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

RE: Docket No. FDA-2022-D-2997; Key Information and Facilitating Understanding in Informed Consent, Guidance for Sponsors, Investigators, and Institutional Review Boards—Draft Guidance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 yearⁱ 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we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance “**Key Information and Facilitating Understanding in Informed Consent.**”

Clinical research is vital for improving our understanding of diseases and developing safe and efficacious treatments to address them. In diseases like lung cancer, with multiple defined subtypes and new molecular drivers still being discovered, patient participation in research is paramount for advancing the treatment landscape as well as providing access to potentially life-saving therapies when no alternative options exist. LUNGevity has long promoted the potential benefits of clinical trials to patients with lung cancer and is working on multiple fronts to ensure that research is designed and conducted with their input and best interests in mind.

For example, LUNGevity’s Patient-Focused Research Center (Patient FoRCe) was created to change the paradigm in the lung cancer treatment ecosystem from operating under assumptions about patient preferences to acting on evidence-based, data-driven conclusions about what patients value in their care. Through Project REFORM (Streamlining InfoRmed Consent FORMs for Lung Cancer Clinical Trials), Patient FoRCe researchers are exploring how to make the informed consent process more patient friendly by creating a template to summarize information patients identified as being necessary for making an informed choice about trial participation.^{iii, iv} In surveys and focus groups, patients and caregivers described or ranked information that was important to include in a summary; some information was consistent with elements of consent (e.g., voluntariness of participation, most common side effects) and some extraneous to them (e.g., contact information for trial/hospital staff, eligibility criteria). Additionally, participants responded positively to the information being presented in a pamphlet format and primarily arranged in bulleted lists. This multi-phase, multi-stakeholder project was not initiated with the key information section proposed for 21 CFR 50.20(e)(1) in mind, but the parallels are obvious and the takeaways relevant.

LUNGevity appreciates the FDA’s efforts to harmonize its informed consent regulations with the revised Common Rule. This has the potential to ease confusion when clinical trials are subject to both sets of regulations. Furthermore, we are encouraged by the possibility that inclusion of a key information section may enhance the informed consent process, leading to improved patient understanding and, hopefully, greater participation in clinical trials. Here we present our suggestions for improving the draft guidance and maximizing the utility of the key information section of informed consent documents.

General Comments

LUNGevity supports the concept of the proposed key information section. It has long been acknowledged that informed consent forms (ICFs) are too long and complicated.^v Attempts to simplify ICFs and increase reader comprehension have not yielded appreciable results.^{vi, vii} As such, we are pleased that the FDA is moving to require incorporation of a patient-friendly information section intended to enhance the decision-making process by facilitating understanding.

We are concerned, however, that absent a shift in thinking—from regulators, sponsors, investigators, and IRBs alike—around the content and purpose of the proposed key information section that it will end up being as complicated and incomprehensible as most informed consent documents, and could perpetuate rather than alleviate long-standing challenges with patient understanding. The key information section should not be a restatement of **all** key elements of consent. Nor should stakeholders think of it as a replacement for the ICF or consent process; the key information section on its own will not answer all questions nor bestow enlightenment. Instead, LUNGevity advocates framing the key information section as an introduction to what participation in a given trial could entail for participants and caregivers. Reading the key information should enable prospective subjects to decide whether they want to learn more, to read the entire ICF and participate in the consent process—which could still result in the subject not deciding to participate in the trial.

We would like to see the FDA use the implementation of the key information section as an opportunity to change how clinical trial information is presented to patients and their caregivers. As such, we would like to see greater emphasis in the final guidance on flexibility regarding the content and format of the key information section. Repeatedly tying the key information to the elements of consent, as is done in the draft guidance, reinforces the perception that that is the “right” content. Similarly with the singular focus on the bubble format for presenting key information. LUNGevity recommends that FDA conduct, or call for others to conduct, research to determine what information different disease communities consider most important for facilitating decision making and in what format they prefer it be presented.

Finally, LUNGevity suggests removing section *IV. B. Organization and Presentation of the Entire Consent Form* (lines 400-454) from this guidance. Although technically within scope, it comes off as tangential. This material could be further fleshed out into a standalone guidance or incorporated into the August 2023 procedural “**Informed Consent, Guidance for IRBs, Clinical Investigators, and Sponsors.**” In its place, it may be instructive for FDA to provide additional example key information section(s) utilizing different formats, topics, and language.

Specific Comments

- Lines 73-75: *“The presentation of key information at the beginning of the consent process can help facilitate discussions between a prospective subject and an investigator about whether the prospective subject should participate in the trial.”*

We appreciate that FDA highlights that informed consent is a **process**, involving both the prospective subject and the investigator/research team. Leaving a patient and/or their legally authorized representative alone for a long time to read the ICF or watch a video presenting the information does not constitute providing “sufficient opportunity to consider whether or not to participate” in a clinical trial (see 21 CFR 50.20). The consent process should encompass two-way dialogue and sufficient time and resources that the patient/representative feels confident and comfortable in their decision whether to participate in the trial.

