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**RE: Comments on Docket No. HHS–OPHS–2015–0008; Notice of Proposed Rule Making to Revise the Common Rule**

Dear Dr. Menikoff:

The Infectious Diseases Society of America (IDSA), HIV Medicine Association (HIVMA), and the Pediatric Infectious Diseases Society (PIDS) are pleased to have this opportunity to comment on the notice of proposed rulemaking (NPRM) to revise the US Department Health and Human Services (HHS) Common Rule. Our societies applaud HHS's efforts to modernize and simplify Common Rule regulations that reduce burden, delay, and ambiguity for investigators while strengthening the protections for research subjects. In [our comments to the 2011](#) advanced notice of proposed rulemaking (ANPRM), we applauded HHS's comprehensive approach to reforming the Common Rule that considers reforms and their potentially unintended consequences collectively. We also strongly supported many of HHS's proposed revisions, notably the streamlining of institutional review board (IRB) review for multi-site trials, and expressed our hope that the revised Common Rule would instruct reforms to the analogous Food and Drug Administration (FDA) regulations.

However, we also expressed deep concern about the ANPRM's proposed reforms on informed consent for the research use of residual de-identified clinical specimens, citing that these changes would have a portentous effect on a broad range of infectious diseases (ID) research that relies on the use of clinical specimens, including anonymized fresh and stored clinical specimens that are collected during routine standard of care. While we strongly supported improved patient protections, the reforms proposed in the ANPRM would negatively impact patients and public health by inhibiting the clinical and epidemiological research that is critical for new medical breakthroughs and public health surveillance. We [reiterated these concerns](#) last year in a letter to the director of the National Institutes of Health (NIH), Dr. Collins.

Our societies are pleased to see that many of our concerns cited in our earlier correspondence have been addressed by HHS in the NPRM. While several key concerns remain, we look forward to working with the Agency to address these in order to protect the privacy of our

patients while enabling research that positively impacts patient care and public health. Below, we provide specific comments on the areas of greatest interest and concern for our societies.

### **Exemptions from the Common Rule and consent requirements**

In our previous comments, we stated that public health surveillance, a key aspect of responding to ID outbreaks, was not explicitly exempted from the Common Rule, and are pleased to see that HHS has exempted public health surveillance in the proposed rule. However, we note that public health studies to better understand risk factors would not fall under this exclusion. Federal and state public health agencies routinely undertake research of risk factors to enable the risk stratification of publically reported patient outcomes, and to also best target disease prevention strategies to the individuals who would benefit most. While the rule considers these activities exempt in outbreaks, they are crucial in guiding responses to endemic diseases of public health importance. We strongly recommend that HHS exempts research that examines risk factors for any disease of public health importance from the proposed rule (Question 8).

We note that the Common Rule does not provide a provision for research that must be conducted during public health emergencies. While HHS has its own emergency use provision with 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. FDA has adopted a similar provision (21 CFR 50.24), but none of the other Common Rule agencies has provisions regarding emergency research. While HHS has established the Public Health Emergency Review Board (PHERB), the 2014-2015 Ebola outbreak has highlighted that issues remain in rapidly responding to ID outbreaks. Our societies recommend that HHS continue to examine how it can implement provisions and guidances that reduce ambiguity and improve harmonization among agencies during public health outbreaks.

We are also happy to see that quality improvement (QI) activities are excluded from the proposed rule, but are concerned that HHS has stated that comparative effectiveness research of two accepted practices for patient outcome would not fall under the QI exclusion. Our societies strongly believe, as does the National Academy of Medicine, that the ultimate goal of QI is improving patient centered-outcomes. Many federal and state initiatives to improve QI rely on measuring patient-centered outcomes, such as the HHS [Healthcare-Associated Infection Action Plan](#), which includes specific goals for reducing rates of infection during patient care. We recommend that HHS consider expanding the exclusion to encompass all QI research for the purpose of healthcare operations, including patient-centered comparative effectiveness research (Question 8).

IDSA, PIDS, and HIVMA have noted that HHS proposes that research designed to only generate information about a person that is already known would be exempt from any informed consent requirements, regardless of how human subjects are defined. HHS goes on to state that this includes, but is not limited to “the development and validation of certain tests and assays...quality assurance and control activities, and proficiency testing.” In our

previous comments, we stressed that ID diagnostic test development relies heavily on the use of clinical samples from patients with varying characteristics (e.g. age, clinical condition, clinical setting, etc.) to ensure they accurately reflect real world settings. Moreover, the recent Combating Antibiotic Resistant Bacteria (CARB) National Action Plan has emphasized the development of novel diagnostics. We emphatically support exempting diagnostic test development and quality control activities from the Common Rule to ensure unimpeded diagnostic development and use.

