Brigham and Women's Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Submitted June 25, 2024

Re: **Docket No. FDA–2024–D–1377**
Cancer Clinical Trial Eligibility Criteria: Performance Status

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard ("MRCT Center") appreciates the opportunity to comment on the Draft Guidance by the Food and Drug Administration ("FDA") for industry entitled, "*Cancer Clinical Trial Eligibility Criteria: Performance Status*," published at 89 Fed. Reg. 32442-44 (Apr. 26, 2024) (the "Draft Guidance"). Guidance on this topic is important to stakeholders across the clinical research enterprise.

The MRCT Center is a research and policy center that seeks to improve the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.[1]

The MRCT Center appreciates the broader effort across the Department of Health and Human Services to promote appropriate representation in clinical trials, aiming for the population enrolled in clinical trials to mirror those anticipated to be prescribed the product if approved. We find FDA's Draft Guidance on use of performance status is, however, problematic, and we strongly encourage FDA to eliminate (or perhaps severely restrict) the use of performance status as an eligibility criterion. Both the Karnofsky score and the ECOG score as measures of performance status are outdated, highly subjective constructs that are ableist (i.e., discriminatory against people with disabilities) at their core. Indeed, in introducing the Performance Status in 1949, Karnofsky and Burchenal wrote, "[…in describing the patient's ability to carry on his normal activity and work, or his need for a certain amount of custodial care, or his dependence on constant medical care in order to continue alive. These simple criteria serve a useful purpose, in our experience, in that they measure the usefulness of the patient or the burden that he represents to his family or society."[2] Although these presumptions may have applied in the

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[2] Karnofsky DA, Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer. Evaluation of chemotherapeutic agents. Edited by: MacLeod CM. 1949, New York: Columbia University Press, 191-205, as quoted in: Péus, D., Newcomb, N. & Hofer, S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. *BMC Med Inform Decis Mak* **13**, 72 (2013). https://doi.org/10.1186/1472-6947-13-72.

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1940s, when many people with disabilities were institutionalized or placed in nursing homes, they no longer apply today. With the independent living movement of the 1960s, enactment of federal disability civil rights laws, and the *Olmstead v L.C.* Supreme Court ruling under the ADA securing the right for people with disabilities to live in integrated communities, people with what the ECOG and Karnofsky scores would consider significant disabilities are living productively today in their homes and communities.

The prohibition on discriminatory practices has recently been confirmed in the May 9, 2024, final rule of the HHS regulation on Nondiscrimination on the Basis of Disability in Programs or Activities Receiving Federal Financial Assistance (45 CFR Part 84) that states:

> …discrimination based on biases or stereotypes about a patient's disability, judgments that the individual will be a burden on others due to their disability, or a belief that the life of a person with a disability has lesser value or that life with a disability is not worth living is prohibited regardless of whether treatment is sought for a separately diagnosable medical condition or symptom or for a patient's underlying disability. These obligations apply to recipient activities without regard to whether the potential discrimination in the use of a value assessment method is on the basis of an underlying disability or separately diagnosable symptom or medical condition.[3]

The performance status score is grounded by the ability to work, care for oneself, perform "normal activities," and ambulate; it embodies the concept that disability is a burden, an impairment, and a problem. People with disabilities have been excluded systematically from clinical trials: it is time to critically examine structural impediments to their inclusion. Performance status, as an eligibility criterion, is a stigmatizing instrument that leads not only to further marginalization of this population but also to greater health disparities.

We agree with FDA that the imposition of performance status represents a barrier to participation that hampers the "generalizability of the trial results." (p 3, ln 61). There are alternatives to the measures of performance status. FDA should adopt alternative measures that more appropriately reflect both the clinical risks (not the assumption by an evaluator) and the individual participant's experience and preferences.

We appreciate that there is history to the use of performance status as an eligibility criterion in clinical trials. Patients who are sicker, those with more advanced cancer and/or co-morbidities, organ dysfunction, weight loss, cachexia, fatigue, and frailty, may tolerate cancer therapies less well and have a greater number of adverse events than those who are in better health or with less advanced disease. In testing an investigational product, sponsors wish to focus on those who are likely to "do better" and have fewer adverse events to increase the chance that the product will demonstrate that its benefit exceeds its risk. And certainly, in early phase trials before any

