knowledge about dose modification of an investigational therapy to improve efficacy or safety/tolerability	Identification of potential safety issues earlier during closely monitored clinical trials may facilitate earlier development of mitigation strategies, enabling broader uptake after approval, and avoidance of post-marketing harms in a larger number of patients due to length of time required for the passive, postmarketing safety surveillance system to identify safety concerns
Risks/challenges	Patients with comorbidities may have a potentially higher risk of experiencing an adverse event as a result of the investigational drug or their disease	Limited data from small cohorts enrolled with broadened criteria may not be adequate for clinical decision-making	More variability in outcomes may require larger sample sizes and inferences may not be as precise
	Additional procedures for increased safety monitoring in some situations may incur additional costs to patients	Additional procedures for increased safety monitoring in some situations may incur additional costs and increased complexity of patient care	Potential safety concerns may require separate cohorts or analysis plans and early stopping rules for excess toxicity
		Additional resources may be required to ensure staff are able to manage safety monitoring	May complicate attribution of adverse events
			Increased costs associated with additional cohorts, statistical requirements, additional testing, additional data for analysis, or special expertise to manage specific patient needs

modifications, may result in greater efficiency of trial conduct and faster clinical trial accrual. Implementation will increase opportunities for patient participation and generation of generalizable evidence to better inform use of new therapies in populations encountered in clinical practice.

Authors' Disclosures

E.S. Kim reports personal fees from AstraZeneca, Boehringer Ingelheim, and Genentech outside the submitted work. T.S. Uldrick reports other from Merck, Roche, and Celgene/BMS outside the submitted work; in addition, T.S. Uldrick has a patent for U.S. 10,001,483 B2 issued to Celgene and NCI. A. Magnuson reports National Institute on Aging K76 Career Development Award, NCI Loan Repayment Award, and honoraria for an educational lecture provided at the American Society of Radiation Oncology 2020 annual meeting. D.M. Vega reports nonfinancial support from Aetion outside the submitted work. S. George reports personal fees and other from Blueprint Medicines, Deciphera Pharmaceuticals, and Bayer; other from Daiichi Sankyo, Wolter Kluwer, Pfizer, and Novartis; and personal fees from Eli Lilly, NCCN, ResearchToPractice, OncLive, and Medscape outside the submitted work. Dr. George is vice-chair of Alliance for Clinical Trials in Oncology and vice-president, Alliance Foundation. P.A. Spears reports personal fees from Pfizer, Inc outside the submitted work. W.D. Tap reports personal fees from Eisai, Eli Lilly, GlaxoSmithKline, EMD Serono, Nanocarrier, Blueprint, Daiichi, Agios, and Deciphera outside the submitted work. In addition, W.D. Tap has a patent for Companion Diagnostic for CDK4 inhibitors - 14/854,329 pending to MSKCC/SKI, reports scientific advisory board membership with Certis Oncology Solutions (stock ownership), and is co-founder of Atropos Therapeutics (stock ownership). R.L. Schilsky reports grants from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Genentech, Lilly, Merck, and Pfizer outside the submitted work. No disclosures were reported by the other others.

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily reflect the views or policies of the authors' affiliated institutions.

Acknowledgments

The project planning group wishes to acknowledge the volunteers who contributed significant time and effort to developing the consensus recommendations and manuscripts. Additional ASCO staff (Elizabeth Garrett-Mayer, Pam Mangat, Steve Meersman, Jonathan Phillips, and Shimere Sherwood) and *Friends* staff (Madison Wempe) contributed to the development of this article. Finally, the planning group thanks the 2018–2019 ASCO Cancer Research Committee and Health Equity Committee members for their leadership.

Received September 29, 2020; revised November 25, 2020; accepted December 8, 2020; published first January 9, 2021.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3852

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AACR American Association for Cancer Research

Clinical Cancer Research

Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO–Friends of Cancer Research Joint Research Statement

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Clin Cancer Res Published OnlineFirst February 9, 2021.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3855

Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Washout Period and Concomitant Medication Work Group

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ABSTRACT

Purpose: Washout periods and concomitant medication exclusions are common in cancer clinical trial protocols. These exclusion criteria are often applied inconsistently and without evidence to justify their use. The authors sought to determine how washout period and concomitant medication allowances can be broadened to speed trial enrollment and improve the generalizability of trial data to a larger oncology practice population without compromising the safety of trial participants.

Experimental Design: A multistakeholder working group was convened to define problems associated with excessively long washout periods and exclusion of patients due to concomitant medications. The group performed a literature search and evaluated study data from the Pancreatic Cancer Action Network (PanCAN), Emory University School of Medicine (Atlanta, GA), and the FDA to understand recent approaches to these eligibility criteria. The group convened to develop consensus recommendations for broadened eligibility criteria.

Results: The data analysis found that exclusion criteria based on washout periods and concomitant medications are frequently inconsistent and lack scientific rationale. Scientific rationale for appropriate eligibility criteria are presented in the article; for washout periods, rationale is presented by treatment type.

Conclusions: Arbitrary or blanket washout and concomitant medication exclusions should be eliminated. Where there is evidence to support them, clinically relevant washout periods and concomitant medication–related eligibility criteria may be included.

Introduction

Patient access to evidence-based experimental treatments is associated with improved outcomes in the cancer population (1). Expediting enrollment into therapeutic clinical trials in cancer is dependent on removing barriers to patient participation, such as overly restrictive eligibility criteria. Trials that adopt criteria safely reflecting populations most commonly seen in daily practice are more likely to accrue rapidly and be applicable to greater numbers of patients.

Approximately 20% of patients are ineligible for trials on the basis of commonly employed eligibility criteria (2). This makes a strong case for critical analysis of areas where eligibility criteria may be expanded safely. Prior work by American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) recommended numerous areas where expanded eligibility should be employed (3). This list was extensive, but a number of barriers remain. Our working group was formed to evaluate two commonly perceived barriers: washout periods from recent therapies/interventions and prohibited concomitant medications.

A washout period is defined as a time between treatment periods that is intended to prevent misinterpreting observations about study-related treatments that were actually due to prior therapies. Generally, washout/waiting periods prior to enrollment are employed in cancer trials following surgery, radiation, cytotoxic chemotherapy, small-molecule/tyrosine kinase inhibitors, monoclonal antibodies (with and without drug conjugates), and immunotherapies.

Prohibited concomitant medications create eligibility and timing challenges, because patients receiving anticancer therapies often have comorbidities that require drug therapy, such as pain, diabetes, or gastrointestinal or cardiovascular disorders. While some medications may be necessarily prohibited early in investigational agent development, prolonged prohibition across trial phases reduces the applicability of a therapy to a broader patient population in trials and following approval.

Current applications of washout period and concomitant medication eligibility criteria are discussed in **Table 1**. Reducing and/or eliminating a need to include time-based washout periods and prohibit concomitant medications may facilitate both clinical trial participation and greater generalizability of the research findings to a larger oncology practice population.

Process

The multistakeholder group identified concerns regarding washout periods and prohibited medications, with a focus on broadening eligibility criteria as much as possible to increase

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Clin Cancer Res 2021;XX:XX–XX

doi: 10.1158/1078-0432.CCR-20-3855

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3855

Translational Relevance

Washout periods for prior treatments and interventions limit timely accrual and evidence generation and may prevent patient enrollment without adding safety measures or preventing misinterpretation of efficacy results. Exclusion of patients who require concomitant medications for comorbidity or supportive care management prevents early understanding of investigational agent tolerability and dosing in those likely to receive the treatment after approval. Less restrictive requirements for prior therapy washout periods and concomitant medication use, in many instances, should be considered and may facilitate both clinical trial participation and greater generalizability of the research findings to a larger oncology practice population.

efficiency of enrollment and potentially diversify enrolled populations to include greater numbers of patients with comorbidities and chronic medication management needs. The group's observations of current and ideal eligibility criteria and trial design related to washout periods and concomitant medications are described in **Table 2**.

A literature search was performed to understand the historical rationale and background of common eligibility criteria, particularly for washout periods. Because of the relative lack of information obtained, additional data were pursued from three datasets: a series of trials in the Pancreatic Cancer Action Network (PanCAN) portfolio, a sampling of trials performed at the Winship Cancer Institute of Emory University (Atlanta, GA), and a review of new approvals in 2018 by the FDA.

Data Analysis

PanCAN trial dataset

Eligibility criteria for industry-, institutional-, and NCI-sponsored metastatic pancreatic adenocarcinoma treatment studies were reviewed to evaluate the need for specific recommendations related to washout periods and concomitant medications. Eligibility criteria from 16 phase III (including one seamless phase II/III) trials in the PanCAN database between 2010 and 2019 were evaluated (**Table 3**). Eligibility criteria from corresponding phase I and II trials studying treatments that advanced to phase III trials listed in PanCAN's database or on clinicaltrials.gov were also evaluated. In total, 34 trials studying 15 unique investigational agents were evaluated.

Studies were evaluated for washout periods for prior radiotherapy, chemotherapy, monoclonal antibodies, immunotherapy, and investigational agents. Washout periods for surgery, corticosteroids, blood cell stimulating drugs, antibiotics, and hormone therapy were also noted when indicated. When treatment-specific washout periods were not available as a result of inadequate details about entry criteria, more general exclusion criteria that would likely include these specific treatments were included (e.g., "washout from all prior systemic treatment").

Results showed a lack of consistency in washout periods from trial to trial, regardless of study phase and type of therapy, with most trials not mentioning a washout period in eligibility criteria. There was also a lack of consistency when reviewing how washout periods for therapies change over time as an investigational agent moves from earlier phase to later phase trials. While the washout periods often stayed the same for many types of therapies as an investigational agent moved to later phase testing, in some instances the washout periods decreased, increased, or were removed altogether. A rationale for washout periods was rarely provided. Our review demonstrated that about 50% of studies included time-based washout periods from 14 to 28 days.

Table 1. Definitions and applications of washout periods and prohibited concomitant medications.

Washout periods
Definition: a washout period is defined as a time between treatment periods that is intended to prevent clouding of information from one intervention to the next.
Application: washout/waiting time periods prior to enrollment are identified in protocols following surgery, radiation, cytotoxic chemotherapy, small-molecule/tyrosine kinase inhibitors, monoclonal antibodies (with and without drug conjugates), and immunotherapies.
Historical rationale: each aspect of a protocol-required washout period may have a different historical rationale, including prevention of untoward adverse events (e.g., wound healing after surgery and cytopenias), drug interactions (e.g., tyrosine kinase inhibitors overlapping with investigational agents), and incorrect adverse event attribution (e.g., late effects with immunotherapies). While in many cases these may be associated with theoretical concerns, they are often irrelevant to clinical practice.
Example: protocol-based treatment vs. clinical practice, a protocol may require a 21-day washout period from a daily oral EGFR-directed tyrosine kinase inhibitor; whereas in practice, a patient would be rapidly transitioned to next-line therapy after knowledge of progressive disease, with the only interval between doses being that required for insurance approval. These agents have short half-lives, and in some instances, discontinuation may be associated with a disease flare, making rapid transitions to next-line therapies critical (19, 20).
Concomitant medications
Definition: a concomitant medication is any drug or dietary supplement that a study participant uses in addition to the treatment under investigation.
Application: on average, patients with cancer take five chronic noncancer medications, not including those that may be used to manage adverse events associated with anticancer therapy (21). As patients age, the prevalence of comorbidities and associated polypharmacy increases (22).
Historical rationale: exclusion of concomitant medications is intended to prevent adverse drug interactions that may affect pharmacokinetics assessment, increase adverse event risks, and in rarer cases, reduce anticancer agent efficacy.
Example: protocol-based treatment vs. clinical practice, protocols often prohibit patients from taking ondansetron in any dose or route due to fears of QTc prolongation with an investigational agent; however, oral ondansetron is used widely and commonly in practice. The risk of QTc prolongation is solely due to high-dose intravenous ondansetron use and has not been shown with the oral route (23).

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3855

Table 2. Working group observations related to washout period- and concomitant medication–based trial design.

Current state
Real-time learning of adverse event profiles and pharmacology applicable to washout periods and concomitant medication prohibition is often not reflected in updated protocols.
A lack of data exists regarding patients not enrolled on trials due to extensive washout periods or inability to change or discontinue a prohibited medication.
Washout periods are essentially nonspecific surrogates for a clinical (e.g., adverse event) or laboratory (e.g., absolute neutrophil count) measurement that are included to ensure participant safety and prevent confounding of observations (safety or efficacy) on trial.
Lack of rationale for or specificity regarding washout period and concomitant medication exclusions can cause patient confusion about why they are ineligible for certain trials.
Optimal state
Although postmarketing development of drugs occurs, it is optimal and possible to have complete data on concomitant medication allowances at approval.
Evaluating potential safety and pharmacology interactions, such as QT interval prolongation studies and drug–drug interaction studies, early in drug development can liberalize concomitant medication allowances during later phases of drug development.
Nonclinical tools, such as *in silico* modeling, should be optimized to potentially minimize exclusion of medications and/or reduce required sample sizes in trials.

In reviewing the concomitant medications data, the most commonly excluded concomitant medications were infectious disease treatments and anticoagulants. As with washout periods, rationale for the exclusion of these concomitant medications was rarely provided.

Emory dataset

A series of 102 trials, across phases, was retrospectively evaluated for both washout periods and allowance of concomitant medications (**Table 4**). The majority were early-phase trials with pharmaceutical sponsors, and primarily included investigational oral small molecules alone or in combinations. Each trial was assessed for required washout periods for surgery, radiation, chemotherapy, monoclonal antibodies, immunotherapy, and investigational agents. Of the 102 trials, 36 were silent for a washout period from surgery. The remainder are listed in **Table 4**. Overall, washout periods varied; however, many categories had similar proportions in the ≤14 and

Table 3. Summary of PanCAN data review.

	Washout periods as I/E criteria			
	14 days	21 days	28+ days	No washout period I/E criteria
Radiation	11.76%	2.94%	26.47%	58.82%
Chemotherapy	23.53%	5.88%	5.88%	64.71%
Monoclonal antibodies	11.76%	5.88%	2.94%	79.41%
Immunotherapy	14.71%	5.88%	2.94%	76.47%
Investigational agents	20.59%	5.88%	20.59%	52.94%
Surgery	8.82%	14.71%	47.06%	29.41%

	Change in washout periods with later-phase trials					
	Shorter	Same	Longer	Not allowed	Silent	Added
Radiation	6.67%	33.33%	0.00%	40.00%	13.33%	6.67%
Chemotherapy	0.00%	33.33%	6.67%	33.33%	13.33%	13.33%
Monoclonal antibodies	0.00%	40.00%	0.00%	33.33%	0.00%	26.67%
Immunotherapy	0.00%	40.00%	0.00%	33.33%	6.67%	20.00%
Investigational agents	6.67%	13.33%	0.00%	26.67%	20.00%	33.33%
Surgery	0.00%	66.67%	20.00%	0.00%	6.67%	6.67%

Most commonly excluded concomitant medications	
Antibiotics	35.29%
Other anti-infectives	29.41%
Antifungals	26.47%
Anticoagulants	17.65%
Corticosteroids	2.94%
Growth factors	2.94%

Abbreviation: I/E, inclusion/exclusion.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3855

Table 4. Summary of Emory data review.

Trial characteristics ($N = 102$)	
Phase	%
I	37%
I/II	22%
II	28%
III (2 seamless trials)	13%
Sponsor	
Pharmaceutical	77%
National Cancer Institute (NCI)	11%
Academic center	11%
Performance status allowed	
0–1	42%
0–2	55%
0–3	3%
Investigational agent type	
Small molecule[a]	66%
Monoclonal antibody[a]	21%
Chemotherapy[a]	8%
Antibody–drug conjugate	5%

Trial washout periods for prior treatments			
	≤14 days	21 days	≥28 days
Radiation ($n = 87$)	47%	9%	27%
Chemotherapy ($n = 93$)	34%	20%	37%
Monoclonal antibody (non-IO; $n = 78$)	24%	7%	45%
Immunotherapy ($n = 75$)	30%	12%	31%
Investigational agent ($n = 88$)	19%	16%	46%

Exclusions for concomitant medications			
CYP isozyme	Inducers	Inhibitors	Substrates
3A4/5	39%	40%	9%
2D6	2%	2%	2%
2C8/9	2%	3%	3%
1A2	4%	10%	2%
2C19	2%	3%	1%

[a]Includes combinations.

≥28 day timeframes, suggesting periods were not uniformly selected regardless of investigational agent mechanism of action (MOA).

Exclusions for concomitant medications were also evaluated, and common classes leading to ineligibility included corticosteroids (60%), antifungal agents (36%), anticoagulants (15%), human immunodeficiency virus therapy (13%), other anti-infectives (12%), and gastrointestinal medications (11%). Drug–drug interactions leading to exclusions were also evaluated, with a focus on agents that are metabolized by or affect the cytochrome P450 (CYP) enzyme system. Of 102 trials, 49 excluded some type of CYP agent. The most common isozyme leading to exclusions was CYP 3A4/3A5, with similar numbers for agents that induce and inhibit the pathway. The frequency of this exclusion aligns with this isozyme's role in the metabolism of approximately 60% of orally administered drugs (4, 5).

FDA data

The FDA analysis focused on new molecular entities (NME) that were approved in 2018 across all therapeutic areas within the Office of Hematology and Oncology Products (6). The rationale for this selection method of recently approved NMEs was to obtain a sample of products spanning a diverse range of molecules, novel targets, and therapeutic areas. The FDA working group members reviewed characteristics of registrational trials specific to concomitant medications and washouts, as outlined in the publicly available FDA product reviews and product labeling. For washouts, the FDA analysis included whether trials included periods for chemotherapy agents, monoclonal antibodies, immuno-oncology agents, prior investigational agents, and radiotherapy. For concomitant medications, the FDA analysis focused on whether CYP exclusions, drug–drug interactions, and concomitant medication allowances were included in registrational trial protocols.

