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Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
1101 Wooton Parkway, Suite 200
Rockville, MD 20852

RE: Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care (79 FR 63629)

Dear Dr. Menikoff:

The Association of American Medical Colleges ("AAMC"), a not-for-profit association representing all 141 accredited U.S. medical schools, nearly 400 major teaching hospitals and health systems, and 90 academic and scientific societies, appreciates the opportunity to submit comments on the draft guidance issued on October 24, 2014 by the Office for Human Research Protections ("OHRP") entitled "*Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care*." Through the AAMC member institutions and organizations, the AAMC represents 128,000 faculty members, 83,000 medical students, 110,000 resident physicians, and thousands of graduate students and post-doctoral trainees.

The development of an evidence base for medicine that truly improves health and healthcare for all requires robust and often large-scale research studies, not just to study new treatments, but to evaluate current medical practices through comparative effectiveness research. As the field advances, there is an increasing need for clear guidance on the application of federal regulations to this research. Given recent events and the current research environment, it is critical that any guidance document provide clarity to research subjects, investigators, institutional review boards (IRBs), institutions, and regulators about what risks need to be disclosed to subjects, and in what context.

The AAMC recognizes the pressure on OHRP to develop this guidance and appreciates its efforts to encourage public discussion and comment. The document as drafted, however, does not provide the clarity and precision necessary for consistent and predictable application of the regulations, and we urge OHRP to clarify the scope, the context, and the respective obligations delineated in this document. We recommend that the draft be reframed and revised to create a guidance document that better ensures predictability by investigators, IRBs, and OHRP staff in proposing, reviewing, and conducting research that evaluates current medical practice. In these

comments we provide some overarching observations and some specific recommendations to improve the clarity and usefulness of the guidance.

The guidance must have clarity and precision to result in consistent application across studies and to avoid unintended effects on critical research. Although the draft guidance itself does not specifically prohibit or limit any particular type or design of research, the unintended consequences of this guidance may be far-reaching if it is not revised to provide sufficient clarity. This guidance is being released at a time when two competing discussions are at odds: the excitement over the potential for comparative effectiveness research to improve health and healthcare delivery and the anxiety created in the wake of the response to the Surfactant, Positive Pressure, and Oxygenation Trial (SUPPORT). That backdrop forms an ever-present filter through which this draft document must be read, reinforced by public comments from OHRP officials on this guidance and even the supplementary information in the Federal Register description of the guidance and the draft document itself, all of which contain multiple references to SUPPORT. The ensuing highly-charged public discussions have ensured that any ambiguities in the language of the final guidance will be interpreted by investigators, institutions, and IRBs within the context of this environment of uncertainty, potentially leading to results that are neither required by regulation nor meaningfully protective to research subjects. The public discussions of and written reactions to this draft document since it was issued reflect disagreements in interpretations of the draft's meaning and implications, indicating that the draft as written will not be easily and consistently applied.

The guidance should not be limited to the disclosing of risks, but should discuss the information a prospective subject needs to have about research on standards of care. The choice OHRP made to draft guidance that focuses solely on risks, without discussion of the broader context in which risks of research should be presented to potential research subjects, limits the utility of the guidance while appearing to elevate the disclosure of risks above other relevant information. Individuals who are deciding whether to participate in a research study need to understand more than just the risks. The discussions about research should also include the research question being asked, any potential benefits, how the research will be conducted, and the likely next steps should an individual not participate in the research. Without additional clarity and a balanced discussion of how risks fit into the context of meaningful understanding about participation in research, there will be IRBs or investigators who determine that in order to meet the standards set forth in this draft guidance the risks section of informed consent documents should be simply expanded to include, for example, all side effects of any drug in either arm of a study. We recommend that OHRP consider broadening the scope of the guidance to address the information that should be communicated to prospective subjects, not the risks in a subset of studies evaluating standard of care interventions.

The guidance should clarify that not all important outcome measures are "purposes" of a study. The draft guidance does not provide an IRB or investigator with sufficient instruction on how to distinguish the *purpose* of the research from important outcome measures in the context

of this guidance. For example, most research on patients with heart disease will include a cardiac event or death as a primary endpoint, whether or not evaluating these morbidity and mortality measures are the purpose of the study. Further, in narrowing the guidance to apply only to those studies where a purpose of the research is to assess risks, this leaves unanswered questions as to how risks of research should be defined, discussed, or disclosed to subjects when the research has a different primary or sole purpose, such as comparing effectiveness or likelihood of compliance with a treatment regimen.