[3] Department of Health and Human Services. 45 CFR Part 84. RIN 0945-AA15. Nondiscrimination on the basis of disability in health and human service programs or activities. Nondiscrimination on the basis of disability in programs or activities receiving federal financial assistance. Final rule. *Federal Register.* 2024 (May 9);89(91):40066-40195. Available at: https://www.govinfo.gov/content/pkg/FR-2024-05-09/pdf/2024-09237.pdf, p. 40102 (accessed June 20, 2024)

benefit has been demonstrated, there is no scientific necessity to enroll people with severe functional impairment. But for clinical trial populations to represent those for whom the product is intended, then broadening the eligibility criteria in later phase trials is essential—unless one significantly narrows the product label. It is a *change* in organ function, based on disease, that should drive clinical decision-making. In any event, measures of health should not be based on the ECOG or Karnofsky Performance Status, both of which discriminate against people with disabilities.

We offer further comments below to promote more complete guidance.

Comments

Introduction

The MRCT Center appreciates that "some eligibility criteria may have become commonly accepted over time or used as a template across trials," but we strongly advocate that the practice of cutting and pasting language from previous study eligibility criteria should discontinued. Instead, as FDA suggests, eligibility criteria for each study should be "carefully considered and be appropriate for a specific trial context" such that they do not yield "trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug." (p 2, lns 33-38). Thus, in our tools for clinical research practitioners, we caution against copying and pasting eligibility criteria from the protocol of one study into the draft protocol of a new study. We agree with FDA and support its guidance recommendation that moving away from one-size-fits-all eligibility criteria will elicit a more comprehensive and accurate understanding of an investigational drug's benefit-risk profile and thereby improve the quality of clinical research overall.

Background

The MRCT Center shares FDA's concern regarding the application of Performance Status ("PS") as an eligibility criterion for participation in an oncology trial. We agree without reservation that the imposition of such a barrier to participation hampers the "generalizability of the trial results." (p 3, ln 61). This is particularly true for the inclusion of people with disabilities in clinical trials, who have been and will be deemed ineligible because of the use of ECOG, Karnofsky, and/or other PS instruments in the eligibility criteria. For example, anyone who routinely uses a wheelchair will be categorically excluded from trials, and some people who are blind and may need assistance with self-care (e.g., cooking), would be deemed ineligible to participate in clinical trials at ECOG score threshold of 2 ("must be capable of all self-care").

We echo FDA's critique that PS as a metric fails to account for the "underlying etiology" of low PS scores. (p 3, ln 62). Antiquated instruments that conflate illness with disability should not be used to inform eligibility for cancer clinical trials. There are now more specific and objective laboratory and diagnostic measures of cancer disease progression and prognosis (e.g. TNM staging, genetic markers) and level of illness (e.g., co-morbidities) that would be more likely to

correlate with the safety and risk profile for a specific participant than use of a wheelchair or the need for some assistance with self-care. Not only do performance status instruments provide a poor proxy for disease progression but they allow for broad exclusion of people with disabilities that is not based on justifiable scientific, medical, or safety reasons. Such exclusion is discriminatory, and counter to the protections in Section 504 of the Rehabilitation Act, Titles II or III of the Americans with Disabilities Act, and Section 1557 of the Affordable Care Act.

For argument's sake, even if evaluations of performance status excluded people with disabilities, we share FDA's reservations that PS is a "subjective" metric that may yield "inter-rater…bias, particularly for patients at the borderline between PS categories." (p3, lns 67-69). The fact that many new anticancer treatments "have different toxicities than cytotoxic chemotherapy" and that PS is "less predictive of cancer-related outcomes for older adults" adds to the argument that performance status should not be used at all.

Potential Advantages

We appreciate FDA clearly articulating the advantages and disadvantages of implementing the recommendations in the Draft Guidance. We understand and agree that increasing the aperture of eligibility would both significantly reduce the trial enrollment period and enroll trial populations who better reflect both the "clinical and demographic diversity of patients with the indicated disease" (p 4, lns 90-91), thereby providing a more accurate representation of the product's post-approval performance. However, these advantages will hold true regardless of the measure by which eligibility criteria are broadened; we reiterate our caution that it is highly problematic to utilize performance measures such as "ambulatory" and "capacity for self-care" as measures of illness or disease progression.

While we understand the impetus to simplify and standardize eligibility criteria based on PS status and a threshold for inclusion, performance status measures are not appropriate measures of illness. The addition of conditional language (e.g., "the PS scores should only be used to measure current illness and not pre-existing disability" or "PS measures should be determined only after accommodations have been provided," would not eliminate the subjectivity (and potential bias) of the PS score.