The FDA analysis evaluated a variety of products, including therapies for solid and hematologic malignancies. A variety of types of molecular entities were reviewed for this analysis, including small molecules, monoclonal antibodies, radiolabeled analogues, and enzymes. Of the 19 NMEs approved in 2018, there was a wide range of washout periods specified in the registrational trials. Frequently, protocols included blanket language encompassing prior chemotherapy, radiation, and surgery. The most frequently used washout period ranged between 14 and 28 days, however, some protocols did not specify any washout period, and the longest washout period was 3 months. Overall, there was heterogeneity in washout periods specified in registrational protocols, even among similar therapeutic classes and diseases, and absence of rationale was common.

Prohibited concomitant medications were also specified in a heterogenous manner. Many trials of small molecules prohibited the use of CYP3A4 substrate medications, and washout periods varied greatly. For example, one trial used clear language regarding CYP3A4: "the concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A are not allowed," whereas another protocol used less definitive language: "coadministration with moderate/strong CYP3A4 inhibitors was not recommended. However, such medications could be used with caution and only if considered medically necessary. . ." As with washout periods, this analysis revealed a dearth of rationale for prohibited concomitant medications included in these registrational trials.

Recommendations

The consensus recommendations below are made in consideration of the benefits and risks to broadening criteria described above. These recommendations should inform sponsors and investigators as they draft study eligibility criteria, but are not intended as template language for trial protocols. Eligibility criteria should be tailored to the investigational treatment and patient population. For that reason, the recommendations are inclusive, rather than specific and prescriptive. Recommended language such as "clinically significant expected adverse event" should be replaced or supported by disease- and drug-specific, evidence-based examples.

Washout periods

(i) Time-based washout periods should be removed from protocol eligibility criteria in most cases. Any inclusion of time-based washout periods should be scientifically justified and clearly specified.

(ii) Relevant clinical and laboratory parameters should be used in place of time-based washout periods to address safety considerations.

(iii) Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3855

Table 5. Historical rationale for common time-based washout period eligibility criteria and key considerations for scientifically justified washout eligibility criteria, by treatment type: chemotherapy, small-molecule inhibitors, monoclonal antibodies, and antibody–drug conjugates.

Treatment type	Key shortcomings of common/historical washouts	Key considerations for scientifically justified washouts
Chemotherapy	• Many protocols include requirements for washout periods from prior therapy, often ranging from 14 to 28 days, yet a literature search yielded little in the way of published rationale for time-based washout periods from cytotoxic chemotherapy. • Treatment delays are a risk to patients who demonstrate radiographic progression, and screening periods may be employed to establish required intervals between radiographic evaluation.	• The typical 28-day washout period on the basis of the anticipated time for patients to recover from side effects of prior chemotherapy is no longer scientifically justified in many cases. – For example, in the era of growth factors, 3–4 weeks are not necessarily required for myelosuppression recovery.
Small-molecule inhibitors (including, but not limited to TKIs, serine and threonine kinase inhibitors, cyclin-dependent kinase inhibitors, MEK inhibitors, and tropomyosin kinase inhibitors)	• EC are not routinely updated to reflect differing MOAs, elimination half-lives, and toxicity profiles of targeted therapies. • Much of the trial language surrounding kinase inhibitors is the same as cytotoxic agents, antibodies, or other cancer treatments with prolonged washouts without justification. • The rationale for the differences with agents with minimal acute and chronic toxicity profiles is not well elucidated. • An approach to ensure patient safety from treatment withdrawal complications has yet to infiltrate protocol design, despite extensive documentation of effects, such as TKI withdrawal disease flare. – For example, gastrointestinal stromal tumors have a unique biology with rapid disease progression when imatinib is removed after prolonged benefit (9).	• Many targeted agents have rapid time-to-peak concentration, as well as abbreviated elimination half-lives, a unique property (e.g., compared with monoclonal antibodies). • The MOA of a given TKI on the tumor and the effects of any specific TKI on other factors related to the natural history of a given cancer or anticipated clinical course of a trial participant must be understood prior to initiation of treatment. This is imperative for the safety of the patient not only for treatment-related side effects, but also for treatment withdrawal effects. – For example, when outcomes of patients with advanced renal cell carcinoma treated with TKIs before and after cytoreductive nephrectomy are compared, complication rates are variable, but most note potential delayed wound healing and exacerbation of underlying medical conditions specific to perioperative VEGF-targeting TKIs (8).
Monoclonal antibodies (therapeutic tumor-targeted proteins with variable fragments engineered for epitope binding and based on IgG1 or IgG4 backbones)	• Monoclonal antibody therapies have more pharmacologic consistency than other agents (e.g., oral therapies), allowing for more predictable distribution and elimination, with typical half-lives ranging from 14 to 21 days (12). Despite this consistency, washout periods in EC are highly variable, suggesting history rather than pharmacology-driven timing.	• Concerns of clouding investigational therapeutic efficacy are minimal when the most recent therapy has failed the patient. • Because of the target specificity, concrete consideration of adverse events associated with monoclonal antibodies and their impact on next treatments may be determined in the absence of an arbitrary time period.
ADCs (a subset of monoclonal antibodies that comprise a monoclonal antibody, a linker, and a therapeutic payload)	• Payloads utilized to date have been agents such as maytansinoids and topoisomerase inhibitors that are in actuality chemotherapeutic agents, with cytopenias and other conventional acute adverse effects. Washout periods following these agents have varied and have often not been specified for this class; however, their growing use warrants discussion.	• For eligibility purposes, ADCs may be considered for washout periods as two different drugs, the monoclonal antibody and the payload. • The targeted component of the monoclonal antibody portion of the ADC can be considered for its specificity and contribution to a potential adverse event for an investigational agent or regimen. • Like cytotoxic chemotherapy, recovery from toxicities following ADCs are best measured by laboratory and clinical parameters, rather than timeframes. Rarely will a simple time period be justified, adequate, or necessary for ensuring safe and clear management of patients enrolled on trials.

Abbreviations: ADC, antibody–drug conjugate; EC, eligibility criteria; TKI, tyrosine kinase inhibitor.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3855

Table 6. Historical rationale for common time-based washout period eligibility criteria and key considerations for scientifically justified washout eligibility criteria, by treatment type: radiotherapy, surgery, and immunotherapies.

Treatment type	Key shortcomings of common/historical washouts	Key considerations for scientifically justified washouts
Radiotherapy		• CNS edema postradiation: to realize all the potential benefits of enrolling patients with brain metastases and gather real-world experience of such patients, eligibility requirements should establish a 14-day washout after stereotactic radiotherapy or whole-brain radiotherapy for patients as a standard (13). • Myelosuppression risk: postradiotherapy myelosuppression risk is based on the percentage of active bone marrow irradiated, so the percentage of total bone marrow activity by bony site is helpful in determining the RR of marrow acute side effects from radiotherapy (14). • Acute mucosal membrane reactions to radiation: defined washout period times following standard palliative radiotherapy to mucosal or other surfaces are better replaced by clinical observation, particularly because adverse events will be low-grade and self-limited in nature in most patients.
Surgery	• As noted in the PanCAN dataset, eligibility washout timeframes following surgery vary greatly, and are often not mentioned, even within a single cancer type (**Table 1**). • Differing approaches (laparoscopic vs. open), invasiveness, anesthesia employed, and anatomic location are some of the variables that may impact recovery from the variety of surgeries that patients with cancer may undergo prior to trial enrollment. This heterogeneity suggests that the underlying rationale for including a specified number of days or weeks, rather than more specific parameters for recovery following a procedure, is arbitrary and should be removed from protocols.	• Specific clinical and medical assessment should be employed to ensure potential trial volunteers are functionally prepared and healed to safely receive investigational therapies. • For postsurgery treatment as with other treatments, arbitrary time periods do not reflect or replace clinical judgment, are part of a combination of EC that often overlap to ensure safety (e.g., laboratory values and performance status), and cannot be expected to be broadly applicable across multiple patients and procedures.

Immunotherapies	• Trials should not default to historical washout periods based on time or pharmacokinetic parameters (e.g., half-life), as this approach is both impractical and may not be in the patient's best interests, particularly since a new regimen on a trial has most likely been selected because of cancer progression.	• Pharmacologically, this class of agents includes a variety of molecules designed to modulate antitumor immune responses, and that often have an extended period of time for onset of both clinical activity and adverse events.
		• The tempo of median onset and resolution of irAEs have to be considered when patients transition from immunotherapies on trials or in the clinic to investigational agents.
		  • Median time to resolution of irAEs of 12 weeks has been generally consistent among immune checkpoint inhibitor agents (e.g., initial reports of ipilimumab; ref. 10).
		• Data support rapid subsequent trial enrollment when coupled with an initial understanding of investigational agent adverse event profiles and experience in adverse event attribution.
		  • A recent study showed that up to 25% of patients may experience new or worsening irAEs (most commonly hypothyroidism) after 6 or more months of therapy, but only 2.5% will experience a deepening of response after 6 months (23).
		• Late occurring irAEs that may cloud attribution to a single drug or regimen on study have to be accounted for prior to enrollment.
		• A thorough history of agent(s) given, timing of treatment, irAEs experienced, and understanding of the timing of common late effects may assist in differentiating late effects from prior therapies versus new effects from investigational ones.
		• It may be more useful to stratify study participants based on prior immunotherapy use and to avoid washout periods in the absence of unresolved irAEs that threaten participant safety.

Abbreviations: CNS, central nervous system; EC, eligibility criteria; irAE, immune-related adverse events.

Concomitant medications

(i) Concomitant medication use should only exclude patients from trial participation when clinically relevant known or predicted drug–drug interactions or potential overlapping toxicities will impact the safety of trial participants or compromise efficacy.

Scientific Rationale for Washout Periods by Treatment Type

Arbitrary time periods do not reflect or replace clinical judgment, are part of a combination of eligibility criteria that often overlap to ensure safety (e.g., laboratory values and performance status), and cannot be expected to be broadly applicable across multiple patients and procedures. Sponsors and investigators should provide the scientific rationale for washout periods when developing and implementing protocols, rather than relying on historic precedent that may not be appropriate for the treatment or disease being studied.

The group reviewed the rationale for common time period–based washout eligibility criteria for seven treatment types [chemotherapy, small-molecule inhibitors (1, 2 , 4, 5, 8, 9), immunotherapies (3, 10, 11), monoclonal antibodies (12), antibody–drug conjugates, radiotherapy (6, 7, 13–15), and surgery], where it was available. **Tables 5** and **6** outline the shortcomings of these common eligibility criteria and present key patient responses and safety considerations (e.g., potential risk of and recovery from clinically significant adverse events) that should guide clinical assessment of patient readiness for initiation of a new treatment.

Scientific Rationale for Excluding Certain Medications

As with washout periods, exclusion of concomitant medications during protocol-driven treatment should be supported by scientific rationale. Clearance and elimination of many investigational agents are predictable based on agent type, molecular weight, and/or other physicochemical characteristics. These more predictable agents (e.g., monoclonal antibodies) have known pharmacokinetic properties, and have a very low *a priori* likelihood of being involved in drug interactions. Other drugs under investigation, such as many oral small molecules, have a higher likelihood of being substrates, inducers, or inhibitors of metabolic clearance or transporter pathways, and therefore, must be approached more conservatively when considering which concomitant medications should be allowed. Although the preclinical ability to predict interactions has improved over time, no model or approach has sufficiently replaced dedicated studies in patients (16). Another consideration is actual oral bioavailability of a novel formulation and the effects of coadministration of agents that affect gastric pH (antacids, H2 antagonists, and proton pump inhibitors) and/or gastric emptying (food). Because these are unknown, many trials require patients to fast for 2–8 hours prior to and up to 4 hours following ingestion of an investigational agent, as well as prohibit agents that affect gastric pH. Also, as these drugs are available over the counter and prescribed in up to 55% of patients with cancer, it is important to mitigate the effect on investigational agents as early as possible in development and allow for their use in a general population (17).

Because the presence of concomitant medications can result in drug–drug interactions that affect the safety profile and interpretation of efficacy of an investigational drug, there are understandable concerns regarding loosening restrictions on concomitant medications in clinical trials. Unfortunately, polypharmacy tends to be common in patients with cancer, who also tend to be an older population, with multiple comorbid conditions that may require medical management. A review conducted by LeBlanc and colleagues reported the number of prescribed drugs in patients ranged from 3 to 9.1 (18). Without prior nonclinical knowledge of the potential effects of concomitant medications on investigational drug's pharmacokinetics and pharmacodynamics, many concomitant drugs are prohibited in early-phase clinical trials to ensure patient safety, reduce variability of responses, and ensure optimal conditions for proof of concept. This stringent exclusion of concomitant medications is often duplicated in later phases of drug development without much consideration of how growing nonclinical or clinical knowledge may support broader inclusion of concomitant medications.

Clinical pharmacology studies should be conducted as early as possible in drug development to inform concomitant medication use in eligibility criteria. Formulations of oral investigational agents should be optimized as early as possible in drug development to minimize absorption interactions and pharmacokinetic variability and inform allowance of concomitant medications as early as possible. Concomitant medication allowances should be broadened in later phase trials so that safety is assessed in the premarket setting.

Conclusion

Washout periods and concomitant medication exclusions are common in cancer clinical trial protocols. These exclusion criteria are often applied inconsistently (across trials and between protocol-driven vs. off-protocol treatment) and without evidence to justify their use. Arbitrary or blanket washout period and concomitant medication exclusions should be eliminated. Where there is evidence to support them, clinically relevant washout periods and concomitant medication–related eligibility criteria may be included.

Information gained from preclinical studies and earlier trials about investigational agent adverse event profiles and pharmacology should be incorporated as early as possible in drug development to minimize washout periods and liberalize concomitant medication allowances.

Authors' Disclosures

K.F. Mileham reports personal fees from AstraZeneca, Merck, BMS, Takeda, and Bayer outside the submitted work. C. Moravek reports personal fees and nonfinancial support from AstraZeneca Pharmaceuticals outside the submitted work. E.C. Dees reports personal fees from Novartis, STRATA, and Sanofi and other from MERYX, Pfizer, Apollomics, G1Therapeutics, and Lilly outside the submitted work. S.W. Ebbinghaus reports other from Merck outside the submitted work. T.S. Uldrick reports other from Merck, Roche, and Celgene/BMS outside the submitted work, as well as a patent for US 10,001,483 B2 licensed to Celgene and NCI. No disclosures were reported by the other authors.

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily reflect the views or policies of the authors' affiliated institutions.

Acknowledgments

The working group thanks the ASCO-*Friends* project planning group for its guidance throughout the development of its consensus recommendations and article. The group also acknowledges Lawrence He (research assistant) for his data analysis contributions.

Received September 28, 2020; revised November 25, 2020; accepted December 14, 2020; published first January 9, 2021.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3855

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Clinical Cancer Research

Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Washout Period and Concomitant Medication Work Group

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Clin Cancer Res Published OnlineFirst February 9, 2021.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3868

Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-*Friends* of Cancer Research Performance Status Work Group

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ABSTRACT

Purpose: Performance status (PS) is one of the most common eligibility criteria. Many trials are limited to patients with high-functioning PS, resulting in important differences between trial participants and patient populations with the disease. In addition, existing PS measures are subjective and susceptible to investigator bias.

Experimental Design: A multidisciplinary working group of the American Society of Clinical Oncology and Friends of Cancer Research evaluated how PS eligibility criteria could be more inclusive. The working group recommendations are based on a literature search, review of trials, simulation study, and multistakeholder consensus. The working group prioritized inclusiveness and access to investigational therapies, while balancing patient safety and study integrity.

Results: Broadening PS eligibility criteria may increase the number of potentially eligible patients for a given clinical trial, thus shortening accrual time. It may also result in greater participant diversity, potentially reduce trial participant and patient disparities, and enable clinicians to more readily translate trial results to patients with low-functioning PS. Potential impact on outcomes was explored through a simulation trial demonstrating that when the number of Eastern Cooperative Oncology Group PS2 participants was relatively small, the effect on the estimated HR and power was modest, even when PS2 patients did not derive a treatment benefit.

Conclusions: Expanding PS eligibility criteria to be more inclusive may be justified in many cases and could result in faster accrual rates and more representative trial populations.

Introduction

An important goal of the American Society of Clinical Oncology, Friends of Cancer Research, and the oncology community at large is broadening clinical trial eligibility criteria to enhance trial access and accrual, and to ensure trial populations better reflect patients with the disease (1). Performance status (PS) is one of the most common inclusion/exclusion criteria in oncology trials. Many trials are limited to high-functioning participants (i.e., "good" PS) and exclude low-functioning patients (i.e., "poor" PS; ref. 2).

Two main PS scales are utilized in oncology clinical trials: Eastern Cooperative Oncology Group (ECOG; ref. 3) and Karnofsky (KPS) scales (4). Multiple trials in various tumor types and settings have demonstrated that low-functioning PS (i.e., ECOG PS, 2–4 and KPS ≤ 70) is correlated with lower overall survival and progression-free survival compared with high-functioning PS (ECOG PS, 0–1 and KPS, 80–100; refs. 5–13). Because of this, PS is included as a common eligibility criteria and stratification factor. However, this practice prevents trial enrollment for many patients and limits generalizability of trial results. Select trials that have focused exclusively on participants with low-functioning PS demonstrated patient and clinician interest and enrollment (14–17). The underlying etiology for low-functioning PS is also important; for patients whose low-functioning PS is due to disease burden, investigational treatment may result in improved PS with tumor control and symptom alleviation, especially with highly effective treatments. However, current PS scales do not differentiate causes of low-functioning PS.

In addition, there are limitations to PS assessments. PS is inherently subjective, which can affect interrater reliability (18) and invite potential bias particularly for patients at the borderline between values. For example, studies have demonstrated that clinicians assign patients aged >65 years higher numeric PS scores than younger patients, despite no difference in objectively measured physical activity (19). In addition, PS is less predictive of cancer-related outcomes for older adults (20, 21).