If the purpose of a study is to assess the comparative effectiveness of two treatments that are medically recognized standards of care, one may prove to be more effective than the other in medical practice despite similar demonstrated efficacy in clinical trials. Those patients who receive the treatment later determined to be more effective may see slower progression of their disease. Although the draft guidance states that "the risks of research do not include the risks that are created by the medical condition for which the person is being treated," an open question in this draft guidance is when, if ever, the difference in rate of underlying disease progression would ever be a "reasonably foreseeable risk" of the research itself. Without any treatment disease progression is often inevitable, but the guidance does not clarify how that calculation changes when there is an approved or medically recognized treatment for the disease.

The draft would benefit from additional language clearly distinguishing between *risk* and *harm*. As discussed briefly in the document under Question 2, a risk is the likelihood that a harm will occur, not a harm itself. This distinction is important as IRBs try to determine how the purpose of a study should inform the disclosure of reasonably foreseeable risks, but is not carried through the document. In sections of the draft guidance, such as the following paragraph, the terms risk and harm seem to be used interchangeably:

> The evaluation of a risk is considered a purpose of the research when a research study is designed and conducted in order to ascertain the existence, extent or nature of a particular harm. If a study is designed to discover the degree to which that particular harm will or will not occur, the possibility of that harm occurring is clearly foreseen by those responsible for the design and conduct of the study. The risks should accordingly be disclosed to the people who are being asked to be exposed to that risk as subjects in the study.

Additional examples of how to apply the guidance would be helpful. The two examples provided in the document, a medical versus surgical intervention and studying radiation levels in childhood cancer, represent ones in which the differences in risk of the two arms may be readily surmised and discussed with patients or research subjects. In many comparative effectiveness research studies, the difference between the risks of each medically recognized standard of care may be far less stark. The examples also do not help to explain how to assess *when* a risk is "known," but rather assert that "it is known."

Randomization alone is not a risk of research. We recommend that the sentence: "Indeed, in the common study design where subjects are randomized equally between two treatments,

approximately half of the subjects will be assigned to a treatment different from what they would have otherwise received" be deleted from the document as potentially misleading. This statement is only accurate if the rate of the current use of two standards of care is known to be approximately equal. Additionally, this section strongly suggests that the act of randomization automatically increases the risk of harm to a research subject. While randomization may *change* the risks that a subject encounters, that does not mean that risk is always increased. We should not ignore the risks that come from assigning a patient to a medical treatment without a robust evidence base for care. Proposed important comparative effectiveness research studies start with the understanding that there is an insufficient underpinning of evidence to support certain treatment decisions across a population. The best medical judgment should have the benefit of evidence to inform a healthcare provider's choices.

Investigators, institutions, and IRBs need to know what processes are sufficient to make and document the determinations set forth in the draft guidance. Unlike the federal regulations on the protection of human subjects, which delineate specific responsibilities to IRBs and to investigators, the guidance suggests a number of additional determinations that must be made in the context of standard of care research without providing guidance as to where the responsibility lies for making these determinations. For example, who should have responsibility for deciding whether a risk associated with a standard of care treatment is a risk or research, or whether evaluating certain risks is "sufficiently important to justify the conduct of the study" and thus a study's purpose? The guidance should include sufficient information to give an IRB or an investigator confidence in the level of diligence and documentation that would be adequate, to avoid the concern that reasonable judgments and decisions might be second-guessed months or years after the research is completed.

If the final guidance document is ambiguous in how to apply these standards or silent on how to demonstrate appropriate deliberation or diligence, anxiety from not understanding the implications or potential enforcement actions could cause IRBs, investigators, and institutions to decide that the safest approach is to steer clear of comparative effectiveness research altogether. A decision that research on current medical practices or comparative effectiveness research is riskier than continuing to provide care without a robust evidence base for certain treatment decisions could jeopardize the health of patients and deprive caregivers of critical information to improve medical decision-making. We believe that this is a real concern, and not the result that OHRP is trying to achieve. It is only by fully engaging patients, communities, researchers, and regulators that we can continue to improve health and healthcare delivery, address disparities, and promote health equity. Ensuring that this guidance engenders confidence in the ability to conduct important and ethical research on current medical practices is a step in demonstrating a national commitment to that endeavor.

The AAMC's mission is to improve the health of all and we are appreciative of OHRP's commitment to engaging affected stakeholders to assist it in improving this draft document so that it provides clear, unambiguous guidance. We would be happy to provide any further

assistance in this process. Please feel free to contact me or Heather Pierce, Senior Director for Science Policy and Regulatory Counsel at hpierce@aamc.org or (202) 478-9926 with any questions.

Sincerely,

Ann C. Bonham, Ph.D.
Chief Scientific Officer