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 24, 2024

Re: **Docket No. FDA–2024–D–1402**
Cancer Clinical Trial Eligibility Criteria: Laboratory Values

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Trials Center of Brigham and Women's Hospital and Harvard ("MRCT Center") appreciates the opportunity to comment on the Draft Guidance by the Food and Drug Administration ("FDA") entitled, "*Cancer Clinical Trial Eligibility Criteria: Laboratory Values*," published at 89 Fed. Reg. 32450-51 (Apr. 26, 2024) (the "Draft Guidance"). Guidance on this topic is timely, welcome, and 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 applauds FDA's broad efforts to increase representativeness in clinical trials and to reemphasize that participation in clinical trials should reflect the population intended to receive the product, if approved. We offer the comments below to further FDA's efforts.

Comments

General

The MRCT Center believes that eligibility criteria should be assessed de novo for each trial depending on the product, stage of development, mechanism of action, metabolism, excretion, toxicity, intended use and population, and other parameters, and that template language for eligibility criteria should be rejected. Any eligibility criterion that limits participation in clinical trials—whether expressed as an inclusion or exclusion—should be explicitly justified based on scientific, medical, or ethical grounds. If the eligibility criteria limit the population in such a way that the enrolled population does not represent the characteristics of the intended population (i.e., the "patient population that will ultimately use the drug,") subsequent studies should be planned to eliminate that difference, either through additional clinical trials or the collection and analysis

[1] Brigham and Women's Hospital, Mass General Brigham, Harvard Medical School, and Harvard University.

Smith Center #771, 1350 Massachusetts Ave, Cambridge, MA 02138 75 Francis Street, Boston, MA 02115
Tel: 617-827-7413 | Email: bbierer@bwh.harvard.edu www.MRCTCenter.org

of real-world data post-approval as a required commitment. In the absence of planned studies, the product labeling should reflect the population studied.

We agree that moving away from one-size-fits-all eligibility criteria, the habit of "cut and paste" and/or the use of templated eligibility language is critically important. We encourage FDA to strengthen its position and to require written justification of eligibility criteria that fail to reflect the population intended to use the product.

Background

The MRCT Center agrees with FDA that overly restrictive laboratory value-based eligibility criteria are problematic and that such criteria may well exclude the very cancer patients that may benefit from the treatment under study, particularly when the malignancy (or its prior treatment) is affecting those lab values.

The background section of the Draft Guidance references older individuals who often have some degree of organ dysfunction and suggests that normal values may differ based on ethnic or racial population differences. More examples and specific examples would be helpful, whether provided in the background section or in the recommendations (see below).

Recommendations

We agree with the intent of all the recommendations put forward, and we encourage FDA to provide additional clarity, guidance, and examples. The recommendations are broad and directional, and thus will be hard to implement. For example, the Draft Guidance states, "Furthermore, as investigational drugs advance from early phase to late phase development, laboratory eligibility criteria should be adjusted based on additional available clinical data" (p4 ln 104-106). However, since the early phase trials generally have very restrictive laboratory value-based eligibility criteria, such additional clinical data will not likely be available, thus providing an excuse not to liberalize eligibility criteria. FDA should provide further examples of and direction to broadening eligibility as the product development pathway proceeds such that, by the end of Phase 3 and for inclusion of data in the NDA, clinical trial experience largely reflects the intended population.

It would be helpful for FDA to cross-reference its earlier Guidances entitled, *"Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies"* (https://www.fda.gov/media/123745/download) and "*Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs"* (https://www.fda.gov/media/127712/download). Any salient differences in Guidance between the current Draft Guidance and these two earlier documents should be illuminated, as they are not readily apparent.