Potential Disadvantages

Among the listed disadvantages, we disagree conceptually with the suggestion that inclusion of participants with a broader range of PS would yield "increased adverse events." (p 4, ln 102). Even if the absolute number of adverse events did increase, we would not view this as a "disadvantage." One can safely assume that a newly approved treatment would likely be prescribed to patients with both high and low PS. Consequently, we view the exclusion of low-PS individuals from the clinical trials on which that approval was based as likely to yield artificially low numbers of adverse events, relative to the post-approval clinical reality.

Clinicians and patients should both know the predicted benefits and risks of a product for "someone like them" – in good or in poor health.

We have similar concerns with the subsection on "Potential impact on trial outcome data" (p 4-5, lns 110-15). We understand the concept of stratifying enrollment based on the state of health, but not the proposal to exclude patients with "low PS" from the primary analysis. We worry about the implications associated with restricting "a primary efficacy analysis…to the participant subset who meet more conventional eligibility criteria." (p 4-5, ln 113-14). Instead, we argue that these two populations should each be analyzed, and the product label should reflect those analyses. If the benefit exceeds the risk for only one population, why should the label not be restricted to that population? It would be helpful if FDA were to include more information on its approach to approving marketing applications based on the populations enrolled in the trials.

Recommendations

We commend the clarity of FDA's position that inclusion should be the default in trials (and in our view, independent of PS status and eliminating this criterion from consideration), which is akin to protection through research rather than from research, and that a participant's "exclusion [should be] justified by established safety considerations." (p 5, ln 132).

Recommendations for Inclusion Based on PS

If FDA believes that measures of health must inform eligibility criteria, we suggest more objective measures for disease status and use of patient-reported (not measures that are externally and subjectively assessed. We suggest that FDA add practical and procedural guidance to the recommendation in the second bullet point to modify objective health criteria and patient-reported outcomes as the investigational drug moves through the clinical trial process. Further, can these modifications to eligibility criteria be planned at protocol development, reviewed and approved by the FDA/IRB, and then introduced as the data are accumulated, or would such changes require timely review by an IRB and/or FDA? In a scenario when the data clearly support modifying the eligibility criteria while the study sponsor is still blinded to them, would a Data Monitoring Committee ("DMC") be expected – or even permitted – to communicate those data to the study sponsor?

Further, and again only when measures of health status are needed in eligibility criteria, we advise that the wording in the recommendations for inclusion be changed from "Baseline [~~performance~~ health] 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~~ this] information can be considered as a stratification factor" (p5, lns 151-155), to "Baseline health status data may be collected for clinical trials to characterize the enrolled population. Where there may be a large range of baseline patients, this information can be considered as an initial stratification factor that merits further medical review, but exclusion can only be confirmed by

diagnostics (e.g., labs, radiology) that indicate level of illness and a safety risk for taking the tested product."

Recommendations for Alternative Trial Designs

We find FDA's recommendation to consider an adaptive trial design practical and sensible, although we additionally and strongly recommend that this consideration be applied for all trials so that each trial is inclusive for people with disabilities. We note that there appears to be some tension between the recommendation here and the suggestion to stratify the data analysis that appeared in the previous subsection (p 5, lns 154-55). We believe stakeholders would benefit from some recommendations in the final guidance regarding whether and when to pursue stratification of trial populations.

Recommendations for Additional Assessments of Functional Status

We have questions about the application of the recommendations in this subsection. Are these other-than-PS assessments intended to supplant or to complement the role of PS as eligibility criteria? We appreciate that Physical Function and Role Function are core patient-reported outcomes as included in the draft guidance document, "*Core Patient-Reported Outcomes in Cancer Clinical Trials*" (June 2021), but, as with the ECOG and other performance status measures, we are unclear about their applicability as eligibility criteria. The regulated community would benefit from greater clarity regarding how FDA recommends trial sponsors should leverage these additional assessments through the lens of eligibility criteria.

Conclusion

The MRCT Center appreciates the opportunity to comment on this Draft Guidance. We reiterate our support for improving the representativeness and quality of clinical research, and we would welcome an opportunity to discuss the Draft Guidance with FDA's staff.

Please feel free to contact the MRCT Center, Dr. DeCormier Plosky (wdecormierplosky@bwh.harvard.edu), or myself (bbierer@bwh.harvard.edu) if we can be helpful.

Respectfully submitted,

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