PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

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Scott Gottlieb, MD
FDA Commissioner
c/o Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA–2018–N–2727, "Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations" (83 *Federal Register* 57378)

Dear Commissioner Gottlieb:

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s Proposed Rule, "Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations," published in the *Federal Register* November 15, 2018.

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.

As we have indicated in other comments, PRIM&R supports and welcomes efforts to harmonize the FDA human subject regulations with the Common Rule, in the interest of reducing burden on the research community associated with unnecessary and redundant reviews that do not contribute to human subject protections. Harmonization of the provisions regarding waiver or alteration of informed consent will reduce such burden, especially for research that is subject to both the Common Rule and the FDA rules, benefitting investigators, IRBs, and research subjects.

Furthermore, the inability at present to waive or alter informed consent for FDA-regulated research that meets the minimal risk criteria creates significant obstacles for some types of research, such as certain types of cluster randomized and pragmatic trials, and research that uses "big" health data—research that has the potential to contribute in important ways to the evidence base regarding drug and device efficacy. We thus welcome this move toward harmonization.

We do, however, seek clarity on why the FDA is choosing to only partially harmonize with the revised Common Rule in this area, and we urge the FDA to lead the way in providing further guidance on applying the waiver criteria. We elaborate on these two points below.

First, the FDA provides no explanation for why it is not planning to adopt the new fifth waiver criterion in the revised Common Rule, which says that the IRB may waive or alter informed consent if it finds and documents that, in addition to meeting the original four waiver criteria, "if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format." As we understand it, the intent of this additional criterion is to encourage researchers whose research might meet the other four waiver criteria to think carefully about whether use of identifiable information or specimens is necessary to their research, or whether they could feasibly, or reasonably, conduct the research instead using de-identified information or specimens.

Where there are no plans to harmonize, it would be helpful to understand the reasons why. We understand that the Cures Act requires the HHS to harmonize the two sets of rules to the extent possible, and so can only assume that the FDA has reasons for thinking that full harmonization with the Common Rule is not feasible or appropriate at this time. We request that the agency provide the community with further insight into their rationale for not adopting the fifth waiver criterion from the revised Common Rule.

Second, if, in the service of further harmonization, the FDA does plan to adopt the fifth criterion or otherwise allow waiver or alteration of consent for the use of identifiable data or specimens at some point in the future, we urge the agency to provide more justification than has been provided by the Common Rule agencies as to the kinds of research that would qualify. For example, it becomes more difficult for IRBs to confidently determine which research uses of identifiable biospecimens or identifiable private information are truly minimal risk, and therefore would be waiver eligible, as it becomes easier to link various sources of personal data, thus creating additional risks. What may represent innocuous identifiable data on its own may, when combined with other available data, quickly produce more sensitive information about a person. Guidance is needed regarding the relationship and interplay between this new waiver criterion and the minimal risk criterion, and on what kind of information IRBs should seek to make the determination that research, if carried out with identifiable private information or biospecimens, nevertheless qualifies as minimal risk.

Furthermore, this harmonization effort provides the federal agencies that conduct and oversee research with human subjects a new opportunity to provide guidance on the "practicably" criterion as it pertains to the criteria for waiving or altering informed consent. This term does a lot of work in the current regulations, yet is notoriously under-defined. We urge the FDA to lead the way in issuing guidance, beyond what is explained in the proposed rule document, on how IRBs should apply the "practicability" standard.

More specifically, current guidance fails to properly emphasize that waiver of consent decisions—and, in particular, "practicability" determinations—should be made in the context of understanding how valuable or important is the research in question. According to our accepted research ethics framework, there is an obligation to respect research subjects as persons, and the presumptive way we do that is by seeking their prospective informed consent. The default requirement to seek informed consent can be overridden if certain conditions are met, including that it would be "impracticable" to conduct the research if consent had to be sought. But there is wide variation in the way IRBs interpret this "practicability" standard. Some IRBs will say "impracticable" means impossible to do with consent, while others might accept investigator resistance to obtaining informed consent as meeting the "impracticability" threshold.

We believe that consideration of the *importance* of the research in question is crucial to properly making determinations of impracticability. "Impracticable" should be understood to mean that the burdens of getting consent are too high, given the benefit, or value, promised by the research. Consider, for instance, a study that aims to collect real world evidence about how a drug is performing to support a new indication. It may be difficult to get informed consent from all patients currently taking the drug; at the same time, the benefits to society (and perhaps also to the patients themselves), seem potentially substantial, if researchers can learn more about further uses of the drug. IRBs need guidance about how to make judgments of "practicability" against some standard of value. Such guidance would, in turn, promote uniformity in interpreting these regulations, which is sorely needed.

We urge the FDA to consult prior work in this area, including the Secretary of Health and Human Services' Advisory Committee on Human Research Protections (SACHRP) 2008 "Recommendations related to waiver of informed consent and interpretation of 'minimal risk." Specifically, SACHRP makes recommendations concerning how to determine "practicability" that emphasize what impact seeking informed consent would have on the ability to conduct the research. The committee makes clear that practicability should not be determined solely on the grounds of cost, speed, or convenience. For example, SACHRP suggests that determinations of practicability consider ethical concerns that would be raised if consent were required, such as creating additional risks related to privacy or risks of psychological or social harms. It also recommends considering whether scientific validity would be compromised by seeking consent. The FDA may wish to consult the examples SACHRP provides to augment its own examples around scientific bias and rigor.

In closing, we appreciate the FDA's making this important move toward harmonization, and hope that our comments will be valuable as the FDA both finalizes its rule in this area and considers further guidance. Thank you again for the opportunity to comment. My PRIM&R colleagues and I are available to discuss our comments further, should that be of interest. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

Respectfully submitted,

Elisa A. Hurley, PhD
Executive Director

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