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IDSA Headquarters
1300 Wilson Boulevard
Suite 300
Arlington, VA 22209
TEL: (703) 299-0200
FAX: (703) 299-0204
EMAIL ADDRESS:
info@idsociety.org
WEBSITE:
www.idsociety.org

October 26, 2011

By electronic submission to the public docket

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

RE: Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators (Docket ID Number HHS-OPHS-2011-0005)

Dear Dr. Menikoff:

The Infectious Diseases Society of America (IDSA) is pleased to have this opportunity to comment on the advance notice of proposed rulemaking (ANPRM) cited above. IDSA represents more than 9,300 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. IDSA strongly supports the goal of the U.S. Department of Health and Human Services (HHS) to enhance human subject research protections while modernizing and simplifying the Common Rule regulations to reduce “burden, delay and ambiguity” for investigators. The Society applauds HHS for this significant and worthwhile undertaking, and looks forward to seeing changes implemented that will protect the privacy of our patients while enabling research that positively impacts patient care and public health.

IDSA strongly supports the comprehensive approach HHS is taking as it provides the opportunity to consider the reforms and the potential for unintended consequences collectively. It also better enables us to consider the collective impact on other regulations. It is our hope that HHS will extend the proposed reforms to the analogous Food and Drug Administration (FDA) regulations and to the Privacy Rule promulgated under the Health Insurance Portability and Accountability Act (HIPAA). IDSA urges HHS to adopt the Common Rule reforms that will strengthen human subjects research protections and then allow research to be exempt from the HIPAA Privacy Rule, as recommended by the Institute of Medicine (IOM) in 2009. Our specific comments on this ANPRM are focused on the areas of greatest interest or concern for the Society: 1) strengthening data protections to minimize information risks (*section V*), 2) streamlining institutional review board (IRB) review of multi-site studies (*section III*), 3) harmonizing adverse events reporting (*section VI*), and 4) informed consent for biospecimens (*section II.B.3.c, IV.C*).

IDSA notes that the Common Rule does not include clear provisions for research that must be conducted during a public health emergency, as often occurs with infectious diseases. While HHS has adopted its own emergency use provision that allows for a waiver of informed consent, it describes very limited

circumstances in which a patient is physically incapacitated or otherwise unable to give consent, and does not necessarily accurately reflect a public health emergency situation.¹ FDA has adopted a similar provision (21 CFR 50.24), but none of the other Common Rule agencies has provisions regarding emergency research. As discussions proceed within the Office of the HHS Assistant Secretary for Preparedness and Response about establishing a public health emergency research review board, IDSA believes it is important for OHRP and other relevant HHS offices and agencies to be involved so that appropriate provisions and guidances are issued to reduce ambiguity and improve harmonization among various agencies.

Strengthening Data Protections to Minimize Information Risks

IDSA supports the establishment of mandatory data security standards as a more effective way of minimizing information risks than IRB review. IRBs were not established to evaluate information risk and usually do not have the expertise or processes in place to accomplish this task effectively. Creating mandatory standards for data security and information protection would enhance privacy protection for research subjects. Released from reviewing privacy risk, IRBs would be able to devote more time to evaluating medical risks, which would again enhance protection for research subjects and reduce delay for investigators. As HHS seeks to identify the most appropriate data security standards to adopt, IDSA supports the evaluation of various existing regulatory standards and the selection of best practices from among them. Existing data security standards from HHS and other government agencies, such as the HIPAA Security Rule and the National Institute of Standards and Technology, should be evaluated for applicability to different types of research covered under the Common Rule.

Although the HIPAA Security Rule may provide appropriate standards for data security, IDSA does not support a blanket harmonization of the Common Rule with HIPAA, especially with respect to adopting the current HIPAA Privacy Rule definitions for identifiable information, “de-identified” information and “limited data sets.” Adoption of the current HIPAA standards for “de-identification” and use of data would be an enormously regressive step (*question 54*). The current list of 18 identifiers under the Privacy Rule is needlessly broad and includes elements that an informed, reasonable individual would not consider identifying information. “De-identification” of data sets results in loss of information that is critical for analysis. HIPAA-defined “limited data sets” are more useful, as they retain two of the 18 identifiers that are most critical for analysis. However, use of a “limited data set” currently requires investigators to enter into data use agreements with covered entities, which often hinders accessibility of data. IDSA agrees with the goal of greater consistency in this area between the Common Rule and the Privacy Rule, but strongly encourages reform in the Privacy Rule. IDSA would be supportive of continued use of the current Common Rule standards of anonymization, or cautiously supportive of the adoption of a redefined set of HIPAA standards for identifiable information. If the “limited data set” became the new HIPAA standard for de-identification and the requirement for data use agreements were removed (*as in question 62*), it would broaden the utility of “limited data sets.” However, as the Society believes that research should be removed from the purview of HIPAA, we remain concerned that inappropriately relying on elements of HIPAA for the Common Rule will prevent or complicate future reforms to HIPAA.