Materials and Methods

Because clinical trials frequently exclude PS2 patients, the working group chose to focus on this category. To understand the potential effect of including PS2 patients, the working group conducted a simulation study, where randomized trials of a hypothetical agent were simulated under various conditions. We also examined the literature to identify the potential risks and benefits of including PS2 patients on therapeutic clinical trials and evidence of the effectiveness

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Clin Cancer Res 2021;XX:XX–XX

doi: 10.1158/1078-0432.CCR-20-3868

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3868

Translational Relevance

Performance status (PS) is one of the most common eligibility criteria, often resulting in exclusion of patients from trial participation and leading to clinical trial populations that are not reflective of populations afflicted with the disease. Existing PS tools are inherently subjective and invite bias. In addition, PS is less predictive of outcomes for older adults. Broadening PS eligibility criteria to be more inclusive can increase the number and diversity of participants in clinical trials. Trial sponsors should justify any exclusion of low-functioning PS patients and limit exclusions to circumstances of participant safety and trial integrity. A multidisciplinary working group of the American Society of Clinical Oncology and Friends of Cancer Research outlined several strategies to encourage broader trial eligibility criteria. Implementation of these recommendations will require cooperation of multiple stakeholders, and providing incentives for expanded PS eligibility may support this effort.

of PS2 as a prognostic factor, reviewed past and current clinical trials to determine how often PS2 was included in inclusion/exclusion criteria, and developed consensus recommendations on how PS eligibility criteria could be revised while ensuring the safety of participants and integrity of the trial, and additional areas for research.

Benefits

Increase number of patients eligible and shorten enrollment time

Small, mainly single institution studies have demonstrated that of patients deemed ineligible for a clinical trial, exclusion was related to poor PS in a significant proportion of patients, with variability across disease type, investigational therapy, and therapy line (22, 23). Even if other objective eligibility measures can be addressed, PS may remain a broad factor that excludes many patients (**Table 1**).

Improve assessment accuracy, particularly in older adults

Most patients with cancer are aged ≥65 years, however, existing PS scales are inadequate in this population (20). Restrictive PS eligibility criteria contribute to the pervasive age disparity between trial participants and the overall cancer population, raising concerns about whether PS is unjustly limiting older populations' ability to participate in trials (24–26). Multiple studies have demonstrated that other tools, such as the geriatric assessment, are better than PS at evaluating older adults' overall health status (27) and at predicting chemotherapy toxicity (20). While a full geriatric assessment may not be practical due to length, subcomponents may provide a better functional assessment, such as instrumental activities of daily living that measure functional independence.

Improve generalizability

Benefits for patients with high-functioning PS may not reflect outcomes for patients with low-functioning PS (28, 29). Many eligibility restrictions from registration trials, such as line of therapy or cancer stage, are incorporated explicitly into the labeled indications with the exception of PS limitations. Therefore, therapies tested only in participants with high-functioning PS are administered to patients with lower functioning PS. This extrapolation may occur more readily with targeted and immunotherapies given greater efficacy (30). Therefore, evaluation of an investigational agent in participants reflective of the patient population is important. More inclusive PS eligibility will also likely increase enrollment of older adults (24, 31) and address the lack of evidence noted above (32, 33).

Table 1. Risks and benefits of expanding enrollment to patients with worse PS.

	Patients/prescribing physicians	Sponsors/investigators
Benefits	• Earlier access to investigational agents for a larger population of patients • More complete safety and efficacy data to help inform standard-of-care decision-making in the "real world" once the agent is commercially available	• Greater ability to generalize to "real-world" populations • Larger population of potentially eligible patients may afford faster clinical trial accrual times • Efficacy/tolerability in an understudied population provides more informative drug labeling and may facilitate more use in these patients • Higher overall AEs may make PS2 population more sensitive to demonstration of a potential comparative tolerability benefit • Where poor PS is because of advanced disease, benefits in a clinical outcome (survival, symptom, or functional improvement) may be easier to demonstrate for a highly effective drug
Risks	• Potentially higher rates of AEs	• Potentially greater variability in outcomes if not stratified/balanced between treatment groups • Potentially higher rates of AEs/more complicated attribution of AEs; if PS balanced between treatment groups, it should be able to account for this • Diminished treatment effect if PS2 patients do not have the same treatment benefit as patients with good PS

Risks

Increased adverse events

Rates of adverse events (AEs) may be greater in PS2 participants as compared with PS0 and PS1 participants, and this may influence patient's outcomes and ability to comply with study procedures. As a result, investigators and sponsors may be reluctant to consider trial enrollment. PS2 patients risk AEs with standard therapy options as well, and thus participation on a trial may not necessarily pose a greater risk of AEs compared with standard therapy for a particular patient. Because targeted therapies often have higher response rates, PS2 patients may experience a greater therapeutic index in a targeted therapy trial than standard of care (e.g., cytotoxic chemotherapy), even if their absolute rate of AEs is higher than in patients with PS0 and PS1. Where the comparative tolerability between an investigational agent and standard therapy is less clear, including PS2 patients (who may be more sensitive to toxicity) may unmask subtle differences.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3868

Importantly, having a subset of PS2 patients will add important safety data to facilitate decision-making for patients in the post-approval setting (**Table 1**). Determining appropriate timing for including PS2 participants is challenging. When possible, inclusion of a small number of PS2 participants in early-phase trials is recommended to guide separate expansion cohorts for phase II or broader inclusion into registration trials.

Even when clinical trial eligibility allows PS2 patients to enroll, relatively few PS2 participants are actually enrolled (34, 35). This may relate to clinicians' lack of familiarity with the investigational agent and concerns about the tolerability and safety. Enhanced information about safety, tolerability, and efficacy from earlier phase trials with the agent may help to counteract this. In addition, when clinically appropriate, allowing physician discretion in the treatment approach as a component of the clinical trial may help to mitigate this issue (36, 37).

Potential impact on trial outcome data

In trials of novel therapies including PS2 participants, data suggest that outcomes may be inferior compared with participants with PS 0–1, even though low proportions of PS2 participants were included (38–40). This information alone should not be used as a justification for excluding PS2 patients. Instead, similar to other high-risk prognostic markers identified in oncology, PS information could be considered as a stratification factor. When safe, inclusion of participants with low-functioning PS provides valuable evidence to guide clinical care for most patients. Outcomes in low-functioning PS participants can also better inform statistical considerations for future trials.

The risk of inferior outcomes from low-functioning PS participants is a potential concern to sponsors, especially if compared with historical cohorts including high-functioning PS. The FDA has addressed a similar concern in a March 2019 final guidance on enrollment of patients with brain metastases stating, "to mitigate uncertainties about including patients with brain metastases in clinical trials, consider enrolling these patients in a separate subgroup within the trial" (41). In addition, FDA commentary has further indicated a willingness to restrict primary efficacy analysis to the participant subset who meet more conventional eligibility criteria when a sponsor enrolls a broader range of participants (42). FDA also notes that including a broader group of participants could offer benefits, such as additional information in drug labeling and/or reduced postmarketing commitments.

Simulation study methods

To explore the effects on inferences comparing trials that include versus exclude participants with PS2, simulations were conducted under a variety of trial settings with three levels of PS: PS0, PS1, and PS2. **Figure 1** presents results based on: (i) total sample size of 500 participants, (ii) 1:1 randomization to two treatment groups, (iii) accrual time of 24 months, (iv) a time-to-event endpoint, and (v) follow-up until 283 events are observed, achieving power of 85% based on an HR of 0.70 versus a null hypothesis of 1.0 and a two-sided alpha of 0.05. Participants were assumed to vary in their median survival: 12-, 9-, and 6-month median survival in PS0, PS1, and PS2 participants, respectively. Differences in drop-outs due to AEs or other factors varied: 5%, 10%, and 20% of PS0, PS1, and PS2, respectively, and AEs were assumed to have censored event times within the first 4 months. Simulations assumed 45% PS0, 45% PS1, and 10% PS2 participants, and the true HRs reflecting treatment benefit were varied across PS groups. Scenario 1 assumes all three PS groups have the same treatment effect, HR = 0.7. Scenario 2 assumes PS0 and PS1 participants derive benefit, but PS2 participants do not (PS0 and PS1 HR, 0.7 and PS2 HR, 1.0). Scenario 3 assumes PS2 participants derive greater benefit compared with PS0 and PS1 participants (PS0 and PS1 HR, 0.7 and PS2 HR, 0.5). Outcome measures that were assessed to determine the differences in inferences due to the variability in HRs across the groups were (i) the estimated HR, (ii) power, and (iii) time to complete the study because fewer patients would be excluded (measured as the time from the first enrolled participant to the last event required for analysis). Inferences from simulated trials (10,000/scenario) were analyzed under two different approaches: (i) excluding PS2 participants ($N = 450$ PS0 and PS1 patients included in analysis) and (ii) including the PS2 participants ($N = 500$ for analysis). When excluding PS2 participants, the analysis was undertaken when there were 283 events among the PS0 and PS1 participants.

The simulation study demonstrated the following conclusions for including PS2 participants:

(i) when the number of PS2 participants is relatively small (e.g., 10%), the effect on the estimated HR and power is relatively modest, even when the PS2 participants do not have a true treatment benefit (**Fig. 1A** and **B**).

(ii) including PS2 participants is likely to shorten duration of the trial by increasing the number of potentially eligible trial participants (**Fig. 1C**) and due to the higher event rate in PS2 participants relative to PS0–1 participants.

These conclusions may not be generalized to all trial settings. Single-arm trials need attention given that previous trial results (to which the study results will be compared) may not have included PS2 participants. Similarly, trials with smaller (or larger) sample size may have more dramatic or muted effects depending on other trial parameters, such as the fraction of PS2 participants.

Mechanisms for addressing risks associated with expanding PS eligibility criteria

- Assessing safety concerns should take into account the potential increased risk in AE rates between standard-of-care and experimental intervention, rather than the absolute rate of expected AEs.
- Reassess and revise PS eligibility criteria at each phase of drug development, in accordance with growing knowledge about the investigational agent. Early-phase data (AE rates and durable objective responses) for PS2 participants can decrease uncertainty of subsequent randomized trials. For example, trials could:
  - (i) include an exploratory PS2 cohort in early-phase trials to collect data without compromising internal validity and to inform inclusion in later phase trials, incorporating early stopping rules for unacceptable toxicity, or
  - (ii) if tolerability/safety is acceptable during early phase for PS0–1 participants, expand to include PS2 participants in later phases.
- Consider alternate trial designs and settings. Examples may include:
  - (i) trials specifically for PS2 participants and, where appropriate, PS3 participants. This may be most ideal for studies of modified ("deintensified") regimens where the overall goal is to develop a more tolerable therapy.
  - (ii) flexibility in the dosing schema, particularly for palliative trials. For example, enable investigator discretion to allow participants to initiate treatment at a reduced dosage with escalation to full dosage based on tolerability (37). This may be most appropriate for studies in advanced cancer where the goal of therapy is palliation.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3868

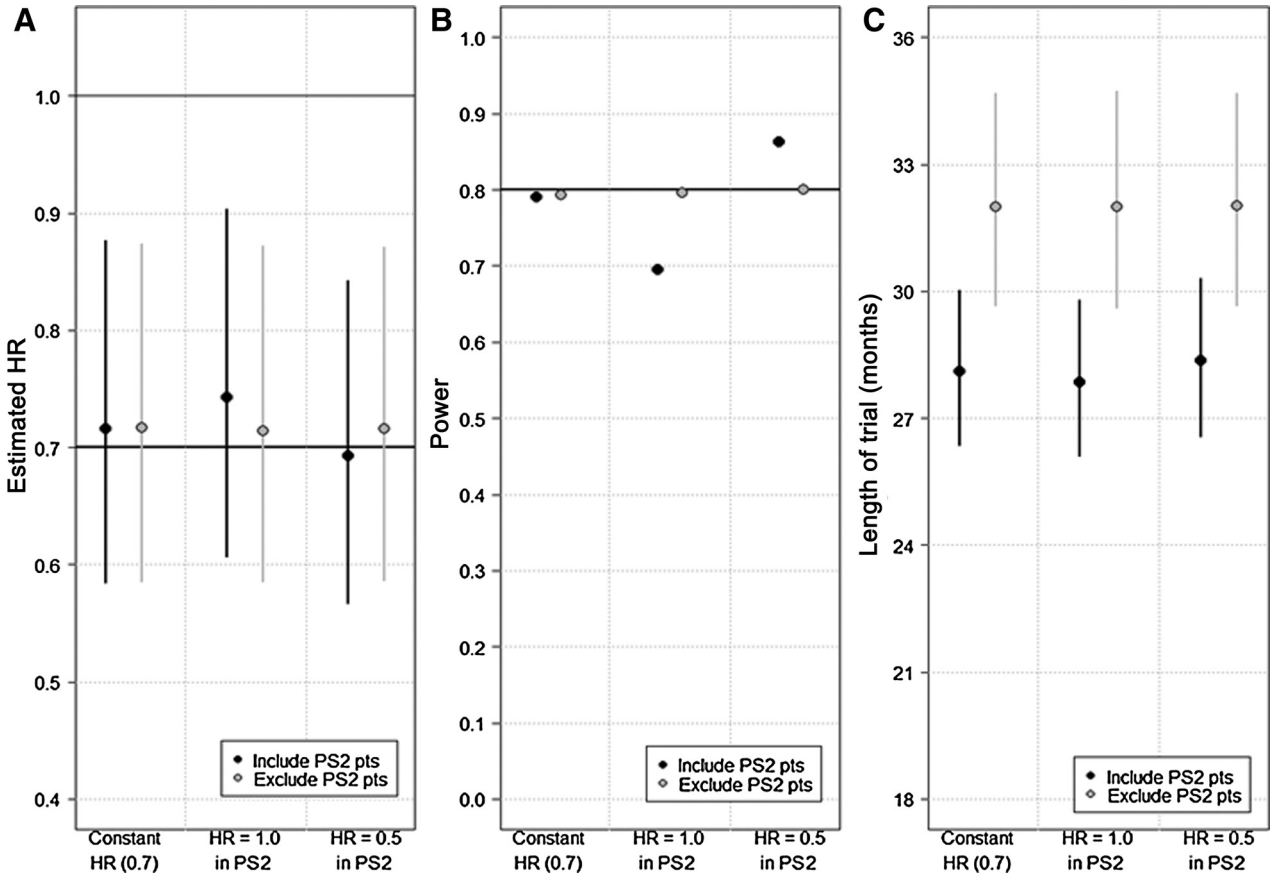

Figure 1.

Simulation study results depicting changes in estimated HR (**A**), power (**B**), and length of trial from first accrual to last required event for analysis (**C**). Within each panel, six analyses are depicted. **A** and **C**, The median from the simulations is plotted as a circle with lines extending vertically to the 5th and 95th percentiles. For each analysis, the HR of PS0 and PS1 patients (pts) remains constant at 0.7 and the HR of PS2 patients is varied. Red points/lines depict results when PS2 patients are included in the final analysis ($N = 500$); blue points/lines depict results when PS2 patients are excluded ($N = 450$). Regardless of sample size, the trial end is assumed to be when the required number of events (283 events) have been accrued per the power calculation.

(iii) Consider expansion cohorts to enhance enrollment of PS2 patients. This may be the most effective strategy for therapies with novel mechanisms or less well-defined AE profiles, whereby initial enrollment includes patients with high-functioning PS and once safety and tolerability are better understood, expansion to include PS2 patients occurs.

(iv) A postmarketing study that focuses on subgroups not well represented in premarket studies (43, 44). This may be most effective strategy for approved therapies where limited data currently exists for patients with low-functioning PS.

- Discuss study design and statistical analysis approaches for broader eligibility and implications for postmarketing research with FDA during trial design, where appropriate. This may include performing simulations under a variety of assumptions regarding fraction of PS2 patients and heterogeneity of efficacy and safety across PS groups.

Recommendations for inclusion of PS2 participants are included in **Table 2**. Although discussion has focused on inclusion of PS2 participants, PS3 participants should also be considered. With targeted therapies for rare alterations, inclusion of PS3 participants may be considered to expand the eligible patient population, if the agent has demonstrated favorable toxicity and efficacy signals.

Areas of Need for Future Research

Methods to incorporate functional status assessment

Alternate methods for assessing physical function exist, such as patient-reported outcome measures (45), objective performance measures (e.g., gait speed; ref. 46), and activity monitoring devices (e.g., wearable devices; ref. 47). Further research is needed to understand how to incorporate and use these alternative methods in oncology trials. Enhancing the objectivity of PS assessments may more accurately characterize functional capacity and improve trial suitability assessment, particularly if low-functioning PS is related to disease burden versus other factors around the time of diagnosis. Incorporating these methods may also reduce bias of PS assessments.

Associations between PS and safety/toxicity in targeted therapies and immunotherapy

The majority of newly approved investigational agents have targeted mechanisms of action, however, the safety and efficacy of many of these therapies remain unclear in the PS2 population given their

Table 2. Recommendations.