However, based on the NPRM's language, we are unsure whether HHS plans to exclude all diagnostic development activities, or only a certain subset. We strongly recommend that HHS consider clarifying what is encompassed in this exclusion, such as whether it exempts the development of both commercial diagnostics as well as laboratory developed tests. Diagnostic developers also rely on blinded chart review via an external source that returns information with a de-identified code for test validation, and we recommend HHS considers excluding these activities to ensure diagnostic development is not hampered unnecessarily (Question 8).

#### **Biospecimens definition as human research subjects**

IDSA, HIVMA, and PIDS note that the NPRM again proposes that all biospecimens should be considered human research subjects, requiring informed consent. While we are pleased to see that HHS has clarified that this would only be a prospective regulation, we remain 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 change from current requirements would have a chilling effect on many types of research that rely on the use of stored biospecimens, including anonymized left-over tissue, blood cultures, and microbial isolates.

While the NPRM proposes that a broad informed consent document be given to all patients to allow for open-ended future research use of biospecimens collected during patient care, the logistics of implementation appear daunting and unrealistic. Requiring informed consent would add considerable time and expense to anticipated studies, potentially limiting the diversity of patient populations and the types of pathogens observed. For example, many outpatient practices would be unable to sustain the expense of hiring study nurses to obtain even a simplified broad consent form, thus severely limiting the ability to detect and study pathogens prevalent in the outpatient setting. Moreover, as the National Academy of Medicine and others have previously argued, informed consent is not an effective way to protect individuals' privacy. If HHS's intention is to improve patient privacy, we firmly believe that a more effective way of protecting individuals' privacy is to institute strong penalties against re-identification of biospecimens.

While our societies support improved patient protections, the reforms proposed here would significantly and negatively impact clinical and epidemiological research (Question 5). A large body of ID research will likely be disrupted, including multi-drug resistant epidemiology studies within a hospital and surrounding community and the use of specimens for clinical trial enrollment. Studies related to understanding the pathogenesis of bacteria,

viruses and parasites, or mechanisms of resistance to antimicrobial agents, would also be seriously impacted. A very large and representative sample of the organisms currently causing infections is required to keep up with the mechanisms that pathogens are developing to avoid both antibiotics as well as host immune defenses. Excluding a significant number of samples where resources to obtain prospective consent are not available or assigned would severely limit our ability to identify these evolving problems. Our societies strongly recommend that HHS abstain from altering its definition of human research subjects.

Our societies appreciate that HHS has provided two alternatives in defining biospecimens as human research subjects. In the event HHS insists on updating the definition, we cautiously support “alternative 1,” which defines human research subjects as whole genome sequencing (WGS) data, or data generated as a result of WGS, even if de-identified (question 3). However, we strongly recommend that this definition distinguish WGS of human DNA from that which targets pathogen DNA, even if human DNA is present (Question 3, 5). We are happy to see that HHS staff indicated that WGS data that excludes human sequencing to focus on identifying pathogens would be exempt from this definition at its October 20, 2015 Town Hall meeting and look forward to HHS clarifying this point in the final rule (question 3, 5).

Should an alternative with pathogen focused WGS as exempt be adopted, we believe this definition strikes a balance between patient protection for specimens and data with the greatest future potential for identifiability while also allowing secondary research that is not WGS of human samples to proceed unburdened (Question 4). Moreover, as many IRB’s are requesting that patient consent be obtained for any research that used WGS of human DNA, this proposal aligns with the stakeholder communities activities to strengthen patient protections.

However, If HHS maintains the NPRM’s original definition that all biospecimens are human research subjects as proposed, we recommend that it clarifies the distinction between the collection and storage of human tissues for future research from human samples collected as a part of the diagnosis of ID, where the emphasis is on identifying and studying the infectious agent rather than investigating the human tissue. We also urge HHS to exclude these samples from informed consent requirements (Question 2, 5).

