Health care professionals and researchers must work together to recognize and overcome barriers to clinical trial enrollment among elderly patients.

Participation of the Elderly Population in Clinical Trials: Barriers and Solutions
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**Background:** Despite the fact that cancer disproportionately affects the elderly, most participants of clinical cancer trials are relatively young. This misrepresentation greatly affects the oncology treatment of the elderly population (> 65 years of age). Few studies have attempted to identify the problems related to discrepancy based on age for clinical trial participation.

**Methods:** A literature review was performed to identify barriers and solutions to enrollment of elderly persons for clinical cancer trials.

**Results:** Physician-related barriers include perception about treatment tolerance, drug metabolism, a lack of evidence for efficacy, and age bias. Lack of autonomy, concerns about quality of life and toxicities, accessibility to clinical trials, and logistical and financial difficulties are common patient-related barriers. Trial-related barriers include eligibility criteria based on performance status, organ dysfunction, and the presence of comorbidities. Solutions, such as improved communication, and coordinating logistical challenges may help overcome some of these challenges. Studies designed for the geriatric population could modify the perception and behavior of health care professionals and improve patient participation in clinical trials.

**Conclusions:** Implementing some of these solutions and increased research may help overcome shortfalls in elderly enrollment, thus allowing for more effective treatment of older patients.

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**Introduction**
Cancer is the second most common cause of death in the United States, exceeded only by heart disease, and accounts for nearly 1 out of 4 deaths.¹ The total cost of cancer treatment by the year 2020 is projected to be as high as $173 billion, which represents a 39% increase from 2010.² Finding innovative and cost-effective ways to treat patients with cancer is more relevant than ever due to the increasing age of the American population.³ It is estimated that the elderly population (defined as age ≥ 65 years) in the United States will reach 70 million by 2030.⁴ As the “baby boomer” generation gets older, the US health care system will be stressed by the increasing age of the population.⁴
Breakthroughs in cancer treatment require many steps, including large randomized clinical trials to evaluate dosing, safety, and effectiveness. A total of 2% to 4% of patients with cancer are enrolled in a clinical trial, most of whom are younger than 65 years of age. The overall proportion of older patients (≥ 65 years of age) in trials conducted by the Southwest Oncology Group was 25%. This same age group accounts for 63% of new cases of cancer in the United States, while comprising 14% of the entire US population. Cancer is a disease that predominantly affects the elderly, yet patients older than 65 years are not well represented in clinical trials. This misrepresentation in clinical trials impacts the care of elderly patients.

Multiple reasons exist for this discrepancy (Table). Compared with their younger counterparts, elderly people have increased rates of comorbidities and complications. Elderly patients also undergo complicated physiological and pathological changes and have higher rates of drug interactions, which may complicate treatment. Furthermore, the perceptions of health care professionals and family members can make it difficult for elderly patients to participate in clinical trials. Other obstacles to enrollment include trial eligibility criteria, financial, and logistic issues.

Such enrollment barriers for older patients have gained interest in the last 20 years. Although numerous solutions have been proposed, those that have been implemented have had limited success. It has been suggested that a larger, more succinct effort is necessary from the medical community.

Methods
The goals of this review are to clarify possible barriers and solutions to participating in clinical trials among the elderly. To do this, we reviewed the medical literature from the last 10 years through PubMed, using the keywords “cancer,” “clinical trials,” and “elderly.” Additional published studies were included based on manual searches as well as references from reviews or original articles. Articles included were original research primarily focused on the barriers or solutions faced by elderly patients with cancer with regard to clinical trial enrollment. It is worth noting that only publications in English were reviewed and may not be representative of situations seen outside of English-speaking countries.

