December 17, 2024
Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2024-D-2052; Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice, Guidance for Industry—Draft Guidance

To Whom It May Concern:

On behalf of the LUNGevity Foundation, the nation's preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the more than 230,000 Americans diagnosed with lung cancer each year[i] and over 600,000 Americans living with the disease,[ii] we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the draft guidance **"Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice."**

Key to LUNGevity's goal of improving outcomes for people diagnosed with lung cancer are efforts to address barriers to clinical trial participation. Patient distance from trial sites and the time and resources necessary for travel can make trial participation impractical for many patients. Integrating randomized controlled trials (RCTs) into routine clinical practice could make trial participation much more accessible, not only improving convenience for patients but also facilitating the enrollment of historically underrepresented populations in clinical research and improving generalizability of study results. We appreciate the FDA's drafting of this guidance document to clarify appropriate contexts for trial integration into clinical practice, the roles and responsibilities of different stakeholders in these trials, and considerations for maintaining trial integrity and patient safety.

Clearly defining appropriate responsibilities of local healthcare providers (HCPs) participating in RCTs integrated into routine care is important to ensure patient safety and minimize risks perceived by sponsors and investigators. The draft guidance distinguishes HCPs as those who "are involved in the trial but based on the limited tasks they perform are not serving as trial personnel (i.e., investigators, sub-investigators, or their clinical support staff)." The document also provides examples of clinical activities sponsors may engage local HCPs to perform as part of a clinical trial (e.g., routine physical exams, ordering blood tests or radiographs, etc.).

According to FDA guidance,[iii,iv] individuals contributing directly and significantly to the trial data are considered sub-investigators to be included on Form FDA 1572, the Statement of the Investigator, in which the principal investigator accepts oversight responsibility of relevant trial personnel. On the other hand, local HCPs performing routine clinical care and of whom extensive knowledge of the protocol is not required are not considered sub-investigators and would not require inclusion on the 1572 form. However, trial sponsors have argued that while activities such as imaging, lab

work, and physical exams performed by local HCPs may be part of routine clinical practice, they could still be considered significant contributions to the trial data. A lack of clarity around how providers falling in this "gray area" should be defined can hinder the incorporation of clinical trials into routine clinical practice, particularly as trial investigators have expressed hesitancy around accepting oversight responsibilities for local personnel they might not see face-to-face. **We recommend that the FDA update relevant guidance to provide greater clarity on trial activities warranting inclusion on the 1572 form, for example, by applying a narrower definition of the term "sub-investigator."**

Bringing RCTs into routine clinical practice depends on efficient integration of real-world data acquired during clinical care into clinical trial case report forms (CRFs). Investigators have cited the enormous amount of time and work involved in transferring data into CRFs. We appreciate the Agency's suggestion that institutions design electronic health record (EHR) systems that capture data in formats aligned with those of the information collected in CRFs, which could streamline the conduct of point-of-care clinical trials, though this is not always easily accomplished.

Incorporating clinical trials into routine clinical practice could encourage the participation of small community healthcare facilities which have historically been less frequently involved in FDA-regulated trials. While the use of EHR systems for clinical trial data capture, aligning trial visits with routine clinical care visits, and other flexibilities can facilitate their involvement, limited research experience and resource constraints may still pose barriers to participation of these sites. We appreciate the draft guidance's recommendation that trial sponsors provide additional resources to help local facilities manage specific research requirements. Sponsors have expressed an eagerness to fill resource needs, including providing personnel for logistical support, participant recruitment, and other trial-related tasks to create efficiencies and enhance capacity for local sites to participate in clinical trials. However, they have also voiced uncertainty and a need for regulatory clarification around what kinds of support from sponsors are appropriate. **We encourage the FDA to provide as much detail as possible on acceptable roles for sponsors in engaging and supporting healthcare facilities in RCTs integrated into clinical practice.**

Implementing a Quality by Design (QbD) approach into RCTs integrated into routine clinical practice will help appropriately balance streamlining of trial protocols with adequate data collection and patient safety. **We recommend additional details on the QbD approach.** For example, clarifying criteria for selecting investigational drugs with well-characterized safety profiles and addressing the management of variability in real-world data collection could provide valuable insights for sponsors. **We also advocate the inclusion of examples of successful integration strategies in the guidance document.** Providing concrete case studies could help trial sponsors more effectively implement these recommendations into their trials.

LUNGevity appreciates the opportunity to comment on this important guidance. Integrating RCTs into routine clinical practice has clear benefits for patients, and clarifying key considerations for these trials through guidance for industry will facilitate their adoption. Please feel free to reach out to me at aeferris@lungevity.org with any questions.

Sincerely,

Andrea Stern Ferris
President and Chief Executive Officer
LUNGevity Foundation

[i] Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.
[ii] Centers for Disease Control and Prevention. United States Cancer Statistics. Available at https://gis.cdc.gov/Cancer/USCS/#/Prevalence/.
[iii] U.S. Food and Drug Administration. Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of the Investigator (Form FDA 1572). 2010 May; Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/frequently-asked-questions-statement-investigator-form-fda-1572.
[iv] U.S. Food and Drug Administration. Conducting Clinical Trials with Decentralized Elements: Guidance for Industry, Investigators, and Other Interested Parties. 2024 Sep; Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-clinical-trials-decentralized-elements.