The MRCT Center supports FDA's position as inclusion-by-default and exclusion-only-when-necessary. We agree with the recommendations presented and the delineation of scientific

justifications, potential variation in laboratory values, and issues attendant with reassessment of the laboratory tests. More specific examples of the appropriate application of these recommendations (and their complexity) would be welcome. For example:

- In recent years, the elimination of the Black race coefficient for estimation of eGFR from serum creatinine has been broadly adopted. As appropriate as that is in some clinical settings (e.g., for consideration of treatment for chronic renal disease), in clinical trials, it may result in inappropriate exclusion from eligibility, in that measured GFR is 16% higher for Black than non-Black people given the same age, sex, and serum creatinine. Direct measurement of GFR and/or use of other endogenous filtration markers (e.g., cystatin C, β-2 microglobulin) should be encouraged and should be explicitly recommended if the eGFR is high, independent of race.
- Race is used as a variable to correct pulmonary function tests; predicted normal spirometry values are artificially inflated for individuals who identify as Black. Alternatives should be explored, and correction factors only used if they result in greater eligibility and inclusion. At a minimum, race-neutral average references ranges (and, if helpful adjusted and unadjusted FEV_1) should be used (see Bhakta NR, Bime C, Kaminsky DA, McCormack MC, Thakur N, Stanojevic S, Baugh AD, Braun L, Lovinsky-Desir S, Adamson R, Witonsky J. Race and ethnicity in pulmonary function test interpretation: an official American Thoracic Society statement. American journal of respiratory and critical care medicine. 2023 Apr 15;207(8):978-95.)
- Most often seen in people of sub-Saharan African descent, Duffy-null associated neutrophil count (DANC) (previously denoted as "benign ethnic neutropenia") is an inherited cause of an absolute neutrophil count (ANC) < 1-1.5 x 10^9/L with no clinical sequelae or increased risk of infection. It results from a polymorphism in a gene (atypical chemokine receptor 1, *ACKR1*) that encodes for Duffy antigen receptor for chemokines (*DARC*, also called Duffy antigen**),** a membrane glycoprotein that acts as a chemokine receptor for proinflammatory cytokines. This "Duffy-negative" (Fy(a-b-) phenotype is caused by one nucleotide substitution within the promoter of ACKR1, which disrupts the sequence binding the erythroid transcription factor GATA-1 and leads to the selective loss of ACKR1 expression in red blood cells but not endothelium; the null phenotype confers a selective advantage against *Plasmodium vivax*. Cancer clinical trials that require a minimum neutrophil count should require Duffy status testing prior to exclusion and/or provide for a known normal DANC variant to be included as an eligibility exception.
- Generally, laboratory tests, risk calculators, and other criteria that use race as a variable should be examined (see, for example, https://clinical-algorithms-with-race.org, cited in Visweswaran S, Sadhu EM, Morris MM, Samayamuthu MJ. Clinical Algorithms with Race: An Online Database. medRxiv. 2023 Jul 6) and, where inclusion of race limits or excludes eligibility, alternative measures should be substituted and/or required.

While these examples relate to race-based differences, additional examples of differences in "normal" laboratory values by age, sex, gender, ethnicity, weight, and other variables are

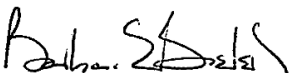
encouraged. Pediatric values for routine analytes vary, as do values for the elderly, etc. Further examples would be helpful, and, wherein the normal values are unknown (e.g., transgender populations in different stages of hormonal treatment), research should be encouraged.

We agree with the suggestion that protocols should include the ability to repeat a laboratory test within a certain time interval. The Draft Guidance suggests that the repetition is indicated if a test falls (just) outside of the required laboratory test value. Laboratory tests, particularly in patients with cancer, may change as a consequence of progression of the disease, and FDA recognition of this fact would be helpful. Can the investigator ignore laboratory values that become abnormal between screening and/or enrollment and first administration of the investigational product?

As mentioned above, the MRCT Center supports the notion that eligibility criteria should be modified as safety data is accumulated and that laboratory value-based eligibility criteria "can be revised early and often." (p6, ln 188). Further guidance (e.g., How early? How often?) would be helpful. Can sponsors and sponsor-investigators propose adaptive trial design to accommodate these changes?

The MRCT Center appreciates the opportunity to comment on this Draft Guidance. We would welcome an opportunity to discuss. Please feel free to contact the MRCT Center or with me (bbierer@bwh.harvard.edu) if we can be helpful.

Respectfully submitted,



Barbara E Bierer, MD
Faculty Director, MRCT Center