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**Barriers**

**Physician-Related**
The understanding of physician-related barriers to elderly enrollment is evolving and becoming increasingly complex. Some studies have implicated physician fears of possible toxicity and comorbidity interactions in the elderly as the main barriers to enrollment, suggesting that response to treatment has been poorly understood due to low numbers of elderly patients in clinical trials. In fact, data on toxicity are limited for patients older than 75 years, and a paucity of data exists for patients older than 80 years of age. However, several studies demonstrate that treatment tolerance in clinical trials is similar across different age groups, while others suggest that age bias among physicians is an independent barrier to enrollment among the elderly patient population. One study reported that 11% of physicians explicitly stated age as a reason for not enrolling a patient in a clinical trial. Perceptions among physicians about age and clinical trial participation are complicated. Physicians acknowledge that they recommend less aggressive treatment to elderly patients, yet their reasonings are multifactorial and not well understood. The biological changes of aging, in addition to the complex pharmacokinetics involved, require more extensive care when administering systemic therapy, and such a perception about treatment tolerance may decrease elderly patient enrollment in clinical trials. Findings from 1 study demonstrated that, among patients eligible for the study, clinical trial participation was discussed with 76% of those younger than 65 years of age and 58% of patients older than 65 years, and advanced age may deter oncologists from choosing intensive cancer therapy, even if patients are highly functional and lack comorbidities.
disparity has been documented, the reasons for this gap have not been well elucidated, but possible barriers to enrollment may be physician fear of a lack of survival benefit among older patients. However, a paucity of evidence supports the belief that elderly people do not derive benefit from participating in a clinical trial. It remains a matter of controversy that physician bias could be based on toxicity difference or age alone, but both of these factors are likely to play a role as a barrier to clinical trial participation among the elderly.

Patient-Related

When patients eligible for a clinical trial consider whether to participate, many cite a lack of autonomy over treatment choice as being a reason for foregoing participation. Many patients also want to choose their own treatment and fear that their participation in a clinical trial will mean they will lose that decision-making capacity. Increased survival was less important than improved quality of life for older patients when declining trial enrollment. These preferences illustrate a cultural or philosophical difference that may exist between age groups, which may be a barrier, yet it is difficult to describe.

Elderly patients also cited other reasons for declining to enroll in a clinical trial, including such concerns as adverse events, friends who oppose participation, or a belief that participation in a clinical trial would provide no value to future generations. Family opposition to enrollment is a more important issue for older patients compared with their younger counterparts.

The role of altruism in trial participation has also been explored, but conclusions about altruism are difficult to make. Moreover, compared with their younger counterparts, elderly patients are less likely to actively seek participation and less informed of the availability of clinical trials, which may be related to the differences seen in literacy rates among the age groups. Other cultural implications from both patients and physicians may also be present and are difficult to assess but do lead to decreased trial enrollment. When patients were surveyed, the reason given for enrolling in a trial was “I trusted the doctor treating me,” although it was also given as a reason for those who chose not to enroll in a trial.

Patient perceptions of trial efficacy appear to play a role in patient enrollment. One study found that 44% of patients who declined enrollment did so when offered participation in a trial comparing standard treatment with a novel agent. Patients surveyed reported a higher likelihood to enroll in trials that included standard treatment with or without the addition of a novel drug. As many as 20% of surveyed patients reported that they chose to enroll in a trial because they felt that the trial provided the best treatment options. In addition, some patients felt that they must receive at a minimum standard treatment and said they could not afford to be assigned to a placebo group.

Logistical barriers present another obstacle to enrollment in clinical trials among the elderly, making a difficult-to-recruit population even smaller. Participation in a clinical trial may require patients to travel to cancer or academic centers, and elderly persons may have a smaller support network than their younger counterparts; however, in 1 study, this factor was not significantly different between older and younger patients. Financial issues may also play a role in elderly patients choosing not to enroll in clinical trials, although no difference was seen among age groups in this study.

Trial-Related

Generally, clinical trials do not limit eligibility based on age alone, but other criteria, including performance status (PS), organ dysfunction, and disease status, may preclude older patients from participating in a study. Previous studies have demonstrated that survival correlates well with PS and comorbidities, and study exclusion criteria often are based on these data. Although these are logical exclusion criteria, they limit elderly enrollment in clinical trials because older patients generally have a higher number of comorbidities than their younger counterparts.

In multiple studies, trial ineligibility was the greatest barrier to clinical trial enrollment among older persons, with both patients and physicians perceiving this barrier as a major obstacle, and up to 60% of elderly patients who did not enroll in a clinical trial stated they failed to do so because of trial unavailability or ineligibility. One study reported that 65% of patients 65 years of age or older were eligible to participate in the trial compared with 78% of younger patients. However, if patients were eligible, trial participation rates did not significantly differ by age (34% for age ≥ 65 years vs 40% for age < 65 years). After considering other factors, overall survival and toxicity rates were similar among the younger and older patients. PS was the most significant determinant of overall 30-day (PS 0–1, 97.5%; PS 2–3, 79%) and 1-year (PS 0–1, 21%; PS 2–3, 9.5%) survival rates (P = .029). Similarly, PS was the most important factor for the development of serious toxicities (P = .034).