Number	Recommendation
1.	Patients with ECOG PS2 (or KPS 60–70) should be included, unless there is a scientific and/or clinical rationale for exclusion justified by established safety considerations.
	a. PS eligibility criteria should be based on the patient population in which the intervention is expected to be applied in clinical practice.
	b. PS eligibility criteria should be continually reevaluated and modified throughout the drug development process to reflect accumulated safety data of the investigational treatment. Decisions about PS eligibility criteria should be based on early clinical safety and efficacy data about the specific investigational agent or based on known data from other drugs in the same class with similar mechanism of action. Later-phase trials (e.g., phase II/III) should generally mirror the intended use population, and ECOG PS2 (or KPS 60–70) patients should be included unless safety concerns have manifested in earlier-phase trials. The rationale for exclusion should be justified and stated explicitly.
	c. Incorporating the rationale for inclusion of a broader population into the protocol could help encourage investigators to enroll these patients.
	d. PS data should still be collected for use as a stratification factor, regardless of how it is incorporated into eligibility criteria.
2.	Consider alternative trial designs, such as prespecified cohorts with lower functioning PS that are exempt from the primary analysis, to encourage inclusion of these patients. These cohorts would generally be small in size and exploratory in nature and could be enrolled in an incremental way to enable an early stopping rule based upon safety data. Consideration of the data analysis approach for the broader eligibility cohort and subgroup analysis should be determined during the study design phase and its implications for marketing and postmarketing requirements discussed with FDA when appropriate.
3.	Additional assessments of functional status should be considered to better characterize the functional status of ECOG PS2 patients and patients aged ≥65 years, such as ADLs and instrumental ADLs.

Abbreviation: ADLs, activities of daily living.

underrepresentation on clinical trials leading to approval (48). Understanding safety and efficacy of novel therapies in PS2 patients, particularly for patients with low-functioning PS due to disease burden, is a critical area of need, as a targeted therapy or immunotherapy with a high objective response rate may afford improvement in PS by improving disease-related symptoms.

Conclusion

Broadening PS eligibility criteria to be more inclusive can increase the number and diversity of trial participants. More effective biomarker-driven therapies warrant reconsideration of this traditional approach. Trial sponsors should justify exclusion of PS2 patients and limit exclusions to those affecting patient safety and trial integrity. Several strategies can encourage broader inclusion of PS2, and in select cases PS3, participants. Implementation of these recommendations will require cooperation of multiple stakeholders and can result in incentives following FDA approval.

Authors' Disclosures

A. Magnuson reports receiving National Institute on Aging K76 Career Development Award, NCI Loan Repayment Award, and honoraria for educational lecture provided at the American Society of Radiation Oncology 2020 Annual meeting. K.D. Wilner reports other from Pfizer Inc outside the submitted work. H.D. Klepin reports personal fees from Pfizer outside the submitted work and is a contributor to UpToDate. M.E. Fleury reports grants from Genentech, Bristol Myers Squibb, Merck, and IQVIA outside the submitted work. A. Melemed reports full-time employment with Chimerix, a biopharmaceutical company, and was previously employed by Eli Lilly and Company as a full-time employee. F.I. Arnaldez reports other from MacroGenics, Inc. outside the submitted work. No disclosures were reported by the other authors.

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily reflect the views or policies of the authors' affiliated institutions.

Acknowledgments

This article was developed as a consensus document of the Performance Status Working Group as part of a collaboration among ASCO, *Friends*, the FDA, and the NCI. The contents of this document were presented on August 2, 2019, as part of an invitation-only, collaborative workshop. The authors thank all the participants of the workshop, as well as the planning committee, ASCO, *Friends*, FDA, and NCI staff, for their expertise and thoughtful input on the project and article, and for logistical support. A. Magnuson was supported by a National Institute on Aging Beeson Career Development Award (NIA K76 AG064394). S.M. Lichtman was supported, in part, through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Received September 29, 2020; revised December 1, 2020; accepted December 11, 2020; published first January 9, 2021.

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Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO- *Friends* of Cancer Research Performance Status Work Group

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Clin Cancer Res Published OnlineFirst February 9, 2021.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3854

Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO–Friends of Cancer Research Prior Therapies Work Group

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ABSTRACT

Purpose: Restrictive eligibility criteria induce differences between clinical trial and "real-world" treatment populations. Restrictions based on prior therapies are common; minimizing them when appropriate may increase patient participation in clinical trials.

Experimental Design: A multi-stakeholder working group developed a conceptual framework to guide evaluation of prevailing practices with respect to using prior treatment as selection criteria for clinical trials. The working group made recommendations to minimize restrictions based on prior therapies within the boundaries of scientific validity, patient centeredness, distributive justice, and beneficence.

Recommendations: (i) Patients are eligible for clinical trials regardless of the number or type of prior therapies and without requiring a specific therapy prior to enrollment unless a scientific or clinically based rationale is provided as justification. (ii) Prior therapy (either limits on number and type of prior therapies or requirements for specific therapies before enrollment) could be used to determine eligibility in the following cases: a) the agents being studied target a specific mechanism or pathway that could potentially interact with a prior therapy; b) the study design requires that all patients begin protocol-specified treatment at the same point in the disease trajectory; and c) in randomized clinical studies, if the therapy in the control arm is not appropriate for the patient due to previous therapies received. (iii) Trial designers should consider conducting evaluation separately from the primary endpoint analysis for participants who have received prior therapies.

Conclusions: Clinical trial sponsors and regulators should thoughtfully reexamine the use of prior therapy exposure as selection criteria to maximize clinical trial participation.

Introduction

An expanding number of innovative approaches to cancer treatment, such as targeted anticancer therapies, are reframing our approach to patient selection for the evaluation of experimental agents in clinical trials (1). For example, targeted anticancer therapies are efficacious in molecularly defined patient subsets, irrespective of previous exposure to other types of treatment; they also tend to have more favorable side effect profiles than traditional cytotoxic chemotherapeutic agents, thus patients treated with targeted agents are often physically well enough to receive subsequent therapies (2–8). With ever-increasing understanding of drug interactions and novel toxicity profiles of innovative therapies, it is important to rethink the use of prior therapy as eligibility criteria for patient exclusion or inclusion into controlled studies.

The prior therapy selection criteria are a key aspect of clinical trial design and vary substantially, depending on the goals of the study. Updating their use would promote patient access to experimental drugs, improve patient participation, clinical trials accrual, and increase the applicability of trial results to a more general population of patients. The rationale for broadening eligibility criteria to make clinical trial participants more representative of the general population has been described previously in a joint effort by the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*; ref. 9). Key recommendations to modernize clinical trial eligibility criteria associated with minimum age (10), organ dysfunction, prior or concurrent malignancies (11), brain metastases (12), and human immunodeficiency virus infection (13) have been published and led to new guidance documents development by the FDA (14–17).

Building on the success of this initial effort, ASCO and *Friends* convened a multi-stakeholder working group of experts from multiple disciplines to evaluate the current practice of using prior therapy as entry criteria for clinical trials, and developed recommendations to support the design and conduct of clinical trials.

Process

The ASCO-*Friends* Prior Therapies Working Group included clinical investigators, clinical pharmacologists, patient advocates, and regulatory and industry representatives. The working group developed a framework for eliminating barriers to participation in clinical trials based on restrictive criteria on the types and timing of prior cancer therapy, to maximize inclusivity in clinical trials. All working group members acknowledged that the use of prior therapies as a criterion for eligibility is deeply tied to clinical

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Clin Cancer Res 2021;XX:XX–XX

doi: 10.1158/1078-0432.CCR-20-3854

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3854

Translational Relevance

With rapid-cycle discovery of new drugs with well-characterized targets and mechanisms of action, the therapeutic index and efficacy of new candidate cancer drugs are significantly better than in the past, reconfiguring the safety and efficacy calculus in using prior therapy exposure to select patients for clinical trials. Concurrently, there is growing awareness that cancer drugs approved in restrictive clinical trials are often used in real-world practice for groups of patients ineligible for such trials, even without evidence for their safety or efficacy. Using a patient-centered conceptual model that considers safety, efficacy, and the ethical principles of distributive justice and beneficence, a multi-stakeholder working group has proposed three recommendations to promote more thoughtful consideration of the use of prior therapy as a selection criterion for oncology trials. The overarching objective is to minimize this potential barrier to clinical trial access for willing patients.

trial design. For example, a trial may require patients to be treatment naïve if investigating an agent as first-line therapy, while another trial may require patients to have received a specific prior therapy or a limited number of prior therapies if investigating an agent as a later line of therapy, or if a prior therapy is known to interact with the investigational agent.

The working group, thus, developed a conceptual framework with which to guide subsequent discussions; and reviewed a sample of the most recently registered, ongoing clinical trials in five disease areas selected from the ClinicalTrials.gov website to examine how prior therapies are being used as eligibility criteria. The working group used these insights to guide subsequent discussions that led to the final proposed recommendations.

Conceptual framework

We developed a conceptual framework for evaluating the advantages and limitations of using prior therapy as eligibility criteria in clinical trials (**Fig. 1**). This framework considers both information about the potential or known toxicity of the experimental agent and its efficacy in relation to existing treatments, to determine the appropriateness of restricting clinical trial participation based on previous treatments. By deconstructing the decision-making process into its basic elements of safety and efficacy, the working group was able to develop recommendations within the context of patient centeredness, keeping with the ethical principles of distributive justice and beneficence (18, 19). These considerations guided the thought process behind the ClinicalTrials.gov exercise and the recommendations proposed by this working group.

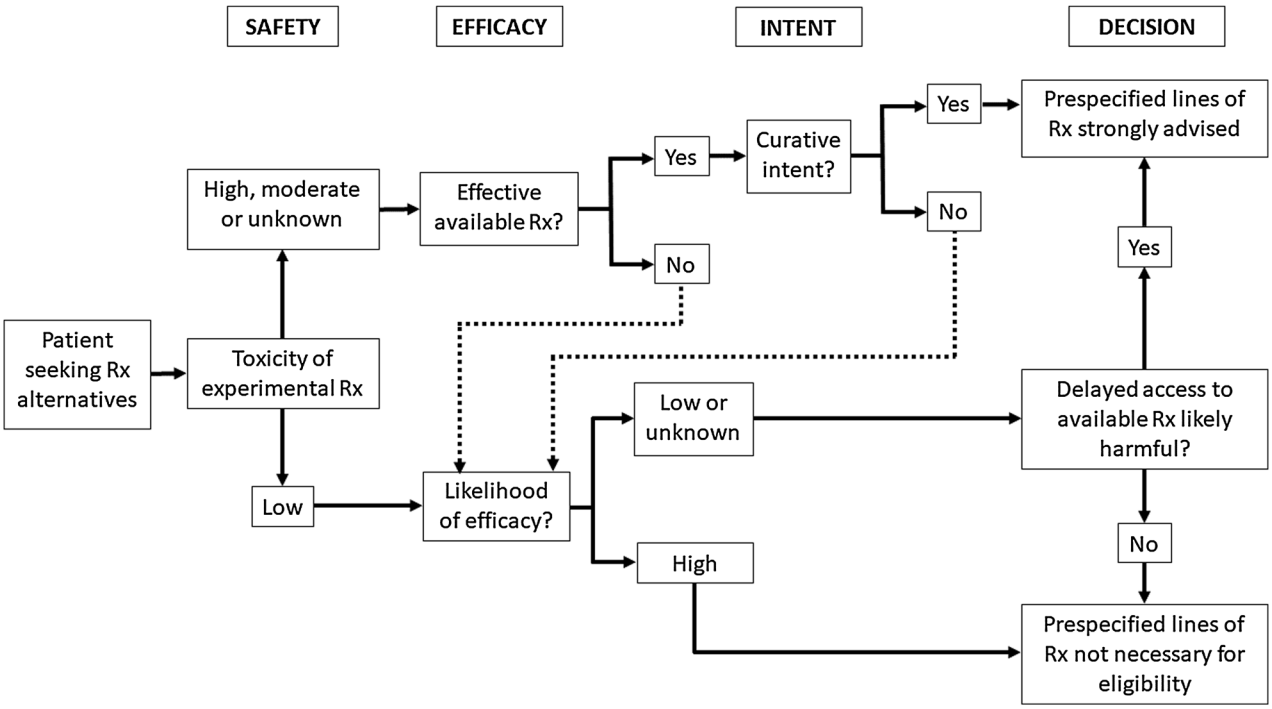

Figure 1.

Conceptual framework to guide the use of prior therapy as selection criteria in clinical trials. We encourage the use of this conceptual framework early in the process of clinical trial design, to minimize the barrier to entry. We encourage shared decision-making between the patient and the health care provider in selecting treatment options, including treatment within a clinical trial. In general, clinical trials should be designed with the aim of achieving greater inclusivity with minimal restrictions placed on trial entry. Decisions regarding whether exposure to existing therapy should be required prior to administering an investigational therapy should consider the risks (i.e., known or unknown safety profile) and the efficacy of the therapy, and the availability of alternative treatments. In a clinical setting, wherein the standard-of-care treatment provides a high likelihood of cure, such as may be the case for some in an adjuvant setting or for some advanced lymphomas or pediatric cancers, it may be appropriate to restrict access to experimental therapy until after disease progression, relapse, or intolerance of such existing treatments. However, in the noncurative setting, a requirement for receipt of such "standard" options is not recommended unless there is sound scientific or clinical rationale to support the restriction. Rx, therapy.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3854

Current use of prior therapies as eligibility criteria, ClinicalTrials.gov assessment

To better understand the scope of the problem, we used the ClinicalTrials.gov website to assess the extent to which prior therapy is currently used as eligibility criteria (20). In July 2019, we accessed the ClinicalTrials.gov website to select the 11–12 most recently registered phase I–III clinical trials in breast cancer, colon cancer, lung cancer, malignant melanoma, and multiple myeloma, for close evaluation of how prior therapy requirements were being used as eligibility criteria. The working group defined inclusion and exclusion criteria based on prior therapies as those criteria that did not have a specified washout period. Any criteria based on prior therapies that included a washout period were categorized as "washout period criteria" and not assessed in this study. Trials were categorized by cancer type, clinical trial phase (with phase I/phase II trials considered phase I due to their emphasis on the exploration of safety endpoints), and by drug class (including immunotherapy, alone or in combination, chemotherapy only, and other).

Findings

The working group reviewed a total of 57 trials to assess whether there were requirements based on prior therapies, specifying whether these were inclusion or exclusion criteria (**Fig. 2**; Supplementary Table S1). Thirty-three clinical trials corresponded to phase I (58%), 15 trials to phase II (26%), and nine to phase III (16%). More than 90% of clinical trials investigated immunotherapies (91%; 52/57), either alone or in combination with other agents or treatment modalities, such as chemotherapy and radiotherapy. Of the remaining five clinical trials (9%), four investigated other therapies, such as retinoid X receptor and hyperbaric oxygen, and one investigated a chemotherapy agent only (Supplementary Table S1). The breakdown of clinical trials by cancer type was 12 trials in breast cancer, 11 in colon cancer, 11 in lung cancer, 11 in melanoma, and 12 in multiple myeloma.

Two-thirds (38/57) of the trials included prior therapy as an eligibility criterion and 19 trials (33%) did not specify prior therapy as an eligibility criterion. Among 38 trials, 19 (50%) specified prior therapy as an exclusion criterion only, 14 (37%) specified prior therapy as both an inclusion and exclusion criterion, and five (13%) specified prior therapy as an inclusion criterion only. When categorized by clinical trial phase, 58% (19/33) of phase I trials specified either an inclusion or exclusion criterion based on prior therapies, while 42% (14/33) did not. Of the 15 phase II trials, 10 (67%) specified either an inclusion or exclusion criterion based on prior therapies, compared with five (33%), which did not. Finally, all nine phase III trials specified either an inclusion or exclusion criterion based on prior therapies, with exclusion criterion only specified in six trials (67%), and both inclusion and exclusion criteria based on prior therapies specified in three trials (33%; **Fig. 2**).

The pattern of use of prior therapies as eligibility criteria in trials categorized by drug class and tumor type is shown in **Fig. 2**. Use was most prevalent in lung cancer trials (82%; 9/11) and least prevalent in melanoma trials (45%; 5/11). The predominance of immunotherapy trials in the survey, which may be indicative of the predominance of immunotherapy trials in recent ClinicalTrials.gov registrations, may limit the extrapolation of our findings to nonimmunotherapy trials.

Recommendations

Taking all available evidence into consideration, the working group proposed the recommendations outlined in **Table 1**, on the basis of the key principles of preserving patient safety, facilitating the assessment

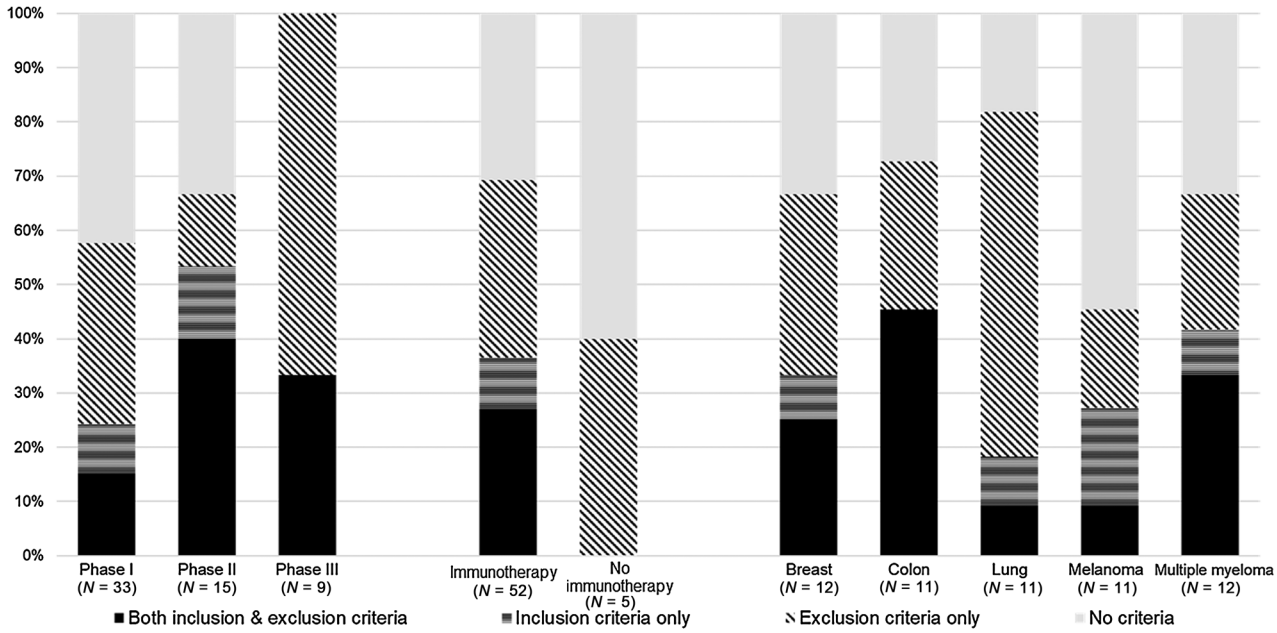

Figure 2.

