THE ENDOCRINE SOCIETY

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October 25, 2011

Jerry Menikoff, MD, JD
Director, OHRP
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: FR Doc No. 2011-18792 Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators

Dear Dr. Menikoff:

The Endocrine Society thanks you for the opportunity to comment on the content of the Advanced Notice of Proposed Rule Making (ANPRM), entitled *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators*. The Endocrine Society is in favor of the Administration's efforts to reduce regulatory burden while maintaining high standards of patient safety. We are pleased to have the opportunity to provide comments on the proposed changes.

Founded in 1916, The Endocrine Society is the world's oldest, largest and most active organization devoted to research on hormones and the clinical practice of endocrinology. Today, The Endocrine Society's membership consists of more than 14,000 scientists, physicians, educators, nurses and students in more than 100 countries. Society members represent all basic, applied and clinical interests in endocrinology.

Clinical research involving human participants is critical for the development of safer and more effective treatments for a large spectrum of diseases, including many endocrine disorders for which specialized treatments have yet to be established. Nonetheless, clinical research activities are in danger of decline in the US as investigators face numerous obstacles and challenges in navigating the regulatory process. The Endocrine Society views patient safety as a top priority in both the implementation of clinical studies and in the practice of patient care and strongly supports regulations that protect human research participants while not hindering the progress of clinical research.

The Endocrine Society applauds the Department of Health and Human Services and Office of Science and Technology Policy in their efforts to revise the Common Rule and

its effectiveness. The paragraphs below address several of the broad concepts proposed in the ANPRM, with subsequent responses to specific questions posed in the document.

Streamlining IRB Review of Multi-Site Studies

The Society highly recommends the centralization of Institutional Review Board (IRB) review to increase efficiency and consistency. The frequency of multi-site trials and the need for those studies to undergo IRB review at each site may lead to significant delays in research progress and, in some cases, numerous minor study revisions to accommodate specific IRBs. In a recently released position statement (see attached), the Society supports the utilization of centralized IRBs for studies involving multiple institutions. The position statement is in line with the changes proposed in the ANPRM. It is critical that the proposed regulations address liability concerns that may result in institutional reluctance to relinquish local control of the review process. Once in place, the use of a central IRB would significantly decrease the burden of repetitive application processes and reviews, and would streamline research efforts spanning multiple institutions.

Moving Away from the Concept of Exempt

The Society agrees with the proposal to redefine the concept of exempt by clarifying that studies may be excused only from IRB review but not from all regulations. We support the goal of eliminating the current practice of preventing researchers from conducting minimal risk studies until a reviewer has determined that the study meets the criteria for being exempt. However, it is not completely clear how the new excused category would be implemented.

While a large portion of the ANPRM is devoted to explaining the proposed new category and how it relates to the current exempt category, the sheer volume of information presented makes it difficult to assimilate. Additional clarification or expansion of the table on page 73 may help to improve the presentation of the information, allowing us to more fully comprehend the proposed changes. Due to our current uncertainties, we abstain from addressing any of the specific questions 14-29, though the topic is of utmost interest to us.

Improving Informed Consent

Regulatory agencies should accumulate data on which to base changes to consent forms and other documents. Consent forms serve a vital role in communicating information between researchers and participants, however, debates between IRBs and investigators regarding the content of consent forms often lead to significant setbacks and added frustration. To decrease delays related to review and approval of consent form content, relevant sections of consent forms should be standardized and changed only when there is evidence to support the change.

Strengthening Consent Protections Related to Reuse or Additional Analysis of Existing Data and Biospecimens

The Society supports the efforts to outline a uniform standardized policy on the handling of biospecimens. Such a policy should include clear guidance on the collection and use of samples, and should state a clear position on de-identification and data sharing. Such

guidelines would serve to prevent inconsistency among institutions and would provide investigators the means by which to appropriately plan for studies. The Society would favor a policy that would allow flexibility in the design of future research studies, as it is often difficult to foresee new questions that inevitably arise from ongoing investigations and the use of biospecimens acquired through those studies.

Responses to Specific Questions

Question 1: Is the current definition of "minimal risk" in the regulations (45 CFR 46.102(i) -- research activities where "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests") -- appropriate? If not, how should it be changed?

The current definition of minimal risk, as stated above, should be clarified by the inclusion of guidance on the contextual basis for risk. For example, acceptable risk may vary depending on the diagnosis a patient carries, the patient's age, and the general risks encountered by the individual patient in his or her daily life.

