



May 2, 2023

Dockets Management Staff
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Dear Sir or Madam:

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit organization that funds research, provides education and support, and builds communities for the more than 230,000 Americans diagnosed with lung cancer each yearⁱ and the more than 600,000 Americans living with the disease,ⁱⁱ we appreciate the opportunity to submit comments on the draft guidance "Considerations for the Design and Conduct of Externally Controlled Trials for Drugs and Biological Products" (Docket No. FDA-2022-D-2983). Our mission is to improve lung cancer survivorship and quality of life for patients living with the disease, and it is with those patients in mind that we submit the following comments.

Many subtypes of lung cancer are rare, affecting fewer than 200,000 people in the United States, including small cell lung cancer (SCLC) and certain non-small cell lung cancer (NSCLC) subtypes.ⁱⁱⁱ Some, but not all, lung cancer subtypes harbor specific driver mutations for which effective targeted therapies have been developed. However, tumors frequently develop resistance to these treatments and patients whose disease progresses after treatment often have limited therapeutic alternatives. Further development of precision medicine for these patients is hindered by small numbers of eligible participants for enrollment in randomized, controlled clinical trials. Furthermore, as additional driver mutations are discovered and corresponding targeted therapies are developed, the pools of available clinical trial participants will continue to shrink. External control arms curated from real world data sources have been demonstrated to replicate randomized trial control arms and serve as reliable comparators to experimental arms in lung cancer clinical trials.^{iv} Using external data to either serve as a control arm for a trial or supplement the control arm of a randomized controlled trial represents an important means of maintaining progress in lung cancer drug development.

The draft guidance provides important considerations for the use of external control arms in clinical trials for drugs and biological products, but stakeholders would benefit from more clarity on the applicability of these considerations in different scenarios. While the expectations for external control arms raised in the guidance are critical to ensuring trials are effectively controlled, not meeting all of the outlined criteria would not necessarily preclude the utility of external data in regulatory decision making. For example, one study revealed that low amounts of missing death data within an electronic health records database have minimal impact on reliably estimating overall survival in patients with advanced NSCLC.^v Furthermore, the use of external control data has contributed to regulatory approvals in oncology despite some evidence of unmeasured confounding.^{vi}



The applicability of the considerations outlined in the guidance may vary in different scenarios. For example, the relevance of certain intercurrent events will differ between disease settings like cancer and heart disease. We recommend providing further detail, particularly in the form of case examples, for the considerations for data comparability in the table for different disease settings, where possible. This would provide a better understanding of the appropriate use of external control arms to better aid sponsors in choosing the most appropriate design for their studies.

Additionally, while outside the stated scope of this guidance, it is important to understand how the outlined considerations apply to the use of external data to supplement a control arm in a traditional randomized controlled clinical trial. We encourage the Agency to address this either in the final draft of this guidance or in future guidance.

LUNGEvity thanks the FDA for the thoughtfulness that went into drafting “Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products.” Detailing important considerations around the use of externally controlled trials to support regulatory decision making represents an important step toward improving access to safe and effective treatments for a broader range of patients.

Please feel free to reach out to me at 240-454-3100 or aeferris@lungevity.org if you have any questions or would like to engage me or my staff in further dialogue.

Sincerely,

A handwritten signature in blue ink that reads "Andrea Stern Ferris".

Andrea Stern Ferris
President and Chief Executive Officer
LUNGEvity Foundation

ABOUT LUNGEVITY: LUNGEvity’s mission is to improve outcomes for people diagnosed with lung cancer. Our goals are three-fold: (1) to accelerate research to patients that is meaningful to them; (2) to empower patients to be active participants in their care and care decisions; and (3) to help remove barriers to access to high quality care. We have the largest lung cancer survivor network in the country and actively engage with them to identify, understand, and address unmet patient needs. We also have a world class Scientific Advisory Board and Health Equity Council that guide the programs and initiatives of the organization.

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/#/NationalPrevalence/>.

ⁱⁱⁱ LUNgevity Foundation. Types of Lung Cancer. Available at <https://www.lungevity.org/for-patients-caregivers/lung-cancer-101/types-of-lung-cancer>.

^{iv} Carrigan G, Whipple S, Capra WB, et al. Using Electronic Health Records to Derive Control Arms for Early Phase Single-Arm Lung Cancer Trials: Proof-of-Concept in Randomized Controlled Trials. *Clinical Pharmacology & Therapeutics* 2020; 107(2):369-377.

^v Carrigan G, Whipple S, Taylor MD, et al. An Evaluation of the Impact of Missing Deaths on Overall Survival Analyses of Advanced Non-Small Cell Lung Cancer Patients Conducted in an Electronic Health Records Database. *Pharmacoepidemiology and Drug Safety* 2019; 28(5):572-581.

^{vi} Misrha-Kalyani PS, Kordestani LA, Rivera DR, et al. External Control Arms in Oncology: Current Use and Future Directions. *Annals of Oncology* 2022; 33(4):376-383.