One study found that the most common reasons for nonenrollment due to ineligibility were poor PS (13.7% [32 patients]), the need for emergent radiotherapy (8.6% [20 patients]), patient refusal (6.0% [14 patients]), geographical issues (4.3% [10 patients]), and insurance issues (4.3% [10 patients]). These results support the claim that poor PS is the most common reason for nonenrollment into a clinical trial, while also emphasizing the complex nature of trial
enrollment. Therefore, criteria should be thoughtfully revised to include these large numbers of patients being excluded because of poor PS and trials should be aimed at elderly patients to increase enrollment among this difficult-to-recruit population.

Solutions

Physician-Related

Enrollment in clinical trials relies heavily on physicians, creating many barriers for the elderly. Both physician bias and perception have been shown to be impediments to enrollment of older persons in clinical trials. Therefore, it is imperative to create a cultural shift among oncologists to boost trial enrollment of older patients.

The factors influencing physician culture can be complex and difficult to manipulate. One commonly cited issue is the lack of data on toxicity and survival rates among elderly patients, a challenge that may enable bias. Physicians report that how elderly patients are likely to tolerate a specific treatment has not been well elucidated, a barrier that creates unknown variables favoring conservative treatment for this patient population. Because of the low numbers of participation among elderly patients in clinical trials, the problem of lacking data on treatment tolerance is further compounded. Although some studies have demonstrated that age itself does not change tolerance to treatment, additional studies are needed to further clarify this issue. As more specific data become available, physician attitudes toward trial participation are likely to change.

It is important to increase trials specifically targeting elderly patients, because older patients with cancer may require more thorough care when instituting systemic therapy compared with younger patients with cancer. This is due to the biological changes of aging and uncertainties of the pharmacokinetic profiles of some medications, including chemotherapy, which is a concern common among oncologists that may hinder patient enrollment. Studies of pharmacodynamics and pharmacokinetics directed at elderly populations will be important for solving these challenges.

Late-stage clinical trials can also stratify patients based on age, and increasing data on the elderly patient population may improve treatment and decrease physician-related barriers. The prognoses of elderly patients referred to a phase 1 study are comparable with the rest of the study population. In fact, elderly patients enrolled in phase 1 trials had improved survival rates when compared with elderly patients who did not receive treatment during a phase 1 trial. However, some physicians do not perceive clinical trials as being beneficial for their patients. Therefore, increasing data on the older population, as well as changing physician perceptions, will be important in increasing the numbers of trials specifically targeting the elderly, possibly acting as the key to shifting physician attitudes away from age bias.

Patient-Related

The most common patient-related challenges relate to understanding the benefits of clinical trials and the logistics of clinical trial enrollment. Solutions to these problems are complex and can be approached in different manners. For example, controversy exists as to whether increased patient information will increase levels of enrollment in clinical trials among the elderly. By contrast, logistical issues have been an easier challenge to address.

Transportation is difficult among older patients who, compared with younger patients, more frequently require help from a family member or friend for travel. In addition, older patients have increased time requirements for transportation. Housing is also more complicated among elderly patients. Among older persons, a small inconvenience can become a major issue, such as having access to an elevator. Communication is a key factor in facilitating clinical trial participation, with research indicating that more time is often required for nurses to effectively communicate with the geriatric population, in particular elderly patients who are frail.

Ensuring that trials are accessible is important with any study population, but this is especially true among older patients. Accessibility can be achieved by providing funding for transportation, housing, and coordination, provided that no ethical dilemmas are presented. Although it is unethical to provide direct monetary incentives for trial enrollment, financial support to offset logistical barriers is considered appropriate. Solutions such as home visits and flexible scheduling have also been proposed. Additional research staffing may be needed to account for the extra time and resources required for enrolling older patients into clinical trials.

Increasing the number of research personnel was rated by oncologists as the most important method to increase trial accrual among the elderly. A team approach involving family members, physicians, support staff, and others provides the most effective method to overcoming logistical barriers to patient enrollment. An increase in logistical support will be a key feature in attracting more elderly patients to clinical trials, and, although the data on patient-related solutions are sparse, improving logistical support, follow-up methods, and patient education are likely to increase enrollment among this patient population.

