December 15, 2024

The Honorable Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
Docket No. FDA–2019–N–5959
5360 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA-2024-D-2052: Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice; Draft Guidance for Industry

Dear Commissioner Califf:

The American Cancer Society Cancer Action Network (ACS CAN) appreciates the opportunity to comment on Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice; Draft Guidance for Industry. ACS CAN advocates for evidence-based public policies to reduce the cancer burden for everyone. As the American Cancer Society's nonprofit, nonpartisan advocacy affiliate, ACS CAN is making cancer a top priority for public officials and candidates at the federal, state, and local levels. By engaging advocates across the country to make their voices heard, ACS CAN influences legislative and regulatory solutions that will end cancer as we know it, for everyone. We are providing comments on the proposed rule through the lens of cancer patients.

ACS CAN commends the U.S. Food and Drug Administration (FDA) for recognizing the importance of making clinical trials accessible to patients at their point of care. Clinical trials play an integral role in advancing potential new treatments that improve quality of life and survival for people with cancer. To successfully bring any new treatment from the research setting to the patient, clinical trials must enroll an adequate number of participants to assess a treatment's safety and efficacy. Although most cancer patients offered a clinical trial will participate, our research has shown that 77% of cancer patients will not have a matching clinical trial available at their institution.[1] A recent report from the National Coalition for Cancer Survivorship (NCCS) confirms these findings, reporting that among

[1] Unger, J. M., Hershman, D. L., Till, C., Minasian, L. M., Osarogiagbon, R. U., Fleury, M. E., & Vaidya, R. (2021). "When Offered to Participate": A Systematic Review and Meta-Analysis of Patient Agreement to Participate in Cancer Clinical Trials. JNCI: Journal of the National Cancer Institute, 113(3), 244–257. https://doi.org/10.1093/jnci/djaa155

patients who did not participate in clinical trials, 74% reported that they had not been asked.[2]

Most patients who do enroll in a cancer clinical trial became aware of their trial through their clinician or another member of the study team, and their provider's recommendation is a key driver in the decision to enroll.[1, 3] We support the Guidance's emphasis on engagement of local healthcare providers and clinical investigators in trial recruitment and patient enrollment. Our research has shown that provider barriers include time and effort to screen patients for trials,[4] so we applaud the Guidance's recommendations that sponsors support local providers by streamlining trials (both data collection and inclusion criteria) to align with clinical practice, and encouraging sponsors to provide administrative support to local trial sites when needed. The Guidance mentions the value of the electronic health record (EHR) in assisting providers through features such as embedded consent documents, reminders to record data, and ability to enter data in the EHR in a format aligned with case report forms. These features would greatly facilitate operation of trials; however, the design and functionality of institutional EHRs is typically outside of the purview of trial sponsors or individual would-be referring health care providers at local institutions. While customization of EHRs is possible at larger, more research-oriented institutions, smaller community providers are unlikely to invest in customization for research purposes, and these are the sites most in need of strategies to enhance trial participation opportunities. Absent the broad implementation of EHRs with built-in research functionality (rather than purchased add-ons), sponsors are more likely to impact the efficiency and feasibility of embedded research through the guidance's suggestion of selecting variables typically collected in routine care and by potentially providing sites (especially community providers) with any additional software and maintenance needed to capture or extract these data from EHRs.

A recent stakeholder commentary listed "Clarity with FDA Form 1572" as a key barrier to increasing patient and local clinician access to trials.[5] Particularly confusing is the requirement that Form 1572 be completed by those who make a "direct and significant contribution to the data." [6] Although this

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[2] National Coalition for Cancer Survivorship (2024) State of Survivorship Survey https://canceradvocacy.org/2024-state-of-cancer-survivorship-survey/

[3] CISCRP. 2017 Perceptions & Insights Study: The Participation Decision-Making Process. Center for Information and Study on Clinical Research Participation; 2017. Data based on a subset analysis of U.S. oncology patients. Accessed September 25, 2023. https://www.ciscrp.org/wp-content/uploads/2019/06/2017-CISCRP-Perceptions-and-Insights-Study-Decision-Making-Process.pdf