¹ 45 CFR 46.101(i) allows a waiver of the informed consent requirements of 45 CFR 46 in certain types of research in emergency situations (61 Federal Register 51531[Oct. 2, 1996]).

Streamlining Institutional Review Board (IRB) Review of Multi-site Studies

IDSA strongly supports the proposed reform to mandate a single IRB of record in domestic multi-site research studies. There are significant inefficiencies created by overzealous multiple local IRB reviews of multi-site studies, with median times to approval for multicenter protocols reported as ranging from 1.5 to 15 months² (*question 33*). For example, a slight change in protocol by one site IRB can prompt re-review by all the other sites in an interminable game of round robin. IDSA believes that often, such local reviews are prompted not by a motivation to improve or ensure research protections for local subjects, but rather by fear of regulatory and legal liability. Because of these institutional motives, IDSA strongly believes that HHS must mandate, rather than simply encourage, one IRB of record (*question 30*).

The ANPRM refers to workshops conducted by the Office for Human Research Protections (OHRP), in which IRB institutional officials reveal that one of the key factors influencing institutions to conduct multiple local IRB reviews is fear of compliance penalties from OHRP, even if the regulatory violation is the responsibility of an external IRB. In order to overcome this and other disincentives of regulatory and legal liability (*question 32*), institutions must receive a clear mandate from HHS that they are required to use a central IRB of record. Moreover, several institutional representatives have explained that even with a mandated single IRB of record, additional steps are required to prevent institutional fear from resulting in multiple local ethical reviews which will replicate IRB reviews in practice, if not in name. It is critical for OHRP to proceed with its proposal on IRB accountability released in 2009 and make the “accompanying changes in enforcement procedures to hold external IRBs directly accountable for compliance with certain regulatory requirements,” as cited in the ANPRM.

IDSA believes that in the selection of the IRB of record, HHS should provide latitude to the institutions involved (*question 34*). There likely will be variability in the willingness of institutions to serve as the IRB of record. In instances where institutions may not be willing to take on responsibility as the single IRB of record, HHS should encourage the establishment and use of regional or government central IRBs, such as the National Cancer Institute (NCI) IRBs. If HHS continues to be concerned about inappropriate forms of “IRB shopping”, use of such established, high-quality central IRBs can be encouraged.

Harmonizing Adverse Events Reporting

IDSA supports the goal of harmonizing policies and requirements for the reporting of safety data or adverse events. While the proposals to standardize data elements and implement a Federal-wide portal are positive, IDSA believes HHS should clarify and expand the third proposal, “harmonizing safety reporting guidance across all Federal agencies.” A parallel system of adverse event reporting currently exists for multi-site studies that is not required by the Common Rule, inhibits human subjects protections and is resource-intensive.³ Adverse events in multi-site studies are electronically reported to data centers, which analyze the data and report concerns for review by an independent data monitoring committee. In addition to this, reports are sent to local investigators and IRBs, who usually do not have access to the data elements that would make the reports meaningful. Nevertheless, reports, often in paper format, are processed, reviewed and

² Infectious Diseases Society of America, “Grinding to a Halt: The Effects of the Increasing Regulatory Burden on Research and Quality Improvement Efforts,” *Clinical Infectious Diseases* 49 (2009).

³ *Ibid.*

stored, utilizing 9% of local IRB resources. While both OHRP and FDA have agreed that this system has the effect of “inhibiting rather than enhancing IRBs’ ability to adequately protect human subjects,” the latest relevant guidances from OHRP in 2007⁴ and FDA in 2009⁵ differ, leaving ambiguity and the redundant system in place. Adverse event reporting and analysis in multi-site studies should lie solely with data centers and data monitoring committees, and HHS now has the opportunity to provide clarity in this area and eliminate the ineffective redundancies.

Informed Consent for Biospecimens

IDSA is deeply concerned about the proposed reforms in informed consent that will require written general consent for the research use of biospecimens, even if the investigator does not possess identifiable information. This would be a change from current requirements and would have a chilling effect on many types of research which rely on the use of stored biospecimens, including anonymized left-over tissue, blood cultures, and bacterial strains. While IDSA supports improved patient protections, the reforms proposed here would significantly and negatively impact clinical and epidemiological research. IDSA strongly believes that there should not be a change to the current practice of allowing research on biospecimens that have been collected outside a research study, as long as the subject’s identity is never disclosed to the investigator (*question 47*).

