Cancer Clinical Trial Eligibility Criteria: Performance Status

Guidance for Industry, IRBs, and Clinical Investigators

DRAFT GUIDANCE

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Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2024
Clinical/Medical

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Cancer Clinical Trial Eligibility Criteria: Performance Status Guidance for Industry, IRBs, and Clinical Investigators[1]

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I. INTRODUCTION

The purposes of eligibility criteria for cancer clinical trials are to select the intended patient population and reduce potential risks to trial participants. However, eligibility criteria are sometimes more restrictive than necessary, and expanding eligibility criteria to be more inclusive is one trial design consideration that may improve the diversity of clinical trial populations.[2] This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of investigational drugs[3] regulated by CDER and CBER for the treatment of cancer.[4] Specifically, this guidance includes recommendations regarding expanding eligibility criteria to include patients with a wider range of performance status (PS). This guidance is intended to assist interested parties, including sponsors and/or institutional review boards (IRBs), who are responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population.[5] Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation Research (CBER) at the Food and Drug Administration.

[2] See the guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] For the purposes of this guidance, references to *drugs* include both human drug products and biological products regulated by CDER and CBER, unless otherwise specified.

[4] See other cancer clinical trial eligibility criteria guidances for industry: *Brain Metastases* (July 2020); *Minimum Age Considerations for Inclusion of Pediatric Patients* (July 2020); *Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections* (July 2020); *Patient with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020); *Available Therapy in Non-Curative Settings* (July 2022).

[5] For the purposes of this guidance, the terms *trial* and *study* are used interchangeably.

anticipated safety of the investigational drug, the availability of adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. The agency recognizes that some eligibility criteria may have become commonly accepted over time or used as a template across trials, but such criteria should be carefully considered and be appropriate for a specific trial context. Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug. [6,7]

Appropriately broadening cancer trial eligibility criteria can improve the generalizability of trial results and provide a more detailed characterization of the investigational drug's benefit-risk profile across the patient population likely to use the drug in clinical practice.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Performance status (PS), a measure of how well a patient is able to perform ordinary tasks and carry out activities of daily living,[8] is one of the most common eligibility criteria in oncology trials. Many trials are limited to high-functioning participants (i.e., "good" PS) and exclude lower-functioning patients (i.e., "poor" PS)[9] based on one of two main scales: Eastern Cooperative Oncology Group (ECOG) and Karnofsky (KPS). PS is included as a common eligibility criterion because low PS (i.e., ECOG PS2-4 and KPS ≤70) has been reported to correlate with worse survival, and patients with low PS may not be well enough to receive

[6] Kim ES, Uldrick TS, Schenkel C, et al, 2021, Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO–Friends of Cancer Research Joint Research Statement, Clin Cancer Res, 27(9):2394-2399.

[7] Spira AI, Stewart MD, Jones S, et al., 2021, Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group, Clin Cancer Res, 27(9):2416-2423.

[8] National Cancer Institute Dictionary of Cancer Terms available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/performance-status.

[9] Jin S, Pazdur R, and Sridhara R, 2017, Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015, 35(33):3745-3752.

investigational treatment or tolerate its potential toxicities.[10,11,12] However, this practice may prevent trial enrollment for many patients and limit generalizability of trial results. The underlying etiology for low PS is important. For patients whose low PS is due to disease burden, cancer-directed treatment may result in improved PS with tumor control and symptom alleviation, especially with highly effective treatments. However, current PS scales do not differentiate between causes of low PS.

Additionally, there are limitations to PS assessments. PS determination is inherently subjective, which can affect inter-rater reliability[13] and invite potential bias, particularly for patients at the borderline between PS categories. For example, studies demonstrate that clinicians assign patients aged ≥65 years higher numeric ECOG PS[14] scores than younger patients, despite no difference in objectively measured physical activity.[15] Additionally, PS is less predictive of cancer-related outcomes for older adults[16,17] and may be less relevant for more recently developed anticancer treatments that have different toxicities than cytotoxic chemotherapy.[18]

III. CONSIDERATIONS WHEN INCLUDING PATIENTS WITH LOW PS (i.e., ECOG PS2-4 and KPS ≤70)

[10] Arboe B, Halgren Olsen M, Duun-Henriksen AK, et al., 2018, Prolonged Hospitalization, Primary Refractory Disease, Performance Status and Age are Prognostic Factors for Survival in Patients with Diffuse Large B-cell Lymphoma and Transformed Indolent Lymphoma Undergoing Autologous Stem Cell Transplantation. Leuk Lymphoma, 59(5):1153-1162.

