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Via Electronic Submission to: <http://www.regulations.gov>

RE: Docket ID Number HHS-OPHS-2011-0005

Dear Dr. Menikoff:

The American Society of Hematology (ASH) appreciates this opportunity to comment on the Advance Notice of Proposed Rulemaking on Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators (Docket ID Number HHS-OPHS-2011-0005).

ASH represents over 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases. These diseases encompass malignant hematologic disorders such as leukemia, lymphoma, and myeloma; non-malignant conditions including anemia and hemophilia; and congenital disorders such as sickle cell anemia and thalassemia. In addition, hematologists have been pioneers in the fields of stem cell biology, regenerative medicine, bone marrow transplantation, transfusion medicine, gene therapy, and development of many drugs for the prevention and treatment of heart attacks and strokes.

Clinical research in hematology has never been more important and the opportunities never greater. Protection of individual human subjects must be a top priority. At the same time, thorough evaluation of the bioethical issues of clinical research should also address unnecessary and burdensome policies and regulations that slow clinical research without enhancing protection of individual subjects.

The Society would like to offer comments on a number of the proposed revisions to the federal regulations governing the protection of human subjects in research that will impact hematology clinical research. ASH's comments focus on the following issues:

- Streamlining IRB Review of Multi-Site Studies
- Improving Informed Consent
- Data Collection to Enhance System Oversight
- Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

Streamlining IRB Review of Multi-Site Studies

As the Department of Health and Human Services (HHS) notes in its proposed revisions, a substantial amount of research, particularly that involving clinical trials, takes place by means of multi-site studies wherein a single research study is conducted at numerous institutions. Although, as HHS notes, current regulations do not require that a separate local Institutional Review Boards (IRBs) at each institution review and approve the study, most of these regulations governing clinical research were developed at a time when the vast majority of clinical research studies were taking place at single institutions. The choice to have multi-site research reviewed by a central IRB is completely voluntary and, in practice most institutions have been reluctant to replace review by their local IRBs with review by a central IRB.

As such, it is common practice for local IRBs at each institution in a multi-site trial to independently review the research protocol, informed consent documents, and other materials, sometimes resulting in literally hundreds of reviews for a single study. Further, if any of these reviewing IRBs requires changes to the research protocol that are adopted for the entire study, investigators must resubmit the revised protocol to all of the reviewing IRBs. This process can take many months, or even years, and can significantly delay the initiation of clinical studies and, ultimately, the translation of biomedical research discoveries into therapies and treatment for patients with debilitating or life-threatening diseases.

The future of hematology in particular requires that research in diverse areas of basic and clinical science be integrated and translated into novel, decisive therapies that will effectively prevent and treat serious diseases. An integrated central or national IRB for multi-site trials will lift the regulatory burden, ease the administrative burden, and increase the harmonization of multi-institutional trials, thus increasing access to promising treatments for patients. The centralized rules will increase collaboration between multiple investigators around common themes to support novel clinical trials. ASH supports the establishment of a central or national IRB for multi-site trials that will ultimately accelerate the translation of biomedical research discoveries into approved diagnostics and therapies. Furthermore, ASH supports a model in which COI is minimized to the greatest extent, as in the Central IRB model used by the National Cancer Institute (NCI).

Improving Informed Consent

Current federal regulations require researchers to obtain and document informed consent from patients participating in clinical trials. Rigorous patient protection must be maintained. However, many of these regulations were developed in an era when multicenter studies were uncommon and communication and information technology were very different from what they are today.

Original informed consent forms were clear, concise, short, and in marked contrast to informed consent documents in current use. The forms have become so long and complex that they are no longer effective as documents that truly inform patients about the potential risks and benefits of

participating in research. This creates a burden for both the patient who needs to read and understand the form and the physician who needs to spend extra time explaining the forms to the patient. This, in turn, can deter both patients and physicians from engaging in clinical research.

Complex consent forms and language designed to protect institutions from liability increasingly obscure understandable informed consent for potential subjects. Clear guidelines need to be established that encourage IRBs to review informed consent documents with an eye towards truly informing subjects. Protection of institutions from liability should be considered a separate process. Clearer, shorter, simpler informed consent documents would be easier for clinical investigators to present to patients, easier for those patients to understand, and would do a better job of protecting the rights of the patients. They would also result in enhanced accrual to clinical trials. ASH supports HHS's proposed revisions to existing regulations that would clarify that patient consent forms for all clinical trials must be shortened or include an abbreviated and simplified summary to enhance the provision of informed consent.

Data Collection to Enhance System Oversight

ASH supports efforts to establish an improved, more systematic approach for collection and analysis of adverse event data, including the establishment of a central database for the reporting of adverse events. As HHS notes, the changes proposed in this area are "intended to simplify and consolidate the reporting of information that is *already required* to be promptly reported by an investigator, and *not* to expand the information to be reported." Further, the Society agrees that these proposed changes will help to eliminate much of the existing multiplicity of different and confusing reporting mechanisms and will help to foster greater uniformity and comparability of the safety information that gets reported. Ultimately, the Society believes this increased and consistent communication will lead to increased safety and efficacy of reporting.

Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

The federal government, through the Office of Protection from Research Risks (OPRR), within the National Institutes of Health (NIH) and HHS, has promulgated regulations and policies that govern the protections for human subjects who participate in federally-funded research. The federal government also propagates regulations governing human subject protections through the Food and Drug Administration (FDA). Investigators must comply with these complex regulations that not only lack harmonization between different agencies but, in fact, sometimes appear to be inconsistent with each other and with reimbursement policies established by the Centers for Medicare and Medicaid Services (CMS).

ASH recognizes the importance of providing strict policies and regulations that govern protections for human subjects who participate in federally-funded clinical trials. At the same time, agencies that fund or provide oversight of clinical trials have instituted different regulations that are often inconsistent and unnecessarily burdensome, especially for multi-institutional trials. This has inhibited the initiation of new trials and access to promising treatments for patients. ASH supports HHS's efforts to harmonize existing policies and regulations on clinical trial operations among its various agencies.

The American Society of Hematology will be happy to provide further information and be a resource for the Commission and HHS. Please contact ASH Research Advocacy Manager Tracy Roades at 202-776-0544 or troades@hematology.org if you have any questions or require any additional information.

Sincerely yours,

A handwritten signature in black ink, appearing to read "J. Evan Sadler". The signature is fluid and cursive, with a large initial "J" and a long, sweeping underline.

J. Evan Sadler, MD, PhD
President