### **Broad consent for biospecimens**

In the event that HHS mandates informed consent for biospecimens, IDSA, HIVMA, and PIDS are generally supportive of a simplified informed consent approach. We also agree that any broad consent document should permit the collection, storage and use of a subject’s biospecimens or identifiable private information for secondary research. We recommend that HSS also consider incorporating specimen consent into existing consent for care documents to further streamline the process. We note that the NPRM proposes a 10-year collection limit for biospecimens or information in non-research settings. This limit appears arbitrary, adding unnecessary administrative burden in tracking informed consent timelines, and could adversely impact long-term specimen collection (question 61). Our societies strongly urge HHS to remove any time limits from broad consent of biospecimens in non-research settings.

We also note that HHS is still considering templates for its broad consent documents. In the event that HHS mandates informed consent for biospecimens, we look forward to working with the Agency to develop these further. We recommend that HHS considers a broad consent document that allows patients “opt out,” of participation, rather than “opt in.” We firmly believe that this approach, also forwarded by the Secretary’s Advisory Committee on Human Research Protections (SACHRP), would better facilitate the secondary research of biospecimens while still providing patients who oppose this use to exercise their right to decline access.

### **Strengthening data protections**

In our ANPRM comments, we supported the establishment of mandatory data security standards as a more effective way of minimizing information risks than IRB review, which neither lack the expertise, nor were established with the intention to evaluate these risks. However, we strongly cautioned HHS from adopting Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule definitions for patient information, as it would not necessarily improve patient protection while also creating enormous barriers to the use of patient information. We applaud HHS’s decision to no longer seek HIPAA Privacy Rules as a model to improve patient data protections. We also strongly support its proposal to publish a list of specific measures that an institution or investigator can use to flexibly meet data protection requirements with minimal cost and burden. We look forward to working with HHS to further develop this list when it is released for public comment.

### **Streamlining IRB review for multi-site studies**

Our societies strongly support reforms to mandate a single IRB of record for domestic multi-site research studies, particularly those with greater than three sites. In our 2009 article, [Grinding to a Halt: The Effects of the Increasing Regulatory Burden on Research and Quality Improvement Efforts](#), we cite significant inefficiencies created by overzealous multiple local IRB reviews for multi-site studies, often driven more by the fear of regulatory and legal liability than research protections. We firmly believe that a mandated single IRB review is a realistic option that will significantly reduce administrative burden for cooperative research (Question 74). Our societies also support authority to enforce compliance against a central IRB responsible for review rather than those institutions conducting the research. We believe this will allay concerns over regulatory and legal liability by partnering institutions, creating a smoother and more certain process for cooperative research.

However, we do stress that HHS should clearly define guidance and strategies by which working under a central IRB are acceptable to participating organizations as well as individual researchers. For example, we recommend that HHS, or an organization with experience in this area such as the Federal Demonstration Partnership, develop clear guidance requirements on documenting the selection of a central IRB as well as the responsibilities and enforcement liabilities between all participating sites (Question 75). We also recommend that HHS consider circumstances where major differences in culture, ethics, and medical care may materially impact IRB review as exceptions from the single IRB requirement, where the expertise of a local IRB would be critical (Question 76). Finally, we

support the delayed compliance timeline for this provision to ensure this guidance is appropriately developed, given its complexity and enormous potential impact to research institutions (Question 78).

We also are happy to see that HHS proposes to eliminate the continuing review requirement for studies with expedited review as well as those that have completed study interventions that are analyzing data, and/or performing follow up in conjunction with standard of care. These reviews provide little benefit to patient protection while adding unnecessary administrative burden.

IDSA, HIVMA, and PIDS appreciate the opportunity to comment on this HHS Advance Notice of Proposed Rulemaking. Should you have any questions about these comments, please contact Greg Frank, PhD, IDSA's Program Officer for Science and Research, at [gfrank@idosociety.org](mailto:gfrank@idosociety.org) or 703-299-1216.

Sincerely,



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*About Our Societies*

IDSA, HIVMA, and PIDS represent over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, emerging infections such as Middle East respiratory syndrome coronavirus (MERS-CoV), Enterovirus D68, and Ebola, and bacteria containing novel resistance mechanisms such as the New Delhi metallo-beta-lactamase (NDM) enzymes and others that make them resistant to a broad range of antibacterial drugs, including one of our most powerful classes of antibiotics, the carbapenems (carbapenem-resistant Enterobacteriaceae, or CRE).