Frequency of the use of prior therapies as inclusion and/or exclusion criteria in clinical trials as part of the ClinicalTrials.gov exercise categorized by phase, drug class, and tumor type. ClinicalTrials.gov was accessed on July 23, 2019. Trials with any component of phase I trials (e.g., phase I/II) were categorized as phase I trials. The working group defined inclusion and exclusion criteria based on prior therapies as those criteria that did not have a specified washout period. Any criteria based on prior therapies that included a washout period was categorized as "washout period criteria" and not evaluated in this assessment.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3854

Table 1. Recommendations for the modernization of eligibility criteria based on prior therapies.

Recommendation	Comment
(i) Patients are eligible for clinical trials regardless of the number or type of prior therapies and without a requirement to have received a specific therapy prior to enrollment unless a scientific or clinical rationale is provided as justification.	There needs to be a balance between the desire to conduct a tightly controlled experiment with high internal validity and the reality that patients with much broader demographic and disease characteristics than those patients evaluated in clinical trials are prescribed the approved drugs (22). Clinical trials are the most controlled mechanism for evaluation of the safety and efficacy of investigational agents in a carefully selected patient population. However, arbitrary exclusion of populations of patients who may desire access to clinical trials, and may derive benefit from them, runs counter to the principles of patient autonomy and beneficence. The opportunity cost of such arbitrary restrictions to sponsors and designers of clinical trials may also be largely underrecognized. Overly complex eligibility criteria may, in part, increase the burden on research staff, slow down clinical trial accrual, increase the risk of failure to complete clinical trials, and raise the audit and regulatory stakes for enrolling sites and their staff. Indeed, the Pharmaceutical Research and Manufacturers Association reported that 80% of clinical trials do not finish on time, 20% are delayed 6 months or more, and up to two thirds of clinical trials fail to meet their original patient enrollment goals (39). Reducing barriers that hinder recruitment, such as broadening eligibility criteria, would be beneficial.
(ii) Prior therapy (either limits on the number and type of prior therapies or requirements for specific therapies before enrollment) could be used to determine eligibility in the following cases:	To promote greater clinical trial inclusivity in trials, minimally restrictive criteria should be used, with patient safety and autonomy as the primary considerations. However, there may be some specific scenarios in which these criteria may be justifiable and necessary to maintain patient safety and ensure treatment efficacy. In these cases, when entry into a trial is contingent upon exposure to a prior therapy (or lack thereof), scientific and/or clinically sound rationale should be provided.
a. If the agents being studied target a specific mechanism or pathway that could potentially interact with a prior therapy.	The working group identified three cases in which prior therapy could be used to determine patient eligibility, and additional specific scenarios are listed in **Table 2**.
b. If the study design requires that all patients begin protocol-specified treatment at the same point in the disease trajectory.	With evolving evidence that investigational agents with known mechanisms of action, which effectively target specific biologic pathways, are highly effective irrespective of the point in the disease trajectory (2–5, 32–36, 38, 43), trial designers are encouraged to continuously reevaluate the use of prior therapies as eligibility criteria.
c. In randomized clinical studies, if the therapy in the control arm is not appropriate for the patient due to previous therapies received.	
(iii) Trial designers should consider conducting evaluation separately from the primary endpoint analysis for participants who have received prior therapies.	There may be concerns that enrolling a subset of patients who may be considered higher risk due to their exposure or lack of exposure to prior therapies might jeopardize drug development by reducing apparent treatment efficacy and/or increasing the risk of severe adverse events in such high-risk patients. To preserve methodologic rigor in clinical trials while maintaining the desire for minimal barriers to entry, multiple strategies can be considered for data analysis and interpretation. Some of these approaches have been suggested in prior publications in this series (9, 22). These concerns can be addressed at the time of trial design by prespecifying how data from this subset of higher risk patients will be handled in executing the trial and the statistical analyses. For example, in early-phase trials, an expanded cohort with perceived high risk due to prior therapy history can be recruited and closely monitored for safety signals, which can be used to prompt closure of that subset without jeopardizing the whole program (9–12). The information generated from this expansion cohort can then be used to inform the criteria for later-phase trials. In addition, patient enrollment into the arms of randomized clinical trials can be stratified on the basis of prior therapy history, with all patients included in the intention-to-treat analysis, but with prespecified analyses restricted to a "modified intention-to-treatment" subset. As suggested by Jin and colleagues, in hierarchical testing, the primary analysis could be restricted to the lower-risk modified intention-to-treat population, with subsequent analyses to include the whole population (22). Another alternative would be to enroll a parallel cohort of patients who do not meet the prior therapy restriction, which would not be part of the intention-to-treat population, but whose data, analyzed separately, would still provide descriptive safety and efficacy information. This alternative, however, might be considered less desirable because toxicity data from such a trial design would be difficult to interpret due to the absence of a control group (22) and because of the time still required to accrue the intention-to-treat population. The rapidly evolving development of adaptive clinical trial designs and statistical analysis methodologies may accommodate the goal of expanding clinical trial participation irrespective of prior therapy history.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3854

Table 2. Scenarios in which selection criteria based on prior exposure to therapy may be applied, rationale, pros, and cons.

Scenario	Rationale	Pros	Cons
Limitation to treatment-naïve patients (i.e., first-line treatment trials)	Comparison with standard first-line treatment Typically, drug registration trials	• Need clearly defined target treatment population • High risk of poor efficacy or greater toxicity when pretreated patients are included • Minimize expense of including patients deemed higher risk for failure • Need to establish a market niche	• Exclusion of healthy individuals, often long-term beneficiaries of prior therapy with recent disease progression (e.g., long-term cancer survivors with subsequent disease) • Progression to metastatic disease after prior systemic adjuvant therapy is a common scenario with arbitrary time interval rules for inclusion/exclusion
Limitation to previously treated patients ("salvage therapy" trials)	Assurance of prior exposure to standard of care. Possibly, drug registration trial	• Secure means of testing promising new agents in the face of existing, highly curative standard treatments • Establishment of market niche • Potentially enable comparison with historically treated population outcomes	• Risks of requiring prior therapy in the face of potentially more effective or safer novel treatment, especially in rare or clinically aggressive disease, when available standard treatment is modestly effective or highly toxic • Violation of patient autonomy/threat to principle of beneficence • Comparisons across clinical trials and over different time frames and populations, even of ostensibly similar groups, is rife with unknown bias, is statistically unsound, and should be discouraged. Furthermore, restricting access to clinical trials in relatively uncommon diseases is particularly wasteful
Strict limitation of the number of allowed prior therapies (typically one or two)	Assurance of prior exposure to standard of care. Often, drug registration trials	• Patients typically still are good candidates for treatment despite prior therapy. • Clearly defined population with relative homogeneity in terms of disease refractoriness and susceptibility to toxicity • Establishment of market niche for registration • Enable comparison of outcomes in a noncomparative trial with historically treated populations	• "Indication creep" occurs in real-world practice, creating exposures with unknown safety or efficacy • Optimal time to identify adverse safety and/or efficacy signals is under the auspices of a clinical trial with greater standardized data collection and evaluation than in routine practice • Potential missed opportunity to detect new efficacy signals that can expand market share • Expansion of eligible cohorts promotes accrual, timely trial completion, with associated cost savings • Given greater success rates and less toxicity of drugs with well-defined mechanisms of action, ethical dilemma created with potential loss of opportunity for access to beneficial treatment, in violation of patient autonomy and the principle of beneficence • Comparisons with historical populations spurious and invalid
Exclusion based on prior exposures to specific treatments	Concerns about interference with action of trial agent (effectiveness and/or toxicity)	• Typically, exclusion of exposure to drugs of the same class, with similar mechanism of action and, therefore, likelihood of adverse interaction with effectiveness or safety of trial agent	• Potential missed opportunity for detection of differential activity • Increasing population of long-term survivors who have had remote prior exposure and no residual effects from prior therapy

of drug efficacy, and promoting patient centeredness. The recommendations reflect the general position that as a default, minimal eligibility restrictions based on prior therapy should be implemented. The working group encourages critical thinking about the appropriate use of eligibility criteria based on prior therapies by considering the need to balance the goals of scientific rigor, and trial efficiency, with the goal of broader clinical trial inclusivity.

Discussion

Traditionally, clinical trials specify prior therapies that are either required for inclusion or exclusion of patients from participation. Tightly controlled eligibility criteria are thought to optimize conditions to test the safety and efficacy of an investigational therapy (21, 22). The working group characterized scenarios under which the use of

prior therapies as exclusion criteria (i.e., no prior therapy or no prior therapy of a certain type allowed) or as inclusion criteria (i.e., a defined number and/or type of prior therapies required for eligibility), may be appropriate. We further outlined the rationale for, and the pros and cons of, these scenarios (**Table 2**). We avoided scenarios in which prior therapies might be specified to exclude overlapping exposure to prior and new therapy (i.e., washout periods), deferring to the ASCO-*Friends* Working Group on Washout Periods and Concomitant Medications, which was charged with the task of addressing this important topic.

For example, to "optimize for safety," prevailing practice may be to specify a maximum number of prior therapy exposures, to minimize the risk that heavily pretreated patients may be more likely to experience excessive toxicity. Another common practice may be to limit prior exposure to specific types of prior therapies whose toxicities potentially overlap those of the experimental therapy, such as would be the case for potentially irreversible toxicities, like bone marrow toxicity, neuropathy, or cardiotoxicity. However, the concerns for excess toxicity may be more appropriately addressed by requiring resolution or improvement in the toxicities of concern, rather than by implementing broad exclusions based upon exposure to prior therapies.

Eligibility criteria may also be designed to "optimize for efficacy" by defining a study population that is comparable with historical trials to permit an evaluation of improvements in outcomes with the new therapeutic in noncomparative trials. Trial designers may seek to define a study population that is most likely to respond to the treatment being studied. For example, positioning a second-generation agent targeting resistance mutations where either relapse after a first-generation compound has selected for the acquired resistance mutation or designing upfront treatment for an *ab origin* mutation (23, 24), or limiting the number of prior treatments to minimize the risk that heavily pretreated patients with refractory disease will bias trial results against treatment response (25, 26). This raises the fundamental question whether restricting patients from enrollment in a clinical trial solely based on prior therapy is justifiable to show the best outcome of the trial treatment for a specified patient population or whether it is more advantageous to open up patient eligibility to enable quantification of outcomes across the spectrum of potential clinical use scenarios (22, 27).

In addition to safety and efficacy considerations, the intent of the trial is an important consideration. A trial designed to evaluate safety and effectiveness of an investigational agent for the purposes of gaining marketing licensure may seek to enroll patients with an unmet medical need, for example, patients with advanced refractory disease who have exhausted currently available treatment options, for whom clinical trials may be the only potential treatment option (28, 29). A trial may be designed to compare a new investigational agent against a standard-of-care treatment in a particular treatment setting, such as a specific line of therapy or treatment with a particular class of drugs (30, 31). In this case, trial designers often insist that a study population be naïve to any treatment or restricted to a population that has received a minimum or maximum number, or certain specific types, of prior therapies.

Advances in the understanding of the biological underpinnings of cancer have facilitated the development of therapies that are based on key tumor characteristics, such as gene and protein expression profiles, have relatively well-understood mechanisms of action, are often effective irrespective of prior drug exposures, and have a wider therapeutic index (2–5, 32–38). This has mostly rendered obsolete the clinical rationale for eligibility criteria that specify requirements for prior therapy, simultaneously raising the ethical dilemma of the opportunity cost to the patient, of arbitrary patient selection criteria based on prior therapy (18, 19, 39). Patients increasingly seek access to promising drugs in development, particularly those that treat rare or clinically aggressive cancers. Mandating prior exposure to marginally effective or excessively toxic treatments, in theory, may delay or prevent access to potentially more beneficial novel treatment. Conversely, blanket exclusion of patients who have received any prior treatment may prevent otherwise healthy patients with disease progression from gaining access to potentially health-preserving new treatments.

Finally, the implementation of prior therapy criteria in the absence of scientific or clinical rationale may unnecessarily restrict the post-approval target population and delay evaluation of a new drug's efficacy and safety in the wider population that may ultimately receive the drug once it is approved (40). Limiting patient access to clinical trials based either on exposure to prior therapies or the requirement for patients to have progressed after specific therapies limits patient access to clinical trials and may significantly slow trial accrual or compromise completion of these trials.

Conclusion

The discovery of highly effective anticancer treatments, and the technologies that enable the selection of patients with targetable genomic alterations, has resulted in the traditional line-of-treatment demarcations becoming increasingly blurred. Ultimately, the inclination to conduct clinical trials in homogeneous populations for more robust comparisons (internal validity) must be finely balanced against the pragmatic need to test novel therapies in the "real-world" populations that will eventually be exposed to approved treatments (external validity; ref. 40), as well as the concept of patient centeredness, and the ethical principles of distributive justice and beneficence. The Institute of Medicine, now National Academy of Medicine, defined patient centeredness as "responsiveness to the needs, values, and expressed preferences of the individual patient" (41). In 2010, the same body recommended that the NCI, Cooperative Groups, and physicians should take steps to increase the speed, volume, and diversity of patient accrual and to ensure high-quality performance at all sites participating in cooperative group trials. As an example, they recommended that they should "encourage patient eligibility criteria that allow the broadest participation possible" (42).

Clinical trial designers and sponsors should clearly justify any restrictions based on prior therapies. The working group's overarching consideration in making these recommendations was to promote patient-centered clinical trials with the minimum entry criteria needed to ensure participant safety and broad access. We hope these recommendations will be widely adopted by key stakeholders, especially designers, sponsors, and regulators of clinical trials.

Authors' Disclosures

R.U. Osarogiagbon reports grants from NIH; other from American Cancer Society, Eli Lilly, Gilead Sciences, and Pfizer; and personal fees from Association of Community Cancer Centers, Biodesix, AstraZeneca, and Triptych Healthcare Partners outside the submitted work, as well as a patent for US10,338,073B2 issued to R.U. Osarogiagbon, US10,422,801 issued to R.U. Osarogiagbon, and DE202012013719.0 issued to R.U. Osarogiagbon, and is founder of Oncobox Device Inc. D.M. Vega reports nonfinancial support from Aetion outside the submitted work. P. De Porre reports employment with Johnson & Johnson. J.N. Holloway reports employment with Caris Life Sciences. D.S. Hong reports research/grant funding from AbbVie, Adaptimmune, Aldi-Norte, Amgen, Astra-Zeneca, Bayer, BMS, Daiichi Sankyo, Eisai, Erasca, Fate Therapeutics, Genentech, Genmab,

Ignyta, Infinity, Kite, Kyowa, Lilly, Loxo, Merck, MedImmune, Mirati, miRNA, Molecular Templates, Mologen, Navier, NCI-CTEP, Novartis, Numab, Pfizer, Seattle Genetics, Takeda, Turning Point Therapeutics, Verstatem, and VM Oncology; travel, accommodations, expenses from Bayer, Loxo, miRNA, Genmab, AACR, ASCO, and SITC; consulting, speaker or advisory role to Alpha Insights, Acuta, Amgen, Axiom, Adaptimmune, Baxter, Bayer, Boxer Capital, COG, Ecor1, Genentech, GLG, Group H, Guidepoint, HCW Precision, Infinity, Janssen, Merrimack, Medscape, Numab, Pfizer, Prime Oncology, Seattle Genetics, ST Cube, Takeda, Tavistock, Trieza Therapeutics, and WebMD; and other ownership interests with Molecular Match (advisor), OncoResponse (founder), and Presagia Inc (advisor). R.L. Schilsky reports grants from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Genentech, Lilly, Merck, and Pfizer outside the submitted work. E.S. Kim reports personal fees from AstraZeneca, Boehringer Ingelheim, and Roche outside the submitted work. No disclosures were reported by the other authors.

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily reflect the views or policies of the authors' affiliated institutions.

Acknowledgments

The working group acknowledges Drs. Wayne Rackoff (Janssen) and Lee Krug (Bristol Myers Squibb) for their insightful contribution to the initial development of the concepts discussed in this article. R.U. Osarogiagbon was supported by NIH 2UG1CA189873-06.

Received September 28, 2020; revised November 25, 2020; accepted December 29, 2020; published first February 9, 2021.

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Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3854

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AACR American Association for Cancer Research

Clinical Cancer Research

Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO–Friends of Cancer Research Prior Therapies Work Group

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Clin Cancer Res Published OnlineFirst February 9, 2021.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3853

Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group

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ABSTRACT

Purpose: In clinical research, eligibility criteria promote patient safety and optimize the evidence generated from clinical trials. However, overly stringent eligibility criteria, including laboratory requirements, may limit enrollment, resulting in delayed trial completion and potentially limiting applicability of trial results to a general practice population.

Experimental Design: Starting in 2018, a working group consisting of experts in direct patient care, the FDA, industry, and patient advocacy developed recommendations to guide the optimal use of laboratory reference ranges and testing intervals in clinical trial eligibility criteria and study procedures. The working group evaluated current eligibility criteria across different clinical trial phases and performed a literature review to evaluate the impact of and justification for laboratory test eligibility requirements and testing intervals in clinical trials. Recommendations were developed on the basis of the goals of promoting safety and optimizing the evidence generated, while also expanding eligibility and applicability, and minimizing excess burden of trial participation.

