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.

See related commentary by Giantonio, p. 2369

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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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.

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.

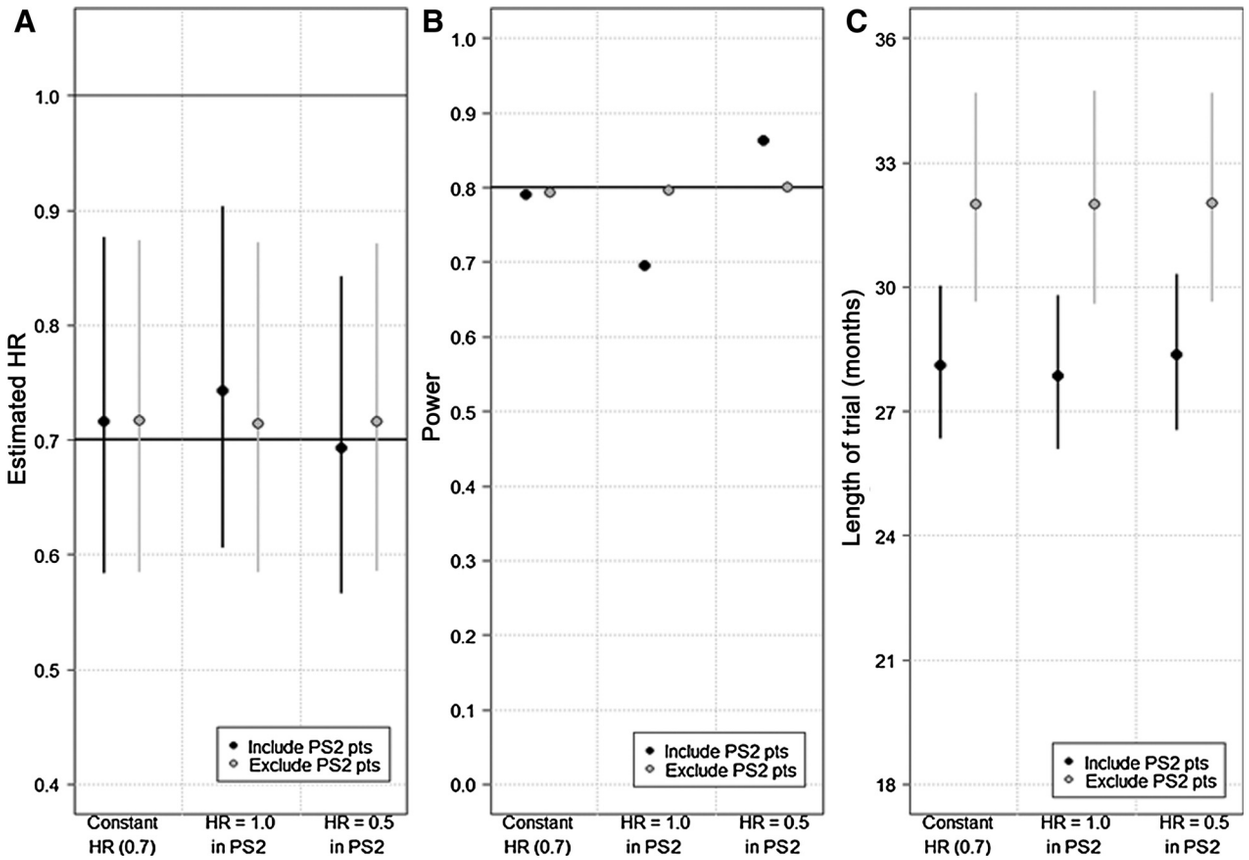

Figure 1.

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.

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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.

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