[11] Song T, Wan Q, Yu W, et al., 2017, Pretreatment Nutritional Risk Scores and Performance Status are Prognostic Factors in Esophageal Cancer Patients Treated with Definitive Chemoradiotherapy, Oncotarget, 8(58):98974-98984.

[12] Wang JR, Habbous S, Espin-Garcia O, et al., 2016, Comorbidity and Performance Status as Independent Prognostic Factors in Patients with Head and Neck Squamous Cell Carcinoma, Head Neck, 38(5):736-42.

[13] Chow R, Bruera E, Temel JS, et al., 2020, Inter-rater Reliability in Performance Status Assessment Among Healthcare Professionals: An Updated Systematic Review and Meta-analysis. Support Care Cancer, 28(5):2071-2078.

[14] Oken MM, Creech RH, Tormey DC, et al., 1982, Toxicity and Response Criteria of the Eastern Cooperative Oncology Group, Am J Clin Oncol, 5(6):649-655.

[15] Broderick JM, Hussey J, Kennedy MJ, and O'Donnell DM, 2014, Patients Over 65 Years are Assigned Lower ECOG PS Scores Than Younger Patients, Although Objectively Measured Physical Activity is No Different, J Geriatr Oncol, 5(1):49-56.

[16] Hurria A, Togawa K, Mohile SG, et al., 2011, Predicting Chemotherapy Toxicity in Older Adults with Cancer: A Prospective Multicenter Study, J Clin Oncol, 29(25):3457-3465.

[17] Ghosn M, Ibrahim T, El Rassy E, et al., 2017, Abridged Geriatric Assessment is a Better Predictor of Overall Survival than the Karnofsky Performance Scale and Physical Performance Test in Elderly Patients with Cancer, J Geriatr Oncol, 8(2):128-132.

[18] Cheng S, Qureshi M, Pullenayegum E, et al., 2017, Do Patients with Reduced or Excellent Performance Status Derive the Same Clinical Benefit from Novel Systemic Cancer Therapies? A Systematic Review and Meta-Analysis, ESMO Open, 2(4):e000225.

When considering inclusion of patients with low PS on clinical trials, sponsors should consider the following potential advantages and disadvantages:

A. Potential Advantages

- **More rapid trial accrual.** Increased number of eligible patients may lead to more rapid accrual. Studies have demonstrated that, of patients deemed ineligible for a clinical trial, exclusion was related to low PS in a significant proportion of patients, with variability across disease type, investigational therapy, and therapy line.[19,20]

- **Improved external validity of trial results.** Restrictive eligibility criteria may result in a group of trial participants who do not reflect the clinical and demographic diversity of patients with the indicated disease. As a result, the efficacy and safety outcomes experienced by participants with high PS may not adequately predict the outcomes for patients with low PS.[21,22] Expanding eligibility to include patients with low PS can mitigate this issue.

  Including a broader group of participants could offer additional benefits, such as additional information in drug labeling to inform clinicians and patients and/or reduce the need for post-marketing commitments.

B. Potential Disadvantages

- **Increased adverse events.** Rates of adverse events (AEs) may be greater in ECOG PS2 participants as compared to PS0 and PS1 participants, and this may influence patients' ability to complete the intended course of treatment, their outcomes and/or their ability to comply with study procedures necessary to assess their outcomes. The risk of overestimating harm or underestimating benefit may be mitigated in randomized trials given baseline PS is often a stratification factor and the effect of low PS on AE rate and other outcomes will impact both arms.

- **Potential impact on trial outcome data.** The potential disadvantage of worse-than-expected outcomes by inclusion of low-functioning PS participants may be a concern to sponsors. In such cases, FDA recommends that sponsors consider discussing with the appropriate review division a primary efficacy analysis that is restricted to the participant

[19] Network ACSCA. Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report. Available at https://www.fightcancer.org/policy-resources/clinical-trial-barriers.

[20] Lara PN Jr, Higdon R, Lim N, et al., 2001, Prospective Evaluation of Cancer Clinical Trial Accrual Patterns: Identifying Potential Barriers to Enrollment, J Clin Oncol, 19(6):1728-1733.