The implementation and enforcement of regulations relating to pediatric populations is open to interpretation by researchers and IRB members and often leads to significant delays in research approval. Specific guidance for research involving children should be established, including examples of and guidance on minimal risk in children and adolescents.

Question 3: For research that poses greater than minimal risk, should annual continuing review be required if the remaining study activities only include those that could have been approved under expedited review or would fall under the revised exempt (Excused) category described in section 3, below (e.g., a study in which a physical intervention occurred in the first year, all subjects have completed that intervention, and only annual written surveys are completed for the next five years)?

Ongoing review should be required for all studies posing greater than minimal risk, but the level and frequency of review should correspond to the remaining study activities. For instance, studies in which subjects are no longer participating and clinical data are no longer being collected may require a different (lesser) level of ongoing review than those in the period of active data collection. These studies should be tracked consistently but should not be required to undergo time-intensive full review that would include irrelevant issues such as consent forms. Continuing review should be streamlined and the intervals between reviews extended so as to expedite review and decrease oversight burden. Consistent guidelines should be established outlining the level of review required based on study activities.

<u>Question 4</u>: Should the regulations be changed to indicate that IRBs should only consider "reasonably foreseeable risks or discomforts"?

To ensure reasonable patient protection and establish consistency across IRBs, the regulations should be changed to indicate that IRBs consider "reasonably foreseeable risks or discomforts" and the classification of those risks should be evidence-based. Consideration of risk should balance the likelihood of an outcome with its severity. Presently, there is variability in the approach that IRBs take to patient protection. At times, IRBs may contemplate patient risks that are highly remote, delaying approval or even not approving studies for such issues. Guidelines should be provided to define reasonably foreseeable risks, including examples to illustrate the intent of this statement.

<u>Question 6</u>: Are there survey instruments or specific types of questions that should be classified as greater than minimal risk? How should the characteristics of the study population (e.g. mental health patients) be taken into consideration in the risk assessment?

Evaluation of survey instruments by IRBs is not consistent, including interpretation of the concept of minimal risk. For example, in a survey of IRB chairpersons, forty-four percent classified a confidential survey of sexual activity as minimal risk, 29% as a minor increase over minimal risk and 19% more than a minor increase over minimal risk [1]. Thus, guidance should be issued regarding the appropriate review of survey questions that may present greater than minimal risk.

The Society believes that the majority of survey instruments and questionnaires should not be classified as greater than minimal risk, and therefore may require a limited level of IRB review. However, survey questions regarding physical or sexual abuse, drug abuse, and suicidal tendencies in particular are of concern and should be evaluated by IRBs. Survey questions that could stimulate an undesirable action or cause significant distress to participants should be reviewed to ensure that follow-up care or observation would be available as clinically needed. Guidance as to how to assess questions for these and other potential risks would help IRBs make reasonable and consistent judgments.

[1] How do institutional review boards apply the federal risk and benefit standards for pediatric research? Shah et al., JAMA 2004; 291: 476–82.

<u>Question 11:</u> What are the advantages of requiring that expedited review be conducted by an IRB member? Would it be appropriate to instead allow such review to be done by an appropriately trained individual, such as the manager of the IRB office, who need not be a member of the IRB? If not, what are the disadvantages of relying on a non-IRB member to conduct expedited review? If so, what would qualify as being "appropriately trained"? Would the effort to make

sure that such persons are appropriately trained outweigh the benefits from making this change?

The Society feels that the chair of an IRB should be ultimately responsible for the reviews overseen by his or her board. However, a chair could delegate the review to an IRB member who is appropriately trained to carry out expedited review. It is important that an IRB member, or former IRB member, be designated to carry out expedited review and have adequate experience serving on an IRB. Current or previous service on an IRB could constitute appropriate training, provided the services were extensive enough to afford a depth of understanding of the responsibilities. In an effort to further standardize the review process, a universal checklist should be developed to encompass the issues that warrant consideration in the expedited review.

<u>Question 12</u>: Are there other specific changes that could be made to reduce the burden imposed on researchers and their staffs in terms of meeting the requirements to submit documents to an IRB, without decreasing protections to subjects? Are there specific elements that can be appropriately eliminated from protocols or consent forms? Which other documents that are currently required to be submitted to IRBs can be shortened or perhaps appropriately eliminated? Conversely, are there specific additions to protocols or consent forms beyond those identified in this notice that would meaningfully add to the protection of subjects? What entity or organization should develop and disseminate such standardized document formats?