Results: In general, we found little variation over time and trial phase in laboratory test requirements, suggesting that these eligibility criteria are not refined according to ongoing clinical experience. We propose recommendations to optimize the use of laboratory tests when considering eligibility criteria.

Conclusions: Tailoring the use of laboratory test requirements and testing intervals may increase the number and diversity of patients in clinical trials and provide clinical data that more closely represent the general practice populations.

Introduction

Clinical trial enrollment has become more challenging over the years, in part, due to increasing number and complexity of eligibility criteria and study requirements. From 2001 to 2015, trial endpoints, eligibility criteria, and procedures steadily increased (1, 2). An evaluation of Eastern Cooperative Oncology Group lung cancer protocols revealed a median increase in number and complexity of eligibility criteria from 17 in 1986–1995 to 27 in 2006–2016 (3). Appropriate and relevant eligibility criteria are necessary to ensure the safety of patients participating in a clinical study and to allow for interpretability of the clinical study results (4). However, overly stringent eligibility criteria may unnecessarily limit enrollment, resulting in delayed trial completion, and limiting generalizability of the research results to a broader practice population. Eligibility for clinical trials should be recognized as a distributive justice issue for individual patients and for vulnerable populations (5). Balancing the need for modernized eligibility criteria with patient safety requires careful review and planning of clinical trial protocols and eligibility criteria.

In 2016, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) initiated a joint project to evaluate eligibility criteria in oncology clinical trials and to investigate potential strategies that could expand trial eligibility while maintaining patient safety (6). This initial effort resulted in the development of key recommendations that catalyzed efforts to improve the applicability and accessibility of clinical studies to patients with brain metastases, human immunodeficiency virus infection, younger age, organ dysfunction, and prior/concurrent malignancies (6–10). However, additional barriers and opportunities remain. Follow-up activities were conducted to identify and prioritize additional criteria that may hinder the rate of trial accrual and unnecessarily restrict patient access to investigational therapies.

Laboratory tests represent one of the most commonly employed categories of eligibility criteria in clinical trials. For instance, minimum renal and hepatic function may be required for therapies that are either metabolized by or pose toxicity to these organ systems. Similarly, threshold blood counts provide a margin of safety for myelosuppressive treatments. Despite this clear rationale, there is obvious potential for unintended consequences. For instance, in oncology, the majority of patients are older, a population in which some degree of organ dysfunction is quite common, but rarely has clinical consequences. It follows that a recent study found that strict renal and hepatic function

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Clin Cancer Res 2021;XX:XX–XX

doi: 10.1158/1078-0432.CCR-20-3853

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3853

Translational Relevance

Stringent eligibility criteria, including laboratory test thresholds, may restrict clinical trial enrollment and limit the relevance of study results. The American Society of Clinical Oncology and Friends of Cancer Research worked with stakeholders throughout the cancer research community to develop evidence-based, consensus recommendations to modernize the use of clinical trial laboratory test–related eligibility and intervals. These recommendations may help to facilitate accrual and render trial populations more representative of the disease population, improving the generalizability of the research results.

requirements were one of the most common reasons for excluding potential patients from clinical trials (11). While not every patient will be a candidate for a clinical trial, the exclusion of patients for what can often be arbitrary reasons, thereby diminishes the desire for those involved to enroll on clinical trials. Laboratory abnormalities may also represent reversible manifestations of the underlying malignancy. ASCO and *Friends* established a working group to understand current practices related to clinical trial laboratory test requirements and intervals. The group also assessed whether reasonable changes could be recommended while preserving patient safety and study scientific integrity. The scope of work did not encompass tumor tissue requirements or biomarker testing for clinical trial enrollment, as they require additional considerations beyond the use of laboratory tests as eligibility criteria (3, 12).

Process

To inform our recommendations related to laboratory test requirements and testing intervals, we reviewed eligibility criteria from a sampling of recently submitted or active cancer clinical trial protocols from diverse sources. Specifically, we included protocols from (i) a clinical practice setting (Sarah Cannon Research Institute, Nashville, TN; industry-sponsored trials activated January 2018–May 2019; $N = 97$), (ii) an industry sponsor (AstraZeneca; late-phase oncology trials active in 2018; $N = 13$), and (iii) a regulatory authority (FDA; applications submitted May 2018–May 2019; $N = 13$). The following information was collected and summarized: disease under study; trial phase; class of therapy (targeted/small molecule, immunotherapy, chemotherapy, or combination therapy); eligibility thresholds for bone marrow, renal, and hepatic function; requirements for transfusion- and growth factor–free periods; and coagulation parameters.

Separately, we reviewed 2019 oncology FDA approvals and identified 26 approvals on the basis of randomized phase III clinical trials. Published articles supporting 23 of the 26 approvals were retrieved (as of March 2020) and the eligibility criteria specifics for each trial were extracted from the article supplementary material (Supplementary Table S1).

Findings

Evaluation of eligibility criteria in clinical trial protocols

Table 1 broadly describes the characteristics of the clinical trials included in our assessment of laboratory test criteria. More than a 100 industry-sponsored trials were represented in the trial review and 13% of the trials only enrolled patients with a hematologic malignancy.

Table 1. Oncology clinical trial distribution by trial phase and therapy.

Trial characteristic	Solid cancer trials, *n* (%) (*n* = 107)	Hematology–oncology trials, *n* (%) (*n* = 16)
Trial phase		
I	71 (66%)	11 (69%)
I/II	19 (18%)	4 (25%)
II	8 (8%)	1 (6%)
III	9 (8%)	0 (0%)
Therapy category		
Targeted/small molecule	37 (35%)	5 (31%)
Immunotherapies	46 (44%)	7 (44%)
Chemotherapy	14 (13%)	1 (6%)
Combination	8 (8%)	3 (19%)

Figure 1 displays the laboratory test–based eligibility criteria for the 107 solid tumor trials included in our analysis. In general, we observed the greatest heterogeneity for renal function, even within a single-drug class. For instance, among immune checkpoint inhibitor trials, creatinine clearance (CrCl) requirements were almost equally distributed among 30, 40, 50, and 60 mL/minute. The justification for such variation is not readily clear, as these drugs tend to undergo similar metabolism and excretion and have similar rates of nephrotoxicity. It is also noteworthy that the most common minimum platelet count requirement was 100,000/μL for all three drug classes, even though thrombocytopenia occurs almost universally with cytotoxic chemotherapy, but in well under 5% of patients treated with immune checkpoint inhibitors. Similarly, hemoglobin eligibility requirement was 9 g/dL for almost all trials, with anemia a common toxicity with cytotoxic agents, but a rare event with immunotherapy.

Hepatic function exceptions for patients with suspected Gilbert syndrome and liver metastases were employed for most clinical trials (66% and 71%, respectively). The guidelines for patients with Gilbert syndrome ranged widely: some trials allowing for a total bilirubin of up to 3× to 5× upper limit of normal (ULN) and a direct bilirubin up to 1.5× ULN; in some cases, no threshold was specified. In addition, the existence of such exceptions raises the question whether laboratory test thresholds could be relaxed more broadly. That is, whether a therapy is considered safe in a patient with elevated hepatic transaminase levels due to liver metastases, might it also be safe in a patient with liver dysfunction due to another reason? As expected, we found that bone marrow function (i.e., minimum blood counts) criteria have different thresholds, if included in hematology malignancy trials (**Fig. 2**).

Importantly, our findings are almost identical to earlier reviews by the FDA and by the ASCO and *Friends* working group (13). This lack of variation over time suggests the possibility that laboratory test–based eligibility criteria template language may be carried forward despite the accumulation of additional clinical experience, on trials or after approval. We noted a similar phenomenon when tracking clinical development across trial phases. Our review of published material (Supplementary Table S1) of 23 of the 26 oncology drugs approved by FDA on the basis of randomized phase III trials in 2019 demonstrated a lack of variation in laboratory test requirements between early-phase and later phase clinical trials of the same agent. Again, this observation may suggest that these eligibility criteria remain static, not taking into account new or developing knowledge.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3853

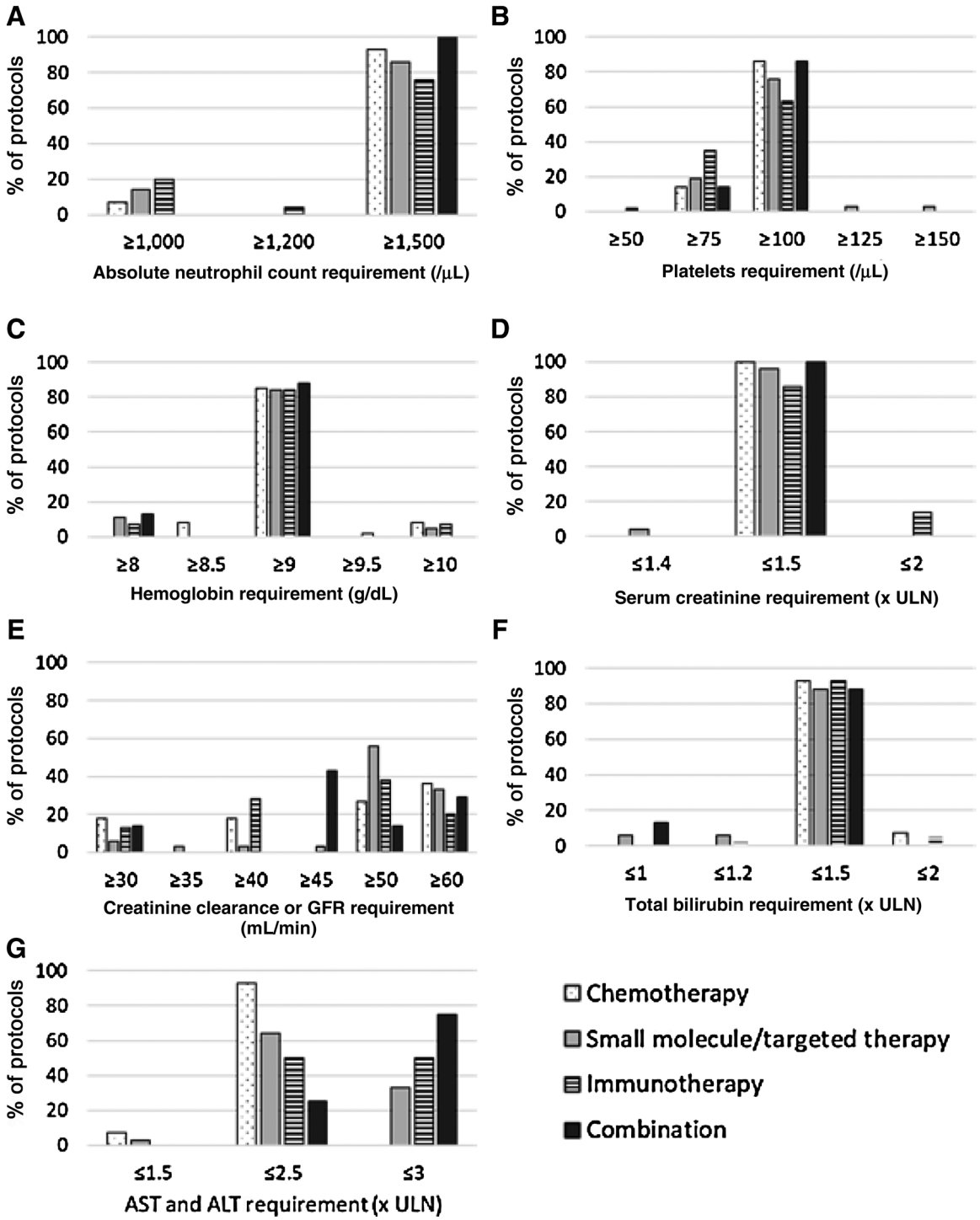

Figure 1.

Frequency of laboratory value requirements according to therapy type for 107 oncology clinical trial protocols for solid tumors. Protocol-specified accepted laboratory test values and number of protocols with each requirement for ANC (**A**), platelet count (**B**), hemoglobin (**C**), serum creatinine (**D**), CrCl or glomerular filtration rate (GFR; **E**), total bilirubin (**F**), and aspartate aminotransferase (AST) and ALT (**G**).

Implications of laboratory eligibility criteria

How do laboratory eligibility criteria impact clinical trial enrollment? A recent study examining 10,500 electronic health records of patients with advanced non–small cell lung cancer (NSCLC) found that expanded criteria that would allow patients with advanced NSCLC and brain metastases, previous or concurrent cancers, and limited kidney function to enroll in clinical trials would nearly double the percentage of patients potentially eligible to enroll in clinical trials (14).

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3853

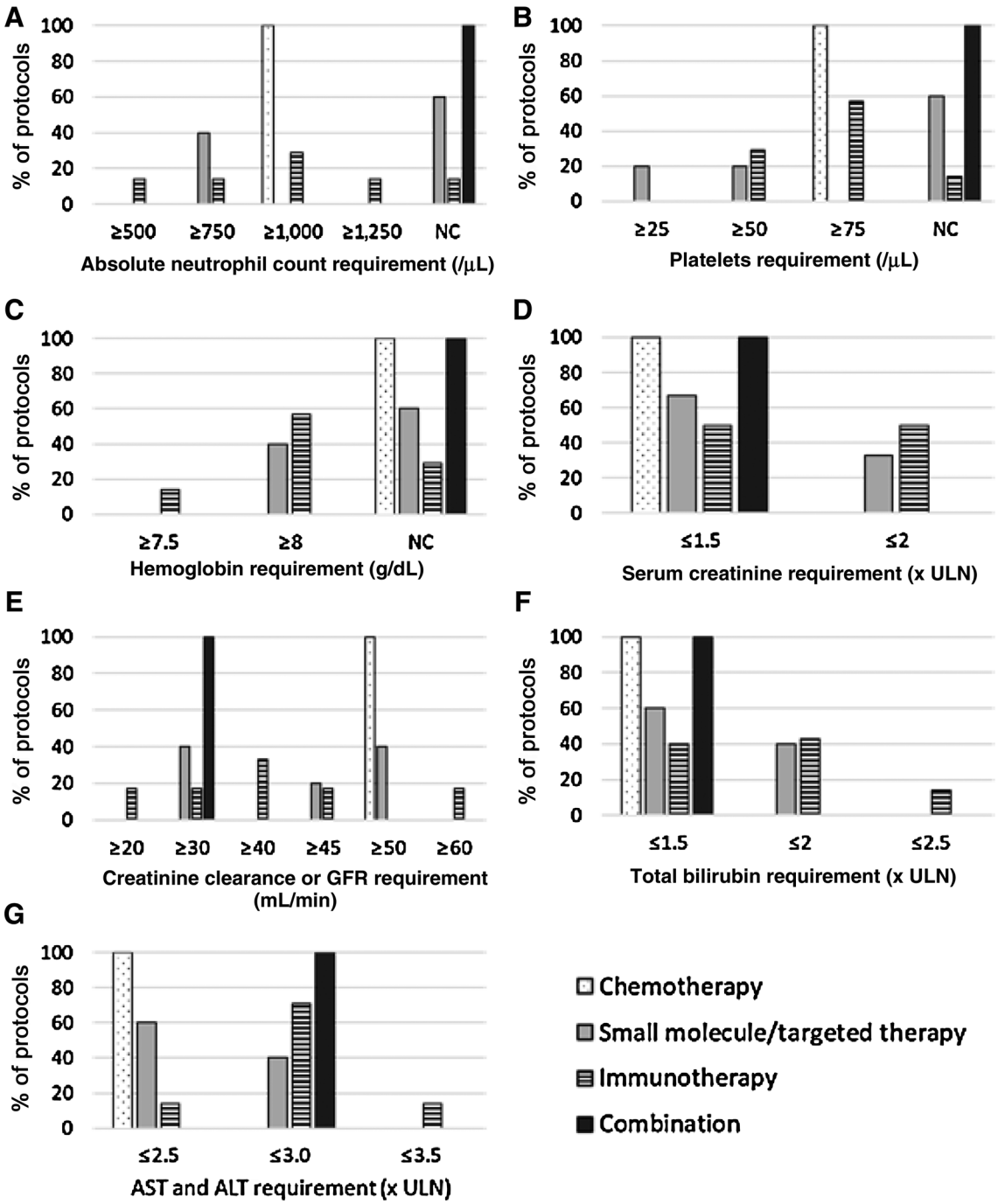

Figure 2.

Frequency of laboratory value requirements according to therapy type for 16 oncology clinical trial protocols for hematologic malignancies. Protocol-specified accepted laboratory test values and number of protocols with each requirement for ANC (**A**), platelet count (**B**), hemoglobin (**C**), serum creatinine (**D**), CrCl or glomerular filtration rate (GFR; **E**), total bilirubin (**F**), and aspartate aminotransferase (AST) and ALT (**G**). NC, no criteria specified.

This analysis demonstrated that requiring CrCl ≥ 60 mL/minute resulted in exclusion of almost 15% of patients. Furthermore, real-world evidence suggests that enrolling patients with renal dysfunction may not necessarily have an adverse impact on study outcomes. In an analysis of more than 12,000 patients with cancer, with evaluable renal function from the Flatiron Health electronic health record database, baseline renal dysfunction was not associated with any differences in on-treatment outcomes or survival (15). Given the prevalence of renal dysfunction in some oncology populations (e.g., more than 20% of individuals with lung cancer), relaxing renal function requirements in the absence of specific contraindications might have major impact on trial enrollment and improve the applicability of trial results (16).

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3853

Instances may still exist where strict eligibility criteria are required for patient safety. For example, a drug that causes hemolytic anemia or risk of bleeding may require patients to have a higher hemoglobin criteria for entry; however, a drug without any known effect on this parameter may not require this and could be adequately managed expectantly according to best oncologic care.

Differences between and within drug classes

Laboratory-based criteria should reflect treatment considerations, including organ function adequate for drug metabolism and elimination, and provide a sufficient margin in the event of hepatic or renal toxicity of investigational treatments. Therapies that may be hepatically metabolized or renally excreted would be expected to have more narrow enrollment criteria than those which are eliminated via other means.