[21] Azad AA, Eigl BJ, Leibowitz-Amit R, et al., 2015, Outcomes with Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer Patients Who Have Poor Performance Status, Eur Urol, 67(3):441-447.

[22] Blackhall F, Ross Camidge D, Shaw AT, et al., 2017, Final Results of the Large-Scale Multinational Trial PROFILE 1005: Efficacy and Safety of Crizotinib in Previously Treated Patients with Advanced/Metastatic ALK-Positive Non-Small-Cell Lung Cancer, ESMO Open, 2(3): e000219.

subset who meet more conventional eligibility criteria when a sponsor enrolls a broader range of participants.[23]

IV. RECOMMENDATIONS

Patients with lower PS should be included in clinical trials in a way that contributes to a greater understanding of the efficacy and safety profile of the investigational drug while maintaining patient safety. In cases where there is a strong rationale for exclusion, the rationale should be described in the trial protocol.

Baseline ECOG and Karnofsky PS should be complemented by emerging patient-reported outcomes, and other assessment tools that can provide a more refined and/or longitudinal understanding of performance status across populations, including older patients with cancer.

A. Recommendations for Inclusion Based on PS

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. Given the potential for differences in AE rates, including PS2 patients could provide important safety data to facilitate decision-making for patients in the post-approval setting.

- PS eligibility criteria should be based on the patient population in which the treatment is expected to be applied in clinical practice.

- PS eligibility criteria should be re-evaluated 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 2/3) 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 in the protocol.

- Incorporating the rationale for inclusion of a broader population into the protocol could help encourage investigators to enroll these patients.

- Baseline performance status data should be collected for all clinical trials to characterize the enrolled population.

- Where there may be a large range of baseline PS patients, PS information can be considered as a stratification factor.

[23] Beaver JA, Ison G, and Pazdur R, 2017, Reevaluating Eligibility Criteria – Balancing Patient Protection and Participation in Oncology Trials, N Engl J Med, 376(16):1504-1505.

B. Recommendations for Alternative Trial Designs

Where there are concerns regarding low PS based on the particular trial context, consider alternative trial designs, such as pre-specified cohorts with low PS (ECOG ≥2) that are exempt from the primary analysis, to encourage inclusion of these patients and collect safety data. These cohorts would generally be small in size and exploratory in nature, and could be enrolled incrementally 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 post-marketing requirements discussed with FDA when appropriate. Refer to FDA guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* (December 2019) for additional considerations when considering a prespecified assessment of cohorts with low PS.

C. Recommendations for Additional Assessments of Functional Status

Additional assessments of functional status should be considered to better characterize the functional status of patients at baseline and over time.

- **Patient-generated physical function and activity data.** Patient reported outcome assessment of Physical Function and Role Function, are two of the core clinical outcomes recently recommended in FDA's core patient-reported outcomes in cancer clinical trials guidance[24] and can provide both baseline and longitudinal data that can complement clinician-assessed PS.[25] Wearable devices can also be explored to add additional objective activity data to compare with clinician and patient report.

- **Assessment of patients' overall health status, particularly in older adults.** Existing PS scales are suboptimal for most patients with cancer aged ≥65.[26] Multiple studies have demonstrated that alternate clinical tools, such as the comprehensive geriatric assessment, are more descriptive than PS at evaluating older adults' overall health status[27] and better than KPS at predicting chemotherapy toxicity.[28] Sponsors may consider using an available geriatric assessment tool to better characterize the functional status of older adults. A simple assessment tool evaluating single or multiple aspects of function with limited burden to the patient is preferred.

[24] See the draft guidance for industry *Core Patient-Reported Outcomes in Cancer Clinical Trials* (June 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[25] Suh SY, Leblanc TW, Shelby RA, et al., 2011, Longitudinal Patient-Reported Performance Status Assessment in the Cancer Clinic is Feasible and Prognostic, J Oncol Pract, 7(6):374-381.

[26] See footnote 13.

[27] Repetto L, Fratino L, Audisio RA, et al., 2002, Comprehensive Geriatric Assessment Adds Information to Eastern Cooperative Oncology Group Performance Status in Elderly Cancer Patients: An Italian Group for Geriatric Oncology Study, J Clin Oncol, 20(2):494-502.

[28] See footnote 12.