Several specific changes could be made to reduce the burden imposed on researchers and their staffs to meet the requirements of document submission to IRBs, including:

- Electronic IRB submission systems should be supported to improve efficiency.
- Continuing review expiration dates should be constant rather than being set by the date of previous IRB review, thus avoiding multiple, shifting deadlines for investigators.
- Information requested by different regulatory agencies should be harmonized such that duplicative administrative reporting and paperwork can be minimized.
- The template legal language in consent forms should be separated from the elements of consent relevant to the particular study in question.
- Information required for IRB submission should not be duplicated in separate documents. For example, detailed protocols and protocol summaries often contain redundant information.

Finally, although not discussed in the ANPRM, an issue of concern to the Society is that some IRBs focus on scientific design of studies, resulting in delays and debates unrelated to patient protection. While some consideration of the scientific design as it relates to patient safety is appropriate, there is inconsistency among IRBs as to the degree of scientific review and the relevance of the review to human subjects' protections. The level of scientific review required is dependent upon the study under consideration. For

example, studies funded by the National Institutes of Health have already undergone extensive scientific review, and the local IRB should need only to consider the study in the context of patient safety and not of scientific validity. Other studies that may not have undergone previous rigorous review may require a more detailed examination of the science by the IRB. To clarify these complex issues, it would be useful for HHS to issue IRBs some guidance as to the extent of scientific review to be undertaken.

The Endocrine Society appreciates the opportunity to weigh in on the critical process of modernizing patient protections and research regulations. We look forward to the next iteration of the proposed changes. If the Society can be of any further assistance in the development of new regulations, please contact Janet Kreizman, Deputy Executive Director and Chief Policy Officer, at jkreizman@endo-society.org.

Sincerely,

Janet E. Hall, MD
President, The Endocrine Society

THE ENDOCRINE SOCIETY®

POSITION STATEMENT

CENTRAL INSTITUTIONAL REVIEW BOARDS
June 2011

INTRODUCTION

Clinical research involving human participants is critical for the development of patient treatments for a large spectrum of diseases, including many endocrine disorders for which specialized treatments have yet to be elucidated. To conduct research with human participants, clinical investigators must apply for approval by Institutional Review Boards (IRBs). When a study utilizes facilities spanning multiple institutions, each institution's individual IRB typically reviews and approves the research proposal, unless a central IRB (CIRB) is employed. When multiple, local IRBs are used, the inherent variability in the requirements and review processes among institutions frequently results in a large increase in application processing time and delays in protocol approval, hindering the overall progress of the study. In addition, individual IRBs may request different and sometimes conflicting changes to study design, necessitating re-review by other IRBs.

There is evidence that multiple independent reviews do not promote superior participant safety or higher ethical standards for clinical research[1]. In an effort to streamline the IRB approval process for endocrine-related studies and others, improve consistency, and assure accountability, the use of central IRBs has been suggested for multicenter clinical research studies.

BACKGROUND

IRB approval is required of all clinical studies involving human participants. IRB review is meant to evaluate the ethical implications of the proposed research and to promote the welfare of all study participants. A significant portion of IRB guidelines involves oversight of the process of informed consent of prospective research study participants and emphasizes full disclosure of information to the potential participant. In addition, the safety and efficacy of test agents and the scientific merit of the project are considered.

The need for IRBs was highlighted by several high profile instances of flagrant human rights abuses in the mid-1900s. Among them was the Tuskegee Syphilis Study, conducted in Tuskegee, Alabama, involving the collection and study of blood samples obtained from economically or educationally deprived African-American men who were never informed that they had syphilis and were never offered treatment. Such infamous cases led to the development of the National Research Act of 1974, and in the US, IRBs are now governed by Title 45 of the Code of Federal Regulations (http://ohsr.od.nih.gov/guidelines/45cfr46.html) with the intention of protecting the rights of study participants and providing full disclosure of medical information related to participation in the study.

Individual institutions are responsible for maintaining IRBs that uphold national, state, and local laws along with institutional policies regarding the safety of human research subjects. Recently, commercial, for-profit central IRBs (CIRBs), independent of specific institutions, have gained traction in an effort to provide appropriate protection for study participants with increased efficiency and consistency across institutions. CIRBs typically conduct both the initial and continuing review of applications and in some cases, CIRBs work in conjunction with individual local IRBs to ensure conformity with local requirements. In other cases, the local IRB cedes authority to the CIRB by written agreement.