Trial-Related

Issues of eligibility and availability to clinical trials continue to be the most obvious trial-related barriers
to enrollment among elderly patients. Therefore, increasing the number of trials aimed at this target population, with protocols specifically written to include elderly patients, will help address these challenges. Trial design must adapt to fit the needs of this unique population. For example, assessing patient status through the use of a comprehensive geriatric assessment rather than through traditional methods might improve cancer treatment in the geriatric population. Researchers should also aim to create study criteria that allow the inclusion of additional elderly participants without interfering with survival statistics. Several methods have been identified for evaluating life expectancy rates and functional status among patients with cancer, and, although these improve the ability of researchers to evaluate patient eligibility, these methods must be further studied and refined. There is a trend in the right direction, but more is needed to address the problem.

Designers of clinical trials must also anticipate the increased costs and time associated with treating an elderly population. Providing extra funding for trials aimed at older populations has the potential to offset these limitations, thus improving data, which could then be used in clinical practice. Members of the team should also have an affinity with older patients and be cognizant that extra time and financial resources will be required when conducting research on frail patients. Resource barriers are a key target when considering clinical trials in an elderly population. Data are lacking on practical and specific solutions to trial-related barriers, which is indicative of the overall issues limiting enrollment in this population. Increased funding for these studies as well as involving the elderly population in breaching these barriers will be crucial when moving forward.

Discussion
What began in 1993 with the National Institutes of Health Revitalization Act was a movement to develop evidence about participation barriers in the elderly population. The scientific community has made some efforts to define these barriers, yet solutions continue to be poorly defined. It is obvious that more information is needed to further refine barriers to identify practical and effective solutions to them.

The largest physician barrier identified is the culture of the medical community, which is a broad and complex area of study that the health care industry may find difficult to change. Currently, the most promising solution is increasing data on the outcomes and tolerances of various therapeutic regimens among the elderly, including increasing clinical trials or providing alternative methods. Currently, models expanded from the analyses of prospectively obtained information are the most effective strategies for gathering information about chemotherapy tolerance in the elderly population. Understanding tumor biology and treatment tolerance could also provide concrete evidence for physicians to base enrollment decisions on, thus decreasing the impact of age bias.

Patient barriers continue to be poorly defined and difficult to assess. This is in part due to the cultural and psychological differences among the elderly population; therefore, such issues are more difficult to generalize and may be best managed on an individual level. Increased communication with older patients is key to increasing clinical trial enrollment among the elderly as well as exploring patient-centered barriers to enrollment.

Barriers related to trial design are the most studied and well understood of the barriers to patient enrollment. Historically, trials excluded patients on the basis of age alone; however, age is no longer an exclusion criterion for most trials. Trial eligibility is now mostly based on PS, comorbidities, and organ function. However, clinical trials do not distinguish methods for evaluating elderly or younger patient functional status.

More research is needed to effectively evaluate elderly patients and target appropriate populations. Trials specifically designed for the elderly have increased in recent years, yet more data are needed to understand how to treat this patient population. As the number of research teams comfortable with elderly patients increases, the solutions to these problems are likely to become obvious. For example, some researchers have discovered they do not fully understand the implications of working with an elderly population, and specifically designed trials for an older patient population may be more complex than previously thought.

It will also be important to address logistical barriers to trial participation, which are some of the most obvious and well-known barriers, yet often they become the most difficult to overcome. Appropriate trial management and allocation of funds are imperative in order to avoid logistical barriers to enrollment.

Conclusions
The issues facing our health are constantly changing and increasingly complex. Enrolling diverse patient populations in clinical trials is just one example of the many challenges we face as health care professionals. Focusing clinical trials on the elderly population is of increasing importance, particularly with the aging population of the United States.

To address the shortage of older patient enrollment, physicians and patients must work together to recognize and overcome barriers. Physicians should be encouraged to reflect on their own practice and consider changes to help alleviate the shortage of el-
older patients in clinical trials. Although more research is needed to elucidate these barriers and solutions to enrollment issues among the older patient population, obvious causes should be addressed. Increasing eligibility of elderly patients, decreasing logistical barriers to participation, and instituting a cultural shift are all major improvements that can be immediately enacted. It is imperative that data collected from clinical trials are applicable to the patient population to be treated. Otherwise, health care professionals will continue to treat the majority of patients with cancer based on perceptions and best clinical judgment rather than on conclusive data.

References