Among medical therapies, substantial differences in metabolism/excretion and toxicity profiles render broad recommendations challenging. In some instances, multiple drugs in a class would be expected to have comparable profiles, as is the case for PD-1/PD-L1 immune checkpoint inhibitors. Minor pharmacologic differences within the class, such as IgG subtype (IgG1 vs. IgG4) or antibody species (human vs. humanized), do not translate into meaningful variation in laboratory requirements. In contrast, ALK inhibitors approved for ALK-positive lung cancer differ substantially in pharmacodynamics properties, resulting in truly distinct metabolic and toxicity profiles (17). With this in mind, there will need to be some variability, but data and experience from similar in-class molecules should be used to inform selection of laboratory requirements for eligibility criteria. Furthermore, as investigational therapies advance from early-phase to late-phase development, those criteria should be adjusted on the basis of earlier experience and observations. The current "cut and paste" approach should be challenged and clinical trial protocols continuously reevaluated as recommended in FDA guidance (18).

Laboratory test value variability

Importantly, laboratory test values may differ substantially between testing facilities and among populations. For instance, the lower limit of normal for hemoglobin is 9.6 g/dL in Black women, which falls below the eligibility threshold for some clinical trials (19). In addition, study criteria that use absolute neutrophil count (ANC) > 1,500/μL can contribute to significant racial disparities in studies as a result of benign ethnic neutropenia (20). Lowering the ANC cutoff level could increase the number of eligible minority patients that may have benign ethnic neutropenia. Across populations, among 38 standard laboratory tests analyzed among more than 3,000 healthy individuals in the National Health and Nutrition Examination Survey, only five (glucose, phosphorus, potassium, total bilirubin, and uric acid) did not show significant racial/ethnic difference in distribution (20). For instance, the normal range of serum creatinine for White females was 0.50–1.10 mg/dL, but 0.43–0.88 mg/dL for Asian females. Furthermore, formulas used to assess CrCl often vary widely (21). Black participants had significantly higher normal ranges in CPK, globulin, and total protein, and lower normal ranges in hematocrit, hemoglobin, total cholesterol, triglycerides, and white blood cell than Whites. There are also differences according to gender. For alanine aminotransferase (ALT), upper reference ranges vary from 35 to 79 U/L for men, and 31 to 55 U/L for women (22). Other laboratory tests with significant differences between males and females include total bilirubin, cholesterol, bicarbonate, calcium, and total protein (20). To the best of our knowledge, we cannot identify the rationale for one of the most common liver dysfunction criteria, transaminases of 2×–2.5× ULN for most patients, and sometimes up to 5× with liver metastases. The number of patients this excludes from studies is unknown, but is felt to represent a significant burden especially in patients who may have adequate synthetic and clearance function, but have elevated transaminases because of liver metastases. Current FDA guidance suggests that patients with transaminase elevation up to 20× ULN may have similar tolerance to therapies as those with normal levels (18, 23).

Advanced age also represents a key consideration in laboratory test interpretation, as many patients with common cancers are elderly. Alkaline phosphatase increases by 20% between the 3rd and 8th decade. CrCl increases by 10 mL/minute/1.73 m^2 per decade. Postprandial glucose increases by 30–40 mg/dL per decade after age 40 years (24). Between the 6th and 8th decades, platelet count decreases by approximately 20,000/mcl (25).

Laboratory test results in cancer populations

Across cancer types, laboratory abnormalities are more common in oncology populations. Anemia, when defined as hemoglobin < 11 g/dL, occurs in up to 40%–60% of patients with common malignancies (26). This is especially true in patients who have already received several treatments for their malignancy, and can be supported easily with transfusions or other care. In terms of renal function, 50% of patients with cancer have CrCl < 90 mL/minute and 20% have CrCl < 60 mL/minute (27). For drugs that are known not to be renally metabolized, this may not be relevant, and only reflect the general performance status of the patient. Furthermore, the formulas used to estimate glomerular filtration rate (e.g., Cockcroft–Gault) often underestimate true CrCl, especially in females and in those that are older with less body mass. More direct measures (e.g., 24-hour urine CrCl) should often be used. Furthermore, the prevalence of laboratory abnormalities is greatest in patients with more advanced cancer, which tend to represent the cases for which a clinical trial may be most appropriate and potentially most beneficial (28, 29).

Recommendations

The group concluded that laboratory tests should be used as exclusionary criteria only when clearly necessary due to safety or efficacy concerns. As demonstrated previously, laboratory-based eligibility criteria are frequently carried forward from earlier protocols to new trials, without critical scientific evaluation of the need and impact of these decisions. Because each clinical trial focuses on specific patient populations and studies specific therapies with differing toxicity and pharmacokinetics considerations, it is not feasible to provide specific laboratory test value thresholds for broad applicability. Nevertheless, the incorporation of the key principles (**Table 2**) may help ensure safety and optimize efficacy, while minimizing unnecessary patient exclusions.

Conclusion

Overall, this working group found that laboratory test–related eligibility criteria (i) may account for exclusion of a meaningful proportion of patients from clinical trials, (ii) rarely change over time or over the course of a therapeutic agent's clinical development, (iii) are highly similar between drug classes that have substantially different pharmacologic and toxicity profiles, and (iv) may have varying impact on patients according to age, gender, and race/ethnicity. We have

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3853

Table 2. Recommendations for broadening laboratory reference ranges and testing intervals.

1. Laboratory tests should only be used as exclusionary criteria when scientifically justified and when abnormal test results confer safety concerns.

Laboratory test requirements should be customized to the therapy/therapies under investigation. Ultimately, laboratory test requirements should reflect study therapy pharmacokinetics and pharmacodynamics and anticipated toxicities. For instance, if a therapy does not undergo hepatic metabolism and is not expected to cause hepatic toxicity, strict hepatic function eligibility criteria may not be necessary, or at a minimum, there should be very broad entry criteria. Wherever data are available from similar agents and previous experience should be used as a guide. For example, in some instances (e.g., PD-1/PD-L1 checkpoint inhibitors), pharmacology and toxicity profiles are similar across agents, allowing use of comparable laboratory-related eligibility criteria. In other instances (e.g., ALK inhibitors), each individual drug may have different requirements depending on its individual pharmacokinetic/pharmacodynamic profile. Importantly, restrictions from earlier clinical trials should not be carried forward automatically, but should be modified to reflect the experiences of patients in earlier trials and in postmarket use.

Laboratory test–related eligibility criteria should not be used as a surrogate for performance status or the presence of comorbidities. Because of the older age of most patients with cancer and the likelihood of identifying laboratory anomalies of no clinical significance, the use of laboratory tests to identify sufficiently healthy individuals is likely to result in unnecessary exclusion of potential patients. Instead, clinical trial protocols should specify functional status and comorbidity requirements in line with previous recommendations, as appropriate (10).

Consider adjusting laboratory-based eligibility criteria broadly rather than in specific clinical scenarios. A frequent clinical trial practice is to relax laboratory-related eligibility criteria in populations more likely to have baseline laboratory abnormalities (e.g., allowing lower levels of renal function in patients with genitourinary malignancies, or allowing greater degrees of hepatic dysfunction in patients with primary or metastatic liver cancer). If these population subgroups can be treated effectively and safely, consideration should be given to applying similar laboratory-related eligibility criteria more broadly.

Laboratory-based eligibility criteria should be limited to the clinical concern. As an example, in clinical trials of therapies that may prolong the QTc interval, low levels of electrolytes, such as potassium, calcium, and magnesium, may increase risk of cardiac arrhythmias. A common response to this concern is to require levels of these electrolytes to be within normal limits. This results in unnecessary exclusion of patients whose electrolyte levels are slightly above the normal range, even though there is no increased risk of QTc prolongation. In these cases, precise protocol writing (e.g., requirements for laboratory tests to be above the lower limit of normal rather than within normal limits) with an understanding of the intent of the criteria and the normal variations among people as outlined above is of utmost importance. Furthermore, opportunities to allow for correction to the near-normal range should be allowed. While safety is of utmost concern, protocols should reflect the intended use population for the treatment being evaluated and not situations where the trial data cannot realistically be applied to post-approval scenarios.

Interlaboratory variation should be accounted for when selecting laboratory-based eligibility criteria. It is important to consider thresholds rather than specific normal values. ULN's can vary across laboratories, and criteria should reflect multiples of ULN, rather than absolute numbers (akin to NCI CTCAE criteria). Across academic medical centers, there are substantial differences in serum creatinine determination, with laboratory site accounting for 50% and time of assay performance accounting for another 15% of this variation (23). CrCl should be accounted for by accurate measurements, and options for direct measurements (24-hour urine CrCl) be allowed, rather than formulas that simply estimate the clearance (e.g., Cockcroft–Gault).

2. Laboratory reference values should account for potential normal variations due to race, ethnicity, age, sex, and gender identity (i.e., due to surgical and hormonal changes).

The impact on trial eligibility, enrollment, and relevance should be assessed when selecting laboratory-based eligibility criteria. Laboratory abnormalities occur frequently without clinical significance. Reference intervals generally include 95% of test results obtained from a presumably healthy population. The chance that a healthy person has a test result falling outside this range is 5% for a single test, but rises to 64% for 20 tests (e.g., complete blood count and metabolic panel; ref. 30). As noted previously, the likelihood of test results outside reference ranges is far greater among individuals with cancer and may not be of clinical significance with respect to the treatment being studied.

Demographic differences in laboratory test results, and their implication across populations, should be understood. Given the differences among ethnicities, those criteria that are included should be sufficiently broad to allow for these natural variations (20, 26). It should be noted that persons who have undergone surgery or take medications to align with their gender identity may have altered "normal" laboratory values despite being healthy (31, 32).

3. Routine reassessment of laboratory test–based exclusion criteria should be conducted during the course of clinical research and drug development as investigational agents progress from earlier to later phase clinical trials.

Eligibility criteria should be expanded on the basis of earlier clinical experience and in the absence of safety concerns. Phase I, first-in-human trials should incorporate strict laboratory-related eligibility criteria as a precautionary measure, as the clinical pharmacology and toxicity profile of the novel therapy are not known. However, once these characteristics have been established, laboratory-related eligibility criteria should be adjusted to reflect this experience, enabling appropriate access to therapies under investigation. Currently, the initial criteria are often carried forward to phase II and phase III trials, resulting in unnecessarily strict requirements and exclusion of potential patients, and limiting applicability of results. Similarly, criteria and experience from drugs of a similar class may be used to formulate eligibility entry criteria.

Broadening eligibility criteria by employing less stringent requirements for laboratory eligibility requirements should be accounted for when assessing on-treatment abnormal laboratory values. In addition to grading of laboratory abnormalities using CTCAE, which accounts for the most severe laboratory value aberration, interpretation of results should take into account CTCAE attribution. If patients have baseline laboratory anomalies prior to starting treatment, they may have more frequent and more severe laboratory abnormalities after initiating therapy. To account for this possibility, one approach is to focus on the degree of change in laboratory values, as conveyed by shift tables (33). Shift tables display baseline laboratory values and the shift at postdose, which helps determine the potential impact of the investigational therapy on these results.

(Continued on the following page)

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3853

Table 2. Recommendations for broadening laboratory reference ranges and testing intervals. (Cont'd)

4. Increasing the intervals between protocol-specific tests should be considered to help reduce patient burden and increase ability to rely on routine clinical testing, especially in later cycles of treatment and over the evolution of protocols from earlier to later phase clinical trials.
Restrictive test intervals could result in reduced interest in and commitment to clinical trials among patients, clinicians, and investigators. Oncology patients, in general, are spending an inordinate amount of time for treatment of their cancer. The average informed consent form for oncology trials is more than 4,000 words and describes hundreds of procedures (34). Unnecessary testing and procedures can lead to more patients choosing not to participate in trials or dropping out over the course of a study. Minimizing testing frequency to reflect what is truly needed to assess safety and efficacy may improve interest, enrollment, and adherence on clinical trials.

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

outlined a number of areas in which modifying current clinical trial eligibility and following the principles of distributive justice may optimize trial participation and efficiency, and applicability of study results to better inform appropriate uses of new therapies. Recommendations outlined in this article can help guide appropriate use of laboratory tests and testing intervals as exclusionary criteria in protocols. This would enable increased clinical trial accrual and provide more relevant data that better mirror the oncology patient populations that ultimately will be treated with these agents. While it is reasonable to establish some minimum criteria for safety, they should be appropriately broad without compromising safety. This will allow oncologists to have more evidence-based discussions with patients and caregivers regarding the potential risks and benefits, ultimately improving shared decision-making in cancer care.

Authors' Disclosures

S. Jones reports other from HCA Healthcare outside the submitted work. A. Fielding reports personal fees and other from AstraZeneca outside the submitted work. L.S. Wood reports personal fees from Bristol Myers Squibb, Eisai, Merck, and Pfizer outside the submitted work. M.A. Thompson reports personal fees from Adaptive, Elsevier ClinicalPath, GRAIL/Illumina, UpToDate; personal fees and other from BMS and Takeda; other from Doximity, AbbVie, Amgen, Denovo, GlaxoSmithKline, Hoosier Research Network, Janssen, LynxBio, Strata Oncology, and TG Therapeutics; and nonfinancial support from Syapse outside the submitted work. L. Jones reports personal fees from Bayer outside the submitted work. B.A. Mahal reports grants from Prostate Cancer Foundation, ASTRO, DOD, and NIH outside the submitted work. No disclosures were reported by the other authors.

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily reflect the views or policies of the authors' affiliated institutions.

Acknowledgments

The working group thanks the ASCO-*Friends* project planning group for its guidance throughout the development of its consensus recommendations and article. Finally, the planning group thanks the 2018–2019 ASCO Cancer Research Committee and Health Equity Committee members for their leadership. D.E. Gerber was supported, in part, by an NCI Midcareer Investigator Award in Patient-Oriented Research (K24 CA201543-01).

Received September 28, 2020; revised November 25, 2020; accepted December 22, 2020; published first February 9, 2021.

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Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3853

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Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3853

Clinical Cancer Research

Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group

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Clin Cancer Res Published OnlineFirst February 9, 2021.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3857

Impact of Broadening Trial Eligibility Criteria for Patients with Advanced Non–Small Cell Lung Cancer: Real-World Analysis of Select ASCO-*Friends* Recommendations

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ABSTRACT

Purpose: Cancer clinical trials often accrue slowly or miss enrollment targets. Strict eligibility criteria are a major reason. Restrictive criteria also limit opportunities for patient participation while compromising external validity of trial results. We examined the impact of broadening select eligibility criteria on characteristics and number of patients eligible for trials, using recommendations of the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research.

Experimental Design: A retrospective, observational analysis used electronic health record data from ASCO's CancerLinQ Discovery database. Study cohort included patients with advanced non–small cell lung cancer treated from 2011 to 2018. Patients were grouped by traditional criteria [no brain metastases, no other malignancies, and creatinine clearance (CrCl) ≥ 60 mL/minute] and broadened criteria (including brain metastases, other malignancies, and CrCl ≥ 30 mL/minute).

Results: The analysis cohort included 10,500 patients. Median age was 68 years, and 73% of patients were White. Most patients had stage IV disease (65%). A total of 5,005 patients (48%) would be excluded from trial participation using the traditional criteria. The broadened criteria, however, would allow 98% of patients (10,346) to be potential participants. Examination of patients included by traditional criteria (5,495) versus those added (4,851) by broadened criteria showed that the number of women, patients aged 75+ years, and those with stage IV cancer was significantly greater using broadened criteria.

Conclusions: This analysis of real-world data demonstrated that broadening three common eligibility criteria has the potential to double the eligible patient population and include trial participants who are more representative of those encountered in practice.

Introduction

Numerous cancer trials accrue slowly or miss enrollment targets (range, 9%–49% of trials; refs. 1–7) due to strict eligibility criteria. A 2016 analysis of corrective actions for poor-accruing trials found that eligibility criteria were among primary causes of enrollment delays, with broadening eligibility criteria as the primary remedy for phase II trials (8). Among 231 phase I trials (1991–2016), common reasons for exclusion were performance status (PS) ≥ 1, brain metastases, and strict renal/hepatic function requirements (9). These restrictions were associated with fewer eligible patients, longer enrollment periods (26 vs. 17 months), and increased study terminations.

Broadening eligibility criteria also addresses study design factors that limit study participation, thereby causing inequities in trial access particularly among certain populations and creating concerns about external validity of results. A 2019 review of trial participation indicated 21.5% of patients were excluded primarily because of strict eligibility criteria (10). An examination of real-world data (RWD) from Denmark showed that clinical characteristics excluded 61% of patients with melanoma from pivotal trials during 2010–2015; brain metastases and/or PS ≥ 2 affected 75% of those excluded (11). These patients (when treated following approval with study agents) showed improvement in outcomes versus historical controls.

In October 2017, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) published recommendations to broaden eligibility criteria (12) for: brain metastases (13), organ function, primary/concurrent malignancies (14), human immunodeficiency virus status (15), and minimum enrollment age (16). This investigation quantified and characterized among patients with advanced non–small cell lung cancer (aNSCLC) trial eligibility using the ASCO-*Friends*' broadened versus traditional eligibility criteria.

