April 19, 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-2023-N-4489; Enhancing Adoption of Innovative Clinical Trial Approaches; Public Workshop; Request for Comments

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 FDA Center for Drug Evaluation and Research (CDER) in response to its request for comments on advancing innovation in the design and conduct of clinical trials.

Significant advances have been made over the past two decades in understanding the biology of and developing treatments for the constellation of diseases collectively referred to as lung cancer. Unfortunately, the shared reality for patients with all types of lung cancer is that, at some point, their disease will progress, their current therapy will become ineffective or insufficient, and the next step will be an open question. As such, clinical trials—whether for new molecular entities or new combinations/sequences of existing therapies—are a critical part of the treatment armamentarium for patients with lung cancer, offering options, hope, and excellent care.

Despite their transformative potential, clinical trials are not a realistic option for many patients. Overly strict eligibility criteria may exclude many who could benefit; complex protocols and intensive data collection create significant time and financial burdens that may deter otherwise eligible patients from participating; and continued reliance on site-based trials conducted primarily at large academic medical centers creates travel barriers for those in remote geographies and/or who do not have a means of transportation.

To understand and begin to address these challenges, in 2016 LUNGevity launched its Transforming Clinical Trials Initiative. This multistakeholder effort brings together industry, regulators, clinicians, and patients and patient advocates for the purpose of identifying and working to mitigate barriers to designing and conducting more patient-centric clinical trials. The "innovations" we work toward are accessibility and feasibility because, ultimately, creative approaches such as digital health technologies and Bayesian statistics will not matter if patients cannot get on and stay on trials. Herein we present what we see as priorities for designing accessible, feasible clinical trials and lay out ways in which CDER can facilitate their adoption.

Meet Patients Where They Are

LUNGevity has championed the use of decentralized clinical trial (DCT) elements for years. Use of remote informed consent, local healthcare providers for follow-up visits, and local facilities for labs and imaging are examples of commonsense practices which would make participating in clinical trials easier for patients without jeopardizing their safety or data integrity.

We were pleased to see the Draft Guidance on DCTs last year, and generally agreed with the considerations for appropriate design and conduct outlined therein. One area of potential confusion, however, is the draft guidance's framing of which clinical trial personnel belong on Form FDA 1572 as a subinvestigator. The guidance states that subinvestigators to be listed on the form include trial personnel who "contribute directly and significantly to the trial data." This phrase could easily be interpreted to include procedures such as radiological imaging, laboratory work, and physical assessments. However, the draft guidance also asserts that local healthcare providers providing trial-related services as part of routine clinical practice, including performing physical examinations and reading radiological images, should not be listed on the form. **More clarity is needed from FDA regarding what constitutes "trial data" in order to address uncertainties from sponsors and investigators alike and improve adoption of decentralized and hybrid trials.**

Additionally, LUNGevity would like to see the Agency allow for flexibility in the timing and extent to which decentralized elements are incorporated into any given clinical trial to better suit the wants and needs of the trial population. Having more visits conducted at a central site before progressively adding decentralized elements, for example, would not only allow for closer monitoring early in the trial in cases where uncertainty around anticipated patient response is high, but also facilitate relationship development between patients and investigators.

Mirror the Real World

Historically, the purpose of clinical trial eligibility criteria was to minimize the potential for harm and maximize the likelihood of response in a relatively homogeneous trial population to provide regulators with the cleanest estimate of a therapy's efficacy. However, the patients who use approved therapies in the real world are often sicker, older, and from a wider range of racial, ethnic, and socioeconomic backgrounds than those who participate in trials, calling into question the generalizability of clinical trial results for the broader population.

Starting in 2020, the FDA Oncology Center of Excellence published a series of guidance on expanding certain eligibility criteria commonly used in oncology clinical trials,[iii-vii] with the stated intent of improving the generalizability of trial results and understanding a therapy's true benefit-risk profile. In parallel and with input from clinicians, regulators, and experts from industry, LUNGevity developed and published recommendations for modernizing eligibility criteria specific to non-small cell lung cancer clinical trials.[viii-x]

The incorporation of these recommendations, however, has been variable at best, due in part to concerns that increased heterogeneity in the trial population will cloud interpretation of results and/or result in less-than-optimal treatment efficacy, potentially jeopardizing approval. **Clarification from FDA regarding situations in which some amount of "messiness" in trial data would be acceptable could ease such concerns and open the doors for greater participation of historically excluded populations in clinical trials.**

Incorporate Efficiencies and Risks Appropriately

The number of procedures and visits in phase 3 clinical trials has increased phenomenally over the past two decades.[xi] In oncology, especially, increased data collection has led to trials that last, on average, four years longer than trials in other disease areas.[xii] The physical, psychological, and financial strain clinical trial participation puts on patients and caregivers is intense[xiii] and is compounded in diseases like lung cancer where patients often take part in multiple trials over the course of their disease.

For drugs with established safety profiles, collecting minimal necessary data should be non-controversial. What constitutes "minimal necessary data" will vary by disease and drug type but could be defined on a case-by-case basis by disease experts. LUNGevity is engaged in just such an exercise, working with trial investigators and drug developers to outline an abbreviated schedule of assessments for a commonly used regimen in non-small cell lung cancer clinical trials.

To encourage risk-averse drug developers to implement the outputs in their own trials, FDA will need to demonstrate the acceptability of such simplified trial designs. **The Agency should provide guidance on circumstances in which reduced data collection is appropriate and outline strategies for achieving that goal.**

Adoption of these and other innovative clinical trial approaches by trial sponsors, investigators, and sites will only be possible if there is consistency across offices and divisions within CDER regarding their potential acceptability. The relevance and appropriateness of a given approach will depend on the investigational therapy, the disease, and the patient population, but general principles should not be applied arbitrarily and capriciously. Implementation of decentralized and hybrid trials, for example, will require upfront investments in infrastructure, technology, and training that stakeholders may hesitate to undertake if there are concerns the trials cannot be widely utilized.

LUNGevity appreciates the opportunity to respond to your request for comments on clinical trial innovation. Please feel free to reach out to me at aeferris@lungevity.org or to Elizabeth Barksdale, PhD, Sr. Director, Regulatory Affairs and Scientific Policy at ebarksdale@lungevity.org with any questions.

Sincerely,

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President and Chief Executive Officer
LUNGevity Foundation

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