American Association for Cancer Research

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Chief Executive Officer

September 9, 2013

Jerry Menikoff, M.D.
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Re: "Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions" (Docket No: HHS-OPHS-2013-0004)

Dear Dr. Menikoff,

On behalf of the American Association for Cancer Research (AACR), we would like to thank the Office for Human Research Protections (OHRP) for the opportunity to provide input on the "Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions." The AACR commends OHRP for soliciting broad input regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to participants in the informed consent process.

The goal of federal human subjects protections regulations must ultimately be to safeguard the rights and welfare of research participants and to do so in a consistent manner that recognizes and, to the extent possible, minimizes their impact on life-saving biomedical research. Institutional Review Boards (IRBs) must have clear, consistent regulatory guidance that enables them to assess the real versus perceived risks of research and communicate their recommendations of the risks and benefits accurately to patients. This is essential even for studies that involve minimal or no risk to patients.

The AACR strongly supports developing evidence-based human subjects protections regulations and harmonizing those regulations across federal agencies, and we encourage the Department of Health and Human Services to lead this effort, which will serve to clarify and improve the regulatory framework for human subjects research. Clarity is especially critical following OHRP's determination that certain risks related to the interventions being studied in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) were not disclosed to trial participants. In the absence of additional guidance from OHRP, the SUPPORT controversy could lead IRBs to adopt unnecessarily conservative recommendations when evaluating risk in studies of standard of care interventions. This would undoubtedly have a chilling effect on human subjects research. As the agency develops new guidance following this important matter, we recommend that OHRP give careful consideration to the following suggestions.

Research on standard of care interventions is essential
Although federal human subjects protections regulations have historically treated research and clinical practice as distinct activities, the separation between the two has become increasingly blurred. Indeed, there has been a deliberate and growing emphasis on creating "learning health care systems" that reduce the separation between research and clinical care by utilizing the vast amount of data available in clinical settings to evaluate and improve patient care on a continual basis.

Moreover, research aimed at evaluating standard of care interventions, including comparative effectiveness research and quality improvement activities, is integral to the scientific enterprise. This work is increasingly important for developing evidence-based medical practices and ensuring that patients receive state-of-the-art care for diseases such as cancer. In fact, these studies are key to cancer research insofar as many cancer clinical trials are designed to assess the effectiveness of a new intervention or the new use of an existing intervention against the current standard of care. Our regulatory system must evolve to enable the ethical conduct of research in the context of the delivery of standard medical care and to the extent possible clarify the relationship between the two.

OHRP should develop guidance to help IRBs evaluate real versus perceived risk
The AACR strongly supports the development of guidance to help IRBs assess reasonably foreseeable risks in research involving standard of care interventions. Insofar as standard practice varies from institution to institution, it will be important for this guidance to define what constitutes a standard of care intervention. In this context, the guidance should also address the level of evidence needed to determine whether or not a risk is reasonably foreseeable. For example, should a risk be considered reasonably foreseeable only if there are robust empirical data demonstrating the risk, or are published case reports that are statistically robust sufficient?

Future guidance should make clear that participation in research is not inherently more (or less) risky than receiving standard of care treatment or foregoing treatment altogether, and it should emphasize that there are consequences of both overstating and understating risk. In addition, the guidance should not consider the risks associated with standard of care interventions—whether known or unknown—to be risks associated with participating in the research itself. Standard of care cancer treatment, for example, often presents significant risks to patients, yet patients elect to receive such treatments because it is their only real hope.

In cases in which there is insufficient rationale to assign participants to one treatment over the other, randomization to a particular treatment should not automatically be considered a risk to participants. However, we note that a physician's decision to provide a specific course of treatment to his or her patients is based on myriad factors including, but not limited to, those unique to the patient. In some cases, randomization to one of multiple standard of care treatments—even treatments without known risks—may result in the patient receiving care that would not have been recommended by his or her physician. We urge OHRP to provide guidance on the circumstances in which randomizing research participants to receive one or another standard of care interventions may presents risks to

these patients. OHRP should also encourage IRBs to recruit additional experts who could help to inform the evaluation of the risks and benefits associated with specific standard of care interventions if such individuals are not already represented on the IRB.

OHRP should develop guidance on communicating risk

Transparency in reporting risk to potential research participants is a critical step in the conduct of human subjects research. Therefore, OHRP should provide clear guidance on how IRBs should communicate risk. Consent forms should distinguish between the risks associated with the research and risks associated with standard of care interventions, and they should also convey how likely and how severe a particular risk could be to the degree that it is known. This information is critical if patients are to make informed decisions regarding whether or not to participate in a particular study.

The AACR strongly supports efforts to harmonize, clarify, simplify, and shorten consent forms. Complexity in consent forms has increased, especially in certain types of research involving patient genomic information, and this is already making it more difficult for potential study participants to understand the risks and benefits associated with the research. In developing additional guidance with regard to communicating risk, therefore, we urge OHRP to discourage researchers from creating lengthier and more complicated consent forms. This must be addressed as it will surely compromise the ability of potential study participants to make informed decisions.

OHRP should develop policies to protect IRB members

Developing thoughtful, evidence-based guidance on assessing and communicating risk in research studying standard of care interventions will undoubtedly help to safeguard the rights and welfare of study participants. No guidance, however, can account for every possible study scenario, and IRB members will always have to rely on their best judgment in making decisions with regard to how the risks and benefits of a study should be communicated to potential participants. The AACR recommends that OHRP consider developing a policy to ensure that IRB members are not personally held liable for decisions of the IRB on which they serve insofar as they execute their duties consistent with a good faith interpretation of the applicable regulations. Without such protection, it is likely that IRBs will be forced to choose the most conservative interpretation of potential risks.

On behalf of the AACR's 34,000 members, we thank you for taking our comments into consideration. If you have any questions or require follow up, please contact Jennifer A. Hobin, Ph.D., Director of Science Policy, at 202-898-6499 or Jennifer.hobin@aacr.org.

Sincerely,

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