- Lines 76-78: “*We recommend that the key information section of a consent document be relatively short (e.g., generally no more than a few pages).*”

The description “...*relatively short (e.g., no more than a few pages)*” is too vague. To prevent the key information section from becoming a restatement of the ICF and/or overrun with scientific and legal jargon, LUNGevity recommends limiting the section to two pages (or the equivalent of two pages of content if presented in another format) unless it can be demonstrated that a longer section improves reader comprehension.

- Lines 98-111: Repeated use of the term “*interested parties*” when talking about developing key information sections.

It would be helpful to know whom the FDA considers “interested parties,” as many groups will provide input on and seek to influence the content of the ICF and key information section. Also, use of “interested” could be construed as indicating that creating and utilizing key information sections is optional for entities conducting FDA-regulated clinical investigations, which is not the case. It may be more straightforward for FDA to list the groups to whom it is referring and/or to use different terminology.

- Lines 106-108: “*Interested parties could consider developing alternate ways to present key information that would facilitate understanding by prospective subjects by, for example, consulting in advance with patient advocacy groups or prospective subjects about their views on key information.*”

We support this suggestion as patient advocacy groups may be better positioned than trial sponsors to connect with the community on the key information section and gather feedback on its content from the patients they serve. Moreover, it will be important to understand what information different disease communities prioritize in their decision-making, as there will likely be differences across and perhaps within diseases (e.g., patients with early- vs late-stage disease).

- Lines 116-118: “*We recommend that the key information section of the consent form begin with an introductory statement to frame the key information included in the consent form and to guide prospective subjects when reading the entire document.*”

Taken together with the opening statement in the example in the Appendix, it is unclear what exactly the FDA envisions as the purpose for an “introductory statement” such as suggested here. Although we agree that reading the entire consent document will be important for enhancing patient comprehension, the language in the provided example reads almost as a disclaimer, putting the onus entirely on the patient to read and understand the information provided both in the key information section and the entire document. This goes counter to the FDA’s earlier positioning of informed consent as a process involving the prospective subject and the trial investigator/coordinator (lines 73-75).

LUNGevity recommends that the FDA follow a different tack here: if an introductory statement is felt to be a necessary and valuable component of the key information section, it should stress the importance of reading the entire consent document as part of a shared consent process. The guidance should clearly convey this sentiment, for example, “*The key information section should not be regarded by trial sponsors, investigators, or IRBs as a replacement for the informed consent document, nor should it be explained to prospective subjects as such. Reading the entire consent form is an integral part of the consent process, which should involve dialogue between prospective subjects and trial investigators to ensure comprehension.*”

- Lines 136-137, 141-142: Addressing repeating information contained in the key information section in the consent form.

In general, we support the idea of repeating/restating, when applicable, the information from the key information section elsewhere in the ICF. Moreover, if the key information section is created de novo, using principles of health literacy, as a summary of what to expect in a given trial instead of copying and pasting elements of consent, repetition in the ICF will be necessary to provide sufficient detail about the trial and meet the regulatory requirements of consent (21 CFR 20.25(a) and (b)).

- Lines 143-144: *“We suggest using page numbers (or hyperlinks for electronic consent forms) to cross-reference information from the key information section to other sections of the consent form.”*

We agree with the suggestion to include cross references, although we acknowledge that it will introduce operational complexities for sponsors and investigators. In our research,ⁱⁱⁱ patients supported the idea of cross-referencing topics raised in both the key information section and the ICF. Cross-referencing could also facilitate the goal of brevity in the key information section, as sponsors could feel empowered to list high-level concepts/topics in the key information because greater detail is provided in the ICF.

- Lines 149-155: Describing the potential for the entire consent document to be the key information section (or vice versa).

Although LUNGEvity would applaud an informed consent document that was written so clearly and concisely that it could also be used as a key information section, we caution that the majority of ICFs for FDA-regulated clinical studies do not, and likely could not, reach this standard while still meeting all requirements laid out in 21 CFR 50.25(a) and (b). We hesitate at the inclusion of this paragraph in the guidance out of concern that it could lead to either overly long key information sections or ICFs with insufficient detail on required elements, neither of which would help with the stated goal of helping prospective subjects decide whether trial participation is right for them.

- Lines 169-212: Including the voluntary nature of research participation and the purpose of the research as key information.

LUNGEvity agrees with the importance of 1) clarifying that participation in the clinical trial is voluntary and can be withdrawn at any time without penalty, and 2) conveying the purpose and basic logistics of the research in the key information section. Patients and caregivers identified these concepts as important for deciding whether to participate in a clinical trial in our research.^{iii,iv} However, the language used to describe these concepts does not need to be complicated or exhaustive, indeed we advise against including too much detail in service of the goal of brevity. Conceptually de-coupling the key information section from the consent document, both in tone and purpose, may help preserve the patient centricity of the key information and keep it from being written and perceived as a legal document (in contrast to what is often the case for the ICF).