[4] Durden K, Hurley P, Butler DL, Farner A, Fleury ME. Provider motivations and barriers to cancer clinical trial screening, referral, and operations: Findings from a survey. Cancer. 2023. doi:10.1002/cncr.35044

[5] Harvey RD, Miller TM, Hurley PA, Thota R, Black LJ, Bruinooge SS, Boehmer LM, Fleury ME, Kamboj J, Rizvi MA, Symington BE, Tap WD, Waterhouse DM, Levit LA, Merrill JK, Prindiville SA, Pollastro T, Brewer JR, Byatt LP, Hamroun L, Kim ES, Holland N, Nowakowski GS. A call to action to advance patient-focused and decentralized clinical trials. Cancer. 2024 Apr 15;130(8):1193-1203. doi: 10.1002/cncr.35145. Epub 2024 Jan 9. PMID: 38193828.

[6] US Food and Drug Administration (FDA). *Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs. Frequently Asked Questions—Statement of Investigator (Form 1572)*. FDA; 2010.

Guidance distinguishes local health care providers from investigators, there may be confusion among those personnel as well as trial sponsors about who is responsible for submitting Form 1572. This confusion, as well as concerns about potential later audits, may discourage local health care providers (HCPs) from engaging with trials. We encourage FDA to clarify in the Guidance the role of local HCPs with respect to Form 1572.

Offering trials at the patient's primary point of care will address several patient-specific barriers to clinical trial enrollment, such as travel time and distance to the trial site as well as non-medical costs like transportation and lodging. Similarly, streamlining trial inclusion/exclusion criteria, as described in the Guidance, will enhance enrollment. We support the suggestion in the Guidance to engage patients early in the trial design process. Patient and community input can provide valuable insight for factors such as recruitment (especially for members of underrepresented population groups), participation burden, and the relevance of inclusion criteria and study endpoints to the target population.

Compared to their cancer burden, some racial and ethnic populations in the U.S. are vastly underrepresented in cancer clinical trials that support new drug approvals. Narrow clinical trial eligibility criteria have been shown to disproportionally affect population subgroups: Black patients (24%) and racial subgroups classified as "other" (23%) had higher ineligibility rates than White patients (17%).[7] Offering clinical trials at patients' point of care will make enrollment opportunities available to a more diverse patient population, potentially increasing the racial/ethnic and geographic diversity of the participant population.

In conclusion, our research shows that, in oncology, structural issues outside a patient's control are the overwhelming cause of low and unequal trial participation.[1, 8] Specific trial design and infrastructure elements such as inclusion/exclusion criteria, where trials are offered, whether providers screen and refer patients, and participant burdens (e.g., costs, time, travel needs) lead to low or inequitable trial enrollment. We support the Guidance's emphasis on offering trials at the point of patient care, streamlining trial design and inclusion criteria, and engaging local health care providers in patient recruitment and data collection.

Thank you for the opportunity to comment on Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice; Draft Guidance for Industry. If you have any

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[7] Kanapuru B, Fernandes LL, Baines A, Ershler R, Bhatnagar V, Pulte E, Gwise T, Theoret MR, Pazdur R, Fashoyin-Aje L, Gormley N. Eligibility criteria and enrollment of a diverse racial and ethnic population in multiple myeloma clinical trials. Blood. 2023 Jul 20;142(3):235-243. doi: 10.1182/blood.2022018657. PMID: 37140031

[8] Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. J Natl Cancer Inst. 2019 Mar 1;111(3):245-255. doi: 10.1093/jnci/djy221. PMID: 30856272; PMCID: PMC6410951.

questions, please feel free to contact me or have your staff contact Mark Fleury, PhD (mark.fleury@cancer.org), Principal, Policy Development - Emerging Science.

Sincerely,

Lisa A. Lacasse, MBA

President

American Cancer Society Cancer Action Network