CONSIDERATIONS

The IRB review process, which was initially set up to protect research participants, has in some cases become increasingly sidetracked by local bias, conflict of interest[2], and increasing institutional demands that distract them from their primary purpose. Instances of non-compliance on the part of individual investigators, along with some high-profile episodes of IRB ineffectiveness[3,4] have led to institutional concern about liability and decreased focus on the basic elements of IRB review. Many institutions have reacted to these concerns with a proliferation of paperwork required of the IRB to document compliance.

The number of IRB approvals necessary to proceed with a multi-site study that utilizes each site's IRB may

involve waiting periods of a year or more as each institution reviews the application and has a separate dialogue with each site's principal investigator. This process delays the progress of the study, discourages the investigator(s) involved, and is highly cost-ineffective[1]. Furthermore, while it is not the purpose of IRBs to review the scientific approach of the proposed research per se, it is not uncommon for IRBs to undertake some level of scientific review[5], thereby further delaying the time to approval. Most studies evaluated by IRBs have been previously peer-reviewed and deemed to be sound. Though it is appropriate and ethical for an IRB to object to poorly conceived scientific premises, it is unnecessarily cumbersome and duplicative for an IRB to engage in extensive review of the minutiae of a protocol, especially if the proposal has already undergone rigorous peer review. Moreover, different IRBs at different institutions may approve or disapprove portions of the same research project according to their own internal guidelines, completely halting progress and/or introducing inconsistencies into protocol implementation that reduce the scientific value of the study and unwittingly create flaws in the study design.

A central IRB is able to incorporate the major concerns that institutions have about liability risk and conflict-of-interest and may better facilitate the progress of multicenter clinical research studies. Several successful CIRBs are already in place, including CIRBs facilitated by the Veterans Administration, National Cancer Institute, and independent committees such as the Western, Independent, and Sterling IRBs.

The emerging emphasis on interdisciplinary and team research, as evidenced by the nationwide establishment of Clinical and Translational Research Service Awards, promotes multi-institutional collaboration, yet the establishment of efficient and effective collaborative research can only be realized with IRB consensus. Interdisciplinary research is critical to elucidate the mechanisms of a wide spectrum of endocrine disorders and diseases and to identify effective treatments for them. Increased acceptance, accessibility and use of central IRBs could facilitate progress in clinical studies without reducing patient protection.

POSITIONS

The Endocrine Society views patient safety as a top priority in both the implementation of clinical studies and in the practice of patient care. The Society strongly encourages the utilization of CIRBs for multicenter clinical studies in order to advance clinical research and improve patient care while maintaining the highest patient safety standards. Steps must be taken by institutions, investigators and funding agencies to promote the use of CIRBs and to more readily facilitate their use. The Endocrine Society supports the following positions:

- The Association for the Accreditation of Human Research Protection Programs (AAHRPP) or some other such entity should enforce a certification process to ensure the quality and compliance of central IRBs.
- Institutions should establish written agreements with certified central IRBs and facilitate their use for investigators conducting multicenter studies.
- The Office for Human Research Protections should issue guidance on the implications of using CIRBs and should provide assurance that users of CIRBs are protected from additional liability.
- Professional organizations should advocate for the use of CIRBs.
- The National Institutes of Health should encourage investigators to prospectively include the use of CIRBs in investigator-initiated proposals involving multi-site studies. In addition, NIH should require the use of CIRBs for multi-site studies it solicits and should explicitly include this requirement in all future grant solicitations.

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[1]Menikoff, J. The paradoxical problem with multiple-IRB reviews. New Engl J Med 2010; 363:1591-1593.
[2]McNeil, C. Central IRBs: why are some institutions reluctant to sign on? J Natl Cancer Inst 2005; 97: 953-955.
[3]Stolberg, Sheryl Gay. The biotech death of Jesse Gelsinger. The New York Times; November 28, 1999.
[4]Bor, Jonathan and Gary Cohn. Research volunteer dies in Hopkins asthma study. The Baltimore Sun; June 14, 2001.
[5]Gunsalus, CK et al. Mission creep in the IRB world. Science 2006; 312:1441.