- Lines 200-202: *“It could be helpful to also include a discussion emphasizing the number of visits and time duration per visit so that prospective subjects understand the total time commitment involved with participating in the study.”*

We agree with the importance of honestly and accurately communicating the time commitment required for participating in a clinical trial. Indeed, we have heard from patients and clinical trial coordinators that creating a calendar showing the timing, intervals, and locations of study-related visits is incredibly helpful for prospective subjects. However, whether this should be included as key information is questionable because of the level of detail and space necessary. This information should certainly be disclosed as part

of the consent process; a trial-specific calendar could be included as an appendix to the ICF for patients to reference during and after the consent process.

- Lines 214-247: Including reasonably foreseeable risks in the key information section.

We agree with the FDA’s assertion that “*The discussion of risks and discomforts is generally among one of the most important...and we recommend that this topic be addressed in the key information section*” (lines 216-218). Although this information could be presented in many ways, our research indicates that patients are interested in knowing the most common risks but are divided on presentation format (e.g., written out, probabilities, icon graphs).^{iv}

- Lines 359-360: “*The language and formatting used are offered as suggestions only, and other language and formatting may be used where appropriate.*”

Used in reference to the example key information section provided in the draft guidance, LUNGevity recommends ending this sentence after “*suggestions only.*” As written, the second half of the sentence serves almost as a caveat, creating the impression that the example is FDA’s desired format, from which trial sponsors should deviate only with justification. In the spirit of flexibility—and to allow for incorporation of research establishing patient preferences on language and format—we recommend that FDA use language consistent with the idea that the provided example is just one of many possible and acceptable ways of presenting key information. FDA could also provide another example key information section using a different format, ideally one that has been developed with patient input.

- **Comments on the example key information section, lines 455-552.**

- Lines 460-465: top bubble, “*Key Information You Should Know Before Agreeing to Participate.*” LUNGevity takes issue with the content of this bubble. Although the text mentions making a decision about trial participation, the wording of the title and the fourth sentence intimate that participation/signing the consent form is a foregone conclusion. Moreover, as highlighted above, the third and fourth sentences de-emphasize the desired back-and-forth nature of the consent process and put the onus on the potential participant to ensure understanding.
- Lines 484-502: bottom left bubble, “*Key Reasonably Foreseeable Risks and Discomforts.*” Patients prefer seeing their actual risk, either as words (e.g., three in five, or sixty percent chance) or as numbers,^{iv} over vague descriptors like “*chance*” (line 487, 497) and “*rare*” (line 491). When discussing risks and discomforts, we suggest presenting data for a set number of risks, whether the most common or most severe side effects, then stating that more detailed information on these and additional side effects can be found on page xx of the consent form.
- Lines 511-534: top left bubble, “*Expected Duration and Procedures to Be Followed.*” We support the inclusion of non-technical language to describe clinical trial design concepts such as treatment arms and randomization. Patients have indicated they value having this knowledge before deciding whether to participate in a clinical trial.ⁱⁱⁱ We question the use of the phrase “*flipping a coin*” (line 523) to describe randomization, however, as it could be perceived as trivializing a very important decision and/or introduce a win-lose element to the research and the decision. The use of metaphors can help facilitate understanding; if one is to be used, we suggest that it not be a gambling metaphor. Alternatively, simply stating “*A computer will assign you randomly to one of x trial arms*” adequately conveys what will happen.
- Lines 538-550: bottom left bubble, “*Appropriate Alternative Procedures.*” If it is determined that prospective subjects value having a brief outline of alternative



procedures in the key information section, we caution against including the first bullet in the example (lines 541-542). This statement muddies rather than clarifies treatment options for subjects assigned to the control arm because it is specific to a particular trial design.

LUNGeVity appreciates the opportunity to provide comments on this important step towards harmonizing the FDA's human subjects protections regulations with those of other federal agencies. Please feel free to reach out to me at aferris@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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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 King-Kallimanis BL, Ferris A, Dropkin L, et al. Initial Steps in Creating a Patient-Centric Addendum to Clinical Trial Informed Consent Forms. 2023. *JTOCRR* 4(10): 100575. DOI: <https://doi.org/10.1016/j.jtoerr.2023.100575>.

^{iv} King-Kallimanis B, et al. OA10.04 A Systems Approach to Improving Clinical Trial Informed Consent Forms in Lung Cancer Clinical Trials. 2023. *JTO* 18(11): S66.

^v Morrow, Gary R. "How readable are subject consent forms?." *Jama* 244.1 (1980): 56-58.

^{vi} Jefford M and Moore R. Improvement of Informed Consent and the Quality of Consent Documents. 2008. *Lancet Oncol* 9: 485-493.

^{vii} Kim EJ and Kim SH. Simplification Improves Understanding of Informed Consent Information in Clinical Trials Regardless of Health Literacy Level. 2015. *Clin Trials* 12: 232-236.