February 28, 2025

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2023-D-5016-0002; Protocol Deviations for Clinical Investigations of Drugs, Biological Products, and Devices; Guidance for Industry - Draft Guidance

To Whom It May Concern:

On behalf of 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we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance "**Protocol Deviations for Clinical Investigations of Drugs, Biological Products, and Devices**."

We recognize that during a clinical trial, deviations from the pre-specified protocol are likely to occur for a variety of reasons that may not be preventable. The Agency's guidance, further clarifying protocol deviations and the responsibilities of various parties in monitoring, mitigating, and reporting them, provide helpful context. Lessons learned from the flexibilities introduced during the COVID-19 pandemic to support ongoing clinical trials provide helpful insights into the impact of deviations on trial integrity. As seen by published work[iii] by Friends of Cancer Research and the American Society of Clinical Oncology, during the initial wave of the pandemic, oncology trial sponsors recorded an increase in protocol deviations, but with minimal to no impact on the overall data integrity of the trials. This signals that some flexibility may be appropriate without large consequences to trial conduct. LUNGevity Foundation fully supports efforts to understand and clarify which deviations may or may not be critical, or important, in terms of impact to patient safety and well-being and data integrity to support greater flexibility in trial conduct. As the Agency finalizes this draft guidance, we provide additional ideas below for consideration.

Additional Clarification on Classification of Protocol Deviations

We appreciate the distinction between important and all other non-important protocol deviations made by the FDA. Although the draft guidance document helpfully provides a non-exhaustive list of protocol deviations considered to be important, it does not factor in how the context of the trial may also determine the importance of a protocol deviation. While we recognize that the FDA cannot provide an all-inclusive list, the Agency may consider providing additional factors or characteristics of protocol deviations that might

cause an event to be considered important in the context of one trial compared to another (e.g., intervention, trial phase, etc.).

Further, while the draft guidance provides examples of important protocol deviations, there is no guidance provided on how the volume of the deviation may impact the consideration of importance. For example, a single patient may have their birthday (protected health information) disclosed, whereas all patients seen at a site may have incorrect dosing. While these are both listed as important deviations, one could argue that a site-level deviation may be more important than a single patient-level deviation in this case.

The need for clarity concerning how volume of deviations and level (e.g., patient, site, trial) may impact importance is also applicable to what the Agency would categorize as "all other protocol deviations". Would the provided examples of non-important patient-level deviations, for instance, rise to a level of importance if they were site-wide? Further guidance from the Agency on how the volume and level of protocol deviations impact importance and may warrant reclassification of protocol deviations is needed.

Reporting Protocol Deviations

The draft guidance document highlights that investigators should report to the sponsor all protocol deviations, and "in the rare instance when an investigator contemplates an intentional departure from the IRB-approved protocol intended for a single participant, then the investigator should get prior sponsor approval and must get IRB approval". This statement is not specific to important protocol deviations only, and we are concerned that interpretation of this may cause undue burden on investigators, sponsors, and IRB administrators for minor, or unimportant, protocol deviations. For example, as listed earlier in the draft guidance, "small deviations from protocol-specified visit windows" may occur on a per patient basis. Requiring an investigator to contact the sponsor and IRB every time a patient may have a slight adjustment to their visit schedule may result in an undue burden. Further clarification is needed as to whether this communication and approval only applies to important protocol deviations, and the types of communication acceptable for sponsor approval (e.g., memo, email, etc.).

Proactivity for Protocol Deviations

Lastly, we applaud the Agency for supporting the development of protocols that are less complex and provide greater flexibility to prevent and/or mitigate protocol deviations. Flexible trial protocols not only minimize risks associated with protocol deviations but facilitate the participation of patients and sites in clinical trials. We support the examples provided, such as establishing flexible enrollment criteria, flexibility in data collection timeframes, remote data collection, and eliminating unnecessary activities. As highlighted in the draft guidance, patients and patient advocates should be part of the study design team to ensure that the proposed schedule of assessments and study protocol are feasible.

LUNGevity appreciates the opportunity to comment on this important guidance. Clinical trials should be conducted in a manner that protects patients' health and safety while generating robust data to evaluate safety and efficacy. The Agency's guidance on protocol deviations supports a better understanding of what and how departures from the trial protocol may impact a study and the responsibilities of the study team in reporting and mitigating them. Please feel free to reach out to me at bmckelvey@lungevity.org with any questions.

Sincerely,

Brittany Avin McKelvey
Senior Director, Regulatory Policy
On Behalf of LUNGevity Foundation

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[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] Joseph M. Unger et al., Sponsor Perspectives on the Impact of the COVID-19 Pandemic on Interventional Cancer Clinical Trial Protocols and Data Quality. *JCO Oncol Pract* **19**, 907-916(2023). DOI:10.1200/OP.23.00185