The diversity of studies that would be affected by the proposed reforms is illustrated by a few examples. De-identified bacterial cultures obtained during the course of routine patient care are often used in a range of activities that are necessary for the development of new *in vitro* diagnostic devices and the re-validation of currently available devices. Current antimicrobial susceptibility testing devices must be re-validated when new drugs are introduced, resistant organisms emerge, or susceptibility breakpoints are changed, before they can be used for surveillance and patient care in clinical microbiology labs around the country. Requiring informed consent to use bacterial strains originating from patient cultures would delay or prevent implementation of improved methods for detecting resistant organisms at a time when antimicrobial resistance is spreading at a rapid rate and surveillance is critical. Development of new diagnostic devices also relies on accessibility by the study sites to these types of stored specimens. Any studies that involve comparison with stored historical samples would be extremely difficult, if not impossible, to conduct. Another illustrative example involves residual blood specimens drawn for blood cultures which are then used to evaluate innovative blood culture media and systems in clinical trials.

The range of studies described above did not previously require informed consent but would if the proposed changes are implemented. Although the ANPRM envisions circumstances where a simple informed consent form would be given to all patients and allow for open-ended future research use of biospecimens collected during patient care, the logistics of implementation appear daunting and unrealistic. If a simple informed consent procedure is not realized, requiring informed consent for all use of biospecimens will be prohibitively expensive for several reasons, including the limited availability of research nurses.

⁴ Office for Human Research Protections, Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events (2007), <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>

⁵ US Food and Drug Administration, Guidance for clinical investigators, sponsors, and IRBs: adverse event reporting to IRBS—improving human subjects protection (2009), <http://www.fda.gov/cder/guidance/OC2008150fml.pdf>

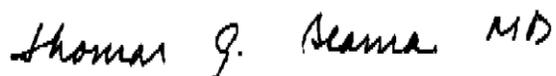
IDSA does not believe that there is a strong basis for many of the concerns that appear to be motivating this proposed change. Attention to this issue has recently been raised by a popular book about the story of cancer patient Henrietta Lacks, whose patient samples led to the development of the HeLa cell line that is still used by investigators around the world. HHS may be driven by a motive to ensure that a similar situation can not occur. However, much of the injustice from the historical HeLa situation resulted from a violation of patient confidentiality. Because of changes in human subjects protections since the 1950s, it is unlikely that a similar situation would occur today, and the proposed change would have no effect on that specific circumstance. As the IOM and others have previously argued, informed consent is not an effective way to protect individuals' privacy. IDSA believes that a more effective way of protecting individuals' privacy is to institute strong penalties against re-identification of biospecimens. Additionally, the proposed change may be a response to the idea that patients should have some ownership of their biomaterials and the "profits" from their use. This may be due to a misconception that cell lines or other patient materials are of intrinsic value and intimately connected with patients. The real value is from the materials (e.g., drugs, vaccines, diagnostics) developed but the patient materials (e.g., human cell lines, bacteria, viruses, parasites) are of no intrinsic value themselves, and often are cultured or otherwise manipulated as to be several steps removed from the patient. Finally, HHS appears to be at least partly driven by the rationale that a biospecimen should be considered inherently identifiable because it contains genetic material (*question 56*). However, significant effort must be exerted to obtain the sequence of the material and a comparison reference sequence before a biospecimen could potentially be traced to a person. Penalties against re-identification of biospecimens would address this concern. If HHS does decide to adopt the new informed consent policy, it is essential that it be applied only prospectively, as retrospective application would destroy the usability of currently available biospecimens (*question 52*).

Additional Issues

IDSA is generally supportive of the proposed reforms to simplify informed consent and to calibrate the level of review to the level of risk. The ANPRM cites the documented growth in the length of informed consent forms over the past several years. More succinct consent forms will more effectively provide patients with risk information and allow them to make a better informed decision. Streamlining the informed consent process will improve protections for patients and improve the conduct of clinical research by reducing selection bias. IDSA is similarly supportive of the proposed reform to eliminate continuing review of expedited studies, as these studies involve no more than minimal risk.

IDSA appreciates the opportunity to comment on this HHS Advance Notice of Proposed Rulemaking. Should you have any questions about these comments, please contact Audrey Jackson, PhD, IDSA's Program Officer for Science and Research, at ajackson@idsociety.org or 703-299-1216.

Sincerely,

Handwritten signature of Thomas G. Slama MD in black ink.

Thomas G. Slama, MD, FIDSA
President