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Elisa A. Hurley, PhD
Executive Director

September 16, 2019 Submitted electronically at www.regulations.gov

Norman E. Sharpless, MD
Acting FDA Commissioner
c/o Division of Dockets Management (HFA- 305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2019-D-3049, "E8(R1) General Considerations for Clinical Studies; International Council for Harmonisation; Draft Guidance for Industry" (84 *Federal Register* 37649)

Dear Acting Commissioner Sharpless:

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to comment on the International Council for Harmonisation's Draft Guidance for Industry, "E8(R1) General Considerations for Clinical Studies," published in the *Federal Register* on August 1, 2019.

PRIM&R is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community, including members and staff of human research protection programs and institutional review boards (IRBs), investigators, and their institutions. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise understand the central importance of ethics to the advancement of science.

PRIM&R welcomes the International Council for Harmonisation (ICH)'s plans to modernize E8(R1) General Considerations for Clinical Studies to better reflect the contemporary clinical trial landscape, and believes the proposed revisions represent an appropriate step in that direction. We especially appreciate the document's focus on patient engagement, particularly as it relates to input on study design, as well as the increased emphasis on transparency when it comes to study reporting, as detailed in section 6.3. We also agree that the protection of the rights, safety, and well-being of human research subjects is a critical element of good study design.

That said, we note that much of the language on protecting human subjects and related ethical issues is very vague. Beyond a passing mention of the Declaration of Helsinki and reference to other ICH documents in the section entitled “Protection of Clinical Study Subjects,” the guidance does not explain the relevance of core ethical principles for human subjects research, such as respect for persons or justice, including fairness in selection of subjects to provide equitable access to research and its potential benefits (e.g. access to a novel therapy post-trial). This is a troubling omission in a document intended to outline general considerations for a variety of stakeholders involved in the design and conduct of clinical studies. It also is surprising given the document’s explicit recognition that consideration of human subjects protections is an element of quality by design for clinical studies.

Stakeholders should understand the broad ethical principles that justify requirements such as selecting appropriate subject populations, seeking patient input, assessing the risk/benefit ratio, providing opportunities for informed consent, putting in place special safeguards for certain groups, and the like. The risk of not grounding these requirements in ethical principles for the appropriate treatment of human research subjects is that they will be seen as merely operational tasks. These imperatives rest on a recognition that people who volunteer to contribute to research do so on the expectation that research will not put them at undue risk, that it will be of benefit to society, and that they have been given the relevant information about what their participation will entail. As currently written, there is very little in the document to help stakeholders understand these foundational ethical concepts or think through their implications for designing a trial, even at the most general level.

We recognize that the ICH guidelines have been created organically, over time, and in response to emerging needs, and that they are meant to be consulted together in a holistic manner. We also recognize, as the document notes, that there is discussion of human subject protections and ethical issues in other ICH guidelines, such as E6, E7, E11, and E18. However, this structure creates challenges, as it requires stakeholders to consult multiple ICH documents to appreciate the full complement of ethical considerations involved in designing and conducting clinical research. For example, to get a complete picture of responsible and well-designed pediatric research, stakeholders must consult different parts of three of the ICH’s guidelines: E6, E8, and E11.

We suggest the ICH could address these issues by, first, creating an overarching “roadmap” to help investigators and sponsors navigate the guidelines and explain how and when they should be consulted and applied to research. Such a roadmap could make clear that E8 is the starting point, providing as it does the “general considerations” for clinical trials, and that stakeholders should first consult E8 as they work their way through the guidelines. It could then, either within the introduction to the E8 guidelines, or separately, make clear how and when to use the other guidelines in conjunction with E8. For instance, the ICH could recommend that stakeholders who are designing research with specific subject populations consult the relevant guidelines, such as E11 Clinical Trials in Pediatric Population or E7 Clinical Trials in Geriatric Population, and that when it comes time to

implement the study, they also consult E6 Good Clinical Practice Guideline, which includes procedures for how IRBs/IECs ought to be set up and function to operationalize the protection of human subjects.

To make this roadmap even more useful, certain sections within E8 (and other guidelines) could link to the specific provisions of other ICH guidelines that users should cross-reference on any particular topic. For example, at lines 405-406, E8 currently says: "Particular attention should be paid to the ethical considerations related to informed consent in vulnerable populations (ICH E6 and E11)." E8 should here direct the reader to the particular sections of E6 and E11 (as well as to other guidelines such as E18 Genomic Sampling) that deal with ethical issues, including informed consent, involved in research with vulnerable populations. Hyperlinking to the relevant sections would ensure that readers can easily access and refer to relevant ethical guidance offered in more detail elsewhere within the ICH guidelines.

Second, if E8 is specifically designated as the starting point for thinking about the design and conduct of clinical trials, which seems appropriate, it should include an expanded discussion of the ethical principles governing research with human subjects in its "General Principles" section, rather than simply referring to other ICH documents that might only be consulted later in the research process. It is not necessary to duplicate the Declaration of Helsinki, which is cited as the ICH's guiding ethical document. However, it would be helpful if the document provided additional discussion of the general ethical principles and concepts of human subjects research, including respect for persons, fair distribution of burdens and benefits, special protections for the vulnerable, risk-benefit evaluation, and the like, and explain why they are important. When research involves human subjects, the principles that establish ethical acceptability are just as fundamental as those that establish scientific validity. Then the document could refer back to those general principles within individual sections of E8 (and other guidelines, per the roadmap idea suggested above) where research practices with ethical underpinnings are mentioned—making it clear, for instance, that requirements such as informed consent and privacy protections are grounded in respect for persons, that provisions for data safety and the appropriate use of secondary data are tied to principles of respect for persons as well considerations of risk minimization, and the like.¹ We would be happy to consult with the ICH on what core ethical principles deserve greater attention within the aforementioned guidelines, should that be of interest.

We appreciate the opportunity to comment on this important process, as the ICH's guidelines influence the conduct of clinical research globally as well as the policies of national regulatory bodies. PRIM&R stands ready to provide any further assistance or input that might be useful. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

¹ For example, ethical considerations made at the following lines could be developed further: 102-104 (In "Quality by Design of Clinical Studies" section); 122-124 (In "Critical to Quality Factors" section); 405-406 (In "Considerations in Special Populations" section); 418-420 (In "Feasibility" section); 473-474 (In "Study Population" section); 497 (In "Control Group" section); 630-634 and 663-665 (In "Study Data" section); 749-751 (In "Considerations in Identifying Critical to Quality Factors" section).

Respectfully submitted,

A handwritten signature in black ink, reading "Elisa A. Hurley". The signature is written in a cursive style with a large initial 'E' and a long, sweeping underline.

Elisa A. Hurley, PhD
Executive Director

cc: PRIM&R Public Policy Committee, PRIM&R Board of Directors