Materials and Methods

This retrospective, observational study examined common eligibility criteria in cancer trials: (i) brain metastases, (ii) renal function, and (iii) prior/concurrent malignancies. Data for the analysis were obtained from CancerLinQ Discovery a safe-harbor deidentified dataset compiled from electronic health records (EHR) of 50 U.S. oncology

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Clin Cancer Res 2021;XX:XX–XX

doi: 10.1158/1078-0432.CCR-20-3857

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3857

Translational Relevance

Overly restrictive clinical trial eligibility criteria make it challenging to translate research findings to all populations likely to receive a new treatment following approval. Less restrictive eligibility criteria over the course of drug development may generate data on a broader population and improve speed of accrual. This may be accomplished by progressive broadening of eligibility criteria across trial phases. We show that expansion of three common eligibility criteria, renal function measures, presence of brain metastases, and history of prior malignancy, increases patients potentially eligible in the dataset analyzed by almost 2-fold. While this analysis was conducted in a population with advanced non–small cell lung cancer, the findings are likely applicable to other advanced malignancies. These expanded eligibility criteria should be widely adopted while pursuing additional expanded inclusion criteria to generate findings more relevant to patients treated in routine clinical practice, maximize patient access to trials, and expedite trial enrollment.

practices (17). We included standardized data and data curated by trained clinical data abstractors from 2011 to 2018 records (18–20).

Study criteria included patients with aNSCLC diagnosis (stage IIIb, IIIc, or IV; see Supplementary Materials and Methods), receipt of systemic therapy, and ≥2 documented clinical visits. Patients with missing serum creatinine laboratory values were excluded.

Criteria for traditional and broadened eligibility criteria are outlined in **Table 1**. Traditional criteria excluded patients with creatinine clearance (CrCl) ≤ 60 mL/minute (21). Broadened criteria included patients with CrCl ≥ 30 mL/minute. A minority of cases (33%) included CrCl in EHR data. CrCl was calculated for 7,031 cases using the Cockcroft–Gault equation (22, 23).

Patients with additional cancer diagnosis codes unrelated to NSCLC were classified as having a prior/concurrent cancer. These patients would be excluded by traditional criteria and included by broadened criteria. All diagnosis codes related to lung cancer metastases sites (e.g., adrenal gland, bone, brain, and other) were considered metastases, rather than another cancer. From a clinical perspective, metastases may be more likely than second primary cancers at these anatomic sites. Miscoding of metastases as primary cancers is not infrequent.

Data curation identified patients with brain metastases, including coding primary brain neoplasms as brain metastases. All patients with brain metastases were excluded under traditional criteria and included under broadened criteria.

PS values were presented using the Eastern Cooperative Oncology Group (ECOG) scale as documented in EHR or converted from Karnofsky (24). If multiple PS values existed, we used the value closest to date of therapy initiation.

Descriptive statistics summarize the two populations, including proportions, means, and interquartile ranges (IQR). Comparisons were made between patients included on the basis of traditional criteria versus patients excluded on the basis of traditional criteria, but included using broadened criteria (i.e., independent, nonoverlapping patient groups) using χ^2 tests. Alpha was set at 0.01 due to the large sample size. Data management and analyses were conducted in Python 3.7.0 and R 3.5.1.

Results

A total of 10,500 cases were included in the analysis (**Fig. 1**; **Table 2**). Median age was 68 years (IQR, 60–74), and 56% were males. A total of 75% of patients were White. Most patients had stage IV disease (65%).

Of the total cohort, 1,509 (14%) patients had prior/concurrent cancers (**Table 3**), most commonly prostate (154 patients, 2%), colorectal (120, 1%), and breast (31, 0.3%) cancers. These 1,509 patients would be excluded under traditional criteria, but included using broadened criteria. All cases were coded for presence/absence of brain metastases. A total of 21% of patients (2,226) had brain metastases and would be excluded by traditional eligibility criteria.

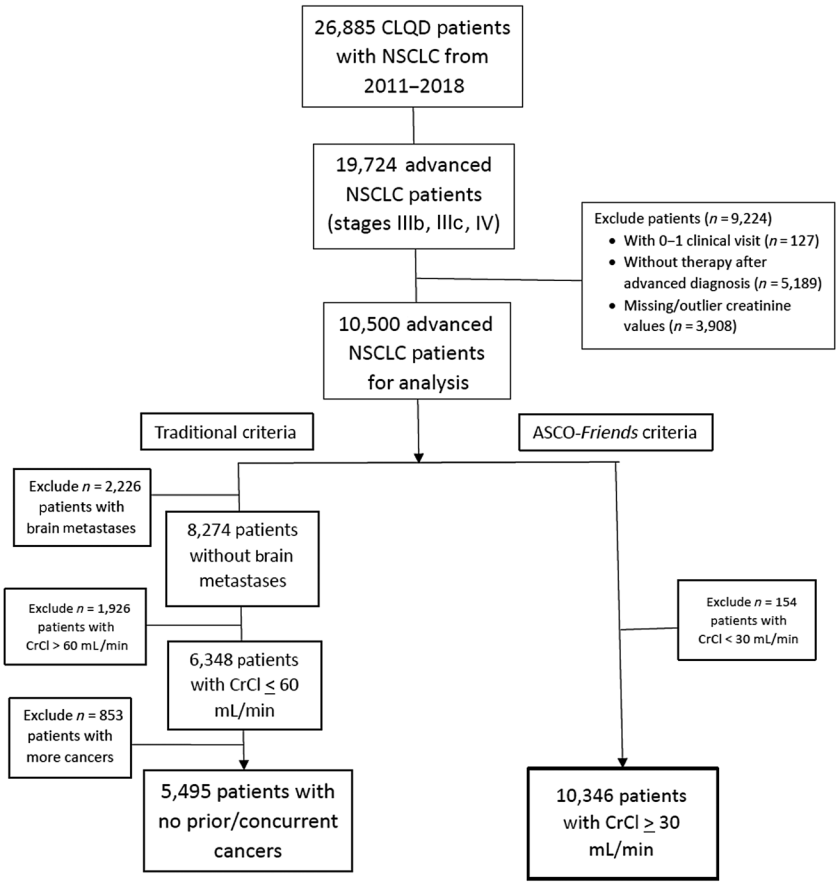
Overall, 5,005 patients (48%) were excluded by one or more of three traditional criteria, leaving only 5,495 (52%) eligible. More than 20% of patients (2,252) were excluded by traditional eligibility criteria due to CrCl ≤ 60 mL/minute alone. Use of the broadened criteria would only exclude 154 patients (1.5%), leaving nearly all patients (10,346, 98%) potentially eligible.

Table 1. Comparison of definitions for traditional clinical trial eligibility criteria, ASCO-*Friends*' broadened criteria, and criteria used in study.

	Traditional eligibility criteria	ASCO-*Friends*' broadened criteria	Criteria used in study
Prior and concurrent cancer: in addition to NSCLC	Exclude patients with another primary cancer in 2 years prior to trial enrollment	Include patients with another primary cancer that does not interfere with safety or efficacy of study therapy	Included all cases with another primary cancer diagnosis: (i) counted primary diagnostic codes at sites of likely NSCLC metastases as metastases
Brain metastases	Exclude patients with brain metastases	Include patients with treated and/or stable brain metastases, as well as patients with active brain metastases	Included all patients with brain metastases (i) irrespective of treatment status and clinical stability (ii) counted primary brain diagnostic codes as metastases
Renal function	Exclude patients if CrCl ≤ 60 mL/minute	Include patients if CrCl ≥ 30 mL/minute for study therapy without kidney toxicity	Included patients if CrCl ≥ 30 mL/minute: (i) used Cockcroft–Gault formula to calculate CrCl for patients without evidence of CrCl measure

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3857

Figure 1.
Cohort comparison with traditional and broadened eligibility criteria.



Patients included by traditional criteria (5,495) versus patients added (4,851) by broadened criteria and excluded by traditional criteria (**Table 2**; columns E and G) differ in important ways (**Fig. 2**). The percentage of women was significantly different; 40% under traditional criteria versus 48% ($P < 0.001$) with broadened criteria. The percentage of patients aged 75+ years was significantly greater with broadened criteria (29% vs. 16%; $P < 0.001$). Comparing by stage, 59% of stage IV patients were included with traditional versus 72% ($P < 0.001$) using broadened criteria. Percentage of patients with ECOG PS 2+ was similar (18% vs. 20%; $P = 0.03$).

Discussion

Broadening three common eligibility criteria can potentially double the number of patients with aNSCLC eligible for trials. Prior analyses of eligibility of patients with aNSCLC demonstrated 60% were ineligible, with common exclusions being brain metastases and poor PS (25).

Support for expanding eligibility criteria examined also comes from analysis of Kaiser Permanente data, which showed 8% of patients would be excluded from trials because of another invasive cancer within 5 years (14). The analysis also revealed 28% of patients with lung, 20% with breast, 25% with colorectal, and 46% with bladder cancers would be excluded because of CrCl < 60 mL/minute. Renal function is of critical importance in aNSCLC, because carboplatin, pemetrexed, and cisplatin are renally cleared. Expanding CrCl eligibility to ≥30 mL/minute would substantially impact the eligible population, adding 20% of patients. It is important to recognize those instances when including patients with CrCl < 60 mL/minute should be avoided, specifically in studies of drugs cleared by the kidneys and without established dose adjustments where drugs cause direct renal toxicity. In other cases, the change to include those with CrCl > 30 mL/minute should be employed once safety is established (perhaps in an exploratory cohort in early development) and certainly in late-phase trials.

In this analysis, the population who met the broadened eligibility criteria are more representative of patients with aNSCLC than the traditional eligibility criteria population. The broadened population included more women, older patients, and/or patients with stage IV disease. Although broadened criteria resulted in a small increase in patients with PS 2+, analysis of PS was inconclusive. Most records (58.5%) lacked structured PS data. Translation of data from highly selected trial populations to patients seen in real-world practice identifies important knowledge gaps and increases confidence in applying trial results to typical patients.

While our analysis demonstrated an increase in the number of patients with aNSCLC potentially eligible for trials, their inclusion could also potentially affect interpretation of safety and efficacy data because of increased heterogeneity. Similar studies including broader populations, however, demonstrated similar safety and survival rates between restricted and broadened populations (9, 25). Our analysis is limited by characteristics of our data source. The population of patients included in CancerLinQ has not been compared with the U.S. cancer population, although CancerLinQ participating practices are geographically diverse and mostly outside academic settings. It was also difficult to match eligibility criteria to EHR data. We simplified the

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3857

Table 2. Characteristics of patients with aNSCLC according to eligibility criteria.

	(A) All patients with aNSCLC	(B) Patients excluded due to brain metastases	(C) Patients excluded due to other prior or concurrent malignancies	(D) Patients excluded due to CrCl ≤ 60 mL/minute	(E) Patients included by 3 traditional criteria	(F) Patients included by 3 broadened criteria	(G) Patients included by broadened and excluded from traditional	(H) Patients excluded by both broadened and traditional	*P*[a]
	10,500 (100)	2,226 (21)	1,509 (14)	2,254 (22)	5,495 (52)	10,346 (99)	4,851 (46)	154 (2)	
Age (median and IQR) at treatment index									
	68 (60–74)	65 (57–71)	69 (62–75)	76 (70–81)	66 (59–72)	68 (60–74)	69 (62–76)	78 (72–84)	
Age (at treatment index)									<0.001
≤49 years	426 (4)	140 (6)	48 (3)	7 (3)	254 (5)	425 (4)	171 (4)	1 (1)	
50–64 years	3,794 (36)	1010 (45)	484 (32)	246 (11)	2,268 (41)	3,781 (37)	1,513 (31)	13 (8)	
65–74 years	3,881 (37)	752 (34)	595 (39)	794 (35)	2,089 (38)	3,840 (37)	1,751 (36)	41 (27)	
75+ years	2,399 (23)	324 (15)	382 (25)	1,207 (54)	884 (16)	2,300 (22)	1,416 (29)	99 (64)	
Sex									<0.001
Female	4,647 (44)	1,086 (49)	624 (41)	1,203 (53)	2,216 (40)	4,550 (44)	2,334 (48)	97 (63)	
Male	5,853 (56)	1,140 (51)	885 (59)	1,051 (47)	3,279 (60)	5,796 (56)	2,517 (52)	57 (37)	
Race									0.49
White	6,813 (73)	1,365 (70)	1,009 (76)	1,505 (75)	3,567 (74)	6,716 (74)	3,149 (73)	97 (68)	
Black	1,255 (14)	241 (12)	163 (12)	320 (16)	660 (14)	1,223 (13)	563 (13)	32 (22)	
Other	1,206 (13)	357 (18)	158 (12)	180 (9)	615 (13)	1,192 (13)	577 (13)	14 (10)	
Unknown	1,226	263	179	249	653	1,215	562	11 (<1)	
Stage at index (closest to first-line advanced treatment)									<0.001
Stage IIIb/c	3,355 (35)	334 (16)	405 (30)	710 (34)	2,086 (41)	3,316 (35)	1,230 (28)	39 (27)	
Stage IV	6,354 (65)	1,714 (84)	965 (70)	1,352 (66)	3,039 (59)	6,251 (65)	3,212 (72)	103 (73)	
Unknown	791	178	139	192	370	779	409	12	
PS (on or ≤1 year prior to treatment index date; native ECOG or translated from Karnofsky)									0.06[b]
0	1,215 (28)	282 (29)	188 (30)	231 (22)	637 (29)	1,199 (28)	562 (27)	16 (18)	
1	2,121 (49)	490 (50)	289 (46)	495 (48)	1,058 (49)	2,079 (49)	1,021 (49)	42 (47)	
2	831 (19)	174 (18)	126 (20)	248 (24)	384 (18)	805 (19)	421 (20)	26 (29)	
3	182 (4)	37 (4)	27 (4)	59 (6)	83 (4)	178 (4)	95 (5)	4 (4)	
4	12 (<1)	1 (<1)	1 (<1)	2 (<1)	8 (<1)	11 (<1)	3 (<1)	1 (1)	
Unknown	6,139	1,242	878	1,219	3,325	6,074	2,749	65	
Smoking status (at treatment index)									<0.001
Never smoked	1,642 (16)	414 (19)	295 (21)	408 (19)	732 (14)	1,616 (16)	884 (19)	26 (17)	
Former smoker	5,225 (52)	978 (46)	708 (49)	1,195 (56)	2,802 (54)	5,145 (52)	2,343 (51)	80 (52)	
Current smoker	3,093 (31)	746 (35)	430 (30)	543 (25)	1,650 (32)	3,057 (31)	1,407 (30)	36 (23)	
Unknown	540	88	76	108	311	528	217	12	

Note: *N* (%) are shown in table cells, except for age, which is presented as median and IQR. When calculating percentages, "unknown" cell counts were excluded.
[a]χ^2 tests were used to calculate *P* values with all categories included, except "unknown."
[b]Comparing PS < 2 versus PS ≥ 2, $P = 0.03$.

Table 3. Numbers of patients excluded by traditional versus broadened clinical trial eligibility criteria.

Original cohort	**10,500 (100%)**
Traditional criteria	
Pts excluded due to brain metastases	2,226 (21.2%)
Pts excluded due to prior/concurrent cancers	1,509 (14.4%)
Pts excluded because CrCl ≤ 60 mL/minute	2,254 (21.5%)
Pts excluded by one or more of 3 traditional criteria	5,005 (47.7%)
ASCO-*Friends*' broadened criteria	
Pts excluded by brain metastases and prior/concurrent cancers	0 (0%)
Pts excluded by CrCl ≤ 30 mL/minute cutoff	154 (1.5%)

Abbreviation: Pt, patient.

definition of brain metastases to present or absent, rather than using ASCO-*Friends*' recommendations' consideration of treated and/or stable metastases. Classification of diagnosis codes for another primary cancer at metastases sites as NSCLC metastases had a small impact (<1%). Record curation helped ensure very few patients were mischaracterized.

Conclusions

Broadening three common eligibility criteria would have allowed nearly twice as many patients (5,495 vs. 10,346) within this RWD analysis to meet eligibility criteria for clinical trials. With broadened eligibility, patients are more representative of the range of patients with aNSCLC, thus increasing the likelihood for definitive trials. Per ASCO and *Friends*' recommendations, eligibility criteria should be carefully selected and reflect safety concerns and compelling scientific rationale

Published OnlineFirst February 9, 2021; DOI: 10.1158/1078-0432.CCR-20-3857

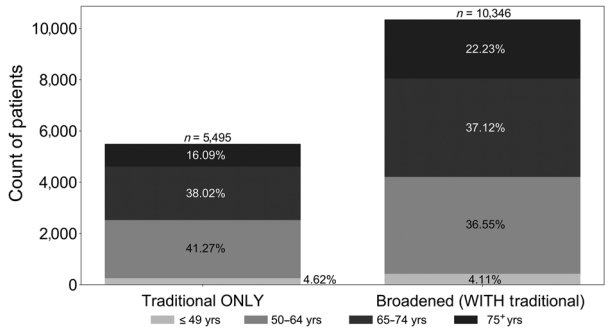


Figure 2.
Effect of traditional versus broadened eligibility criteria by ages represented ($N = 10,500$ patients with aNSCLC).

specific to the investigational therapy. Broadening eligibility criteria will enable improved equitable patient involvement in research and likely accelerate trial enrollment.

Authors' Disclosures

E. Stepanski reports employment with ConcertAI, a company that conducts research using real-world data. T.S. Uldrick reports other from Merck, Roche, and Celgene/BMS outside the submitted work, as well as a patent for US 10,001,483 B2 issued to Celgene and NCI. S. Khozin reports receiving salary from Johnson & Johnson outside the submitted work. R.S. Miller reports employment with American Society of Clinical Oncology. R.L. Schilsky reports grants from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Genentech, Lilly, Merck, and Pfizer outside the submitted work. E.S. Kim reports personal fees from AstraZeneca, Boehringer Ingelheim, and Genentech outside the submitted work. No disclosures were reported by the other authors.

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily reflect the views or policies of the authors' affiliated institutions. W.S. Rubinstein participated in this work prior to joining the FDA. This work and related conclusions reflect the independent work of study authors and do not necessarily represent the views of the FDA or U.S. government.

Received September 28, 2020; revised November 25, 2020; accepted December 11, 2020; published first February 9, 2021.

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Clin Cancer Res Published OnlineFirst February 9, 2021.