January 5, 2016

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

RE: Docket No. HHS– OPHS–2015–0008: Federal Policy for the Protection of Human Subjects; Notice of Proposed Rulemaking

Dear Dr. Menikoff:

The American Cancer Society (the "Society") and the American Cancer Society Cancer Action Network ("ACS CAN") respectfully submit the following comments on the September 8, 2015 Notice of Proposed Rule Making ("NPRM"), "Federal Policy for the Protection of Human Subjects," promulgated by the Department of Health and Human Services ("DHHS") in coordination with multiple departments and agencies (collectively, the "Common Rule Agencies").

The Society is the leading nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem. ACS CAN is the nonprofit, nonpartisan advocacy affiliate of the Society, supporting evidence-based policy and legislative solutions designed to eliminate cancer as a major health problem.

Since 1946, the Society has contributed more than $4 billion to cancer research, making it the largest non-government, not-for-profit funding source of cancer research in the United States. Forty-six Society-supported researchers have won the Nobel Prize, representing a track record unmatched in the non-profit arena. The Society's investment in cancer research facilitates medical advances and is amplified by our support for the training of future professionals who will contribute to more discoveries. In addition, the Society maintains a robust intramural research program focused on epidemiology, behavioral science, surveillance, health services and policy research focused on prevention, early detection and treatment of cancer.

ACS CAN recognizes the importance of ensuring that government tax dollars are spent wisely to accelerate cures for cancer. We continually advocate for a well-funded national cancer research program and for better ways to build on the insights gained through previous discoveries and to develop innovative treatments for patients using existing and new research

resources. ACS CAN is actively engaged in efforts to promote a strong national cancer clinical trials system that would make clinical research more efficient and more cost effective, while ensuring patient safety and privacy. As the leading national voice for cancer patients and their families, ACS CAN views the NPRM as a much needed step toward promoting patient trust and ensuring privacy and confidentiality of sensitive information within the evolving nature of medical research conducted in the United States.

As organizations directly involved in patient and research advocacy, the Society and ACS CAN are pleased to see the NPRM incorporate several recommendations offered in our response to the advanced notice of proposed rulemaking (ANPRM) "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators," published in the Federal Register on July 26, 2011. These incorporated recommendations include: (1) mandating the use of a single Institutional Review Board (IRB) for multi-site research studies, (2) extending privacy and security safeguards to cover biospecimens regardless of whether the biospecimen is associated with individually identifiable information, (3) eliminating continuing IRB review for minimal risk studies, and (4) introducing broad consent for future research use of biospecimens.

In addition, we commend the Common Rule Agencies for including transition provisions in the NPRM, which propose that Common Rule changes be applied prospectively. We also commend the Common Rule Agencies for providing a grace period for compliance with the proposed changes, such that the compliance date for the new Common Rule requirements would generally be one year (and in some instances three years) from the date of publication of the final rule. These transition provisions are especially important in the case of cancer-related research, as biospecimens that were collected decades earlier are still being analyzed and used today to foster new early detection and advanced treatment techniques. To this end, we take exception to the proposed ten-year time limit on the broad consent for use of biospecimens, which can have a chilling effect on cancer research. As the Common Rule Agencies continue their work in finalizing changes to the Common Rule, we respectfully submit the following recommendations on the proposals offered in the NPRM.

Altering the Definition of 'Human Subject'

Arguably, the most significant change in the NRPM is expanding the definition of "human subject" to include all of an individual's biospecimens, including any data generated from the biospecimen samples, regardless of identifiability. This definition of human subject would necessitate obtaining informed consent for almost all secondary research uses of biospecimens, (even if the biospecimen is unidentifiable), which is a practice not currently required. We believe that requiring written consent from subjects for future research using their biospecimen(s) is an important means of ensuring that they understand and agree with such use.

While we support the Common Rule Agencies proposal, in order to clarify the implications of this provision for patients and researchers, we recommend that the Common Rule Agencies provide a definition of "biospecimen" in the Common Rule. As written, the revised definition of

"human subject" lacks sufficient clarity and may result in varying interpretations by investigators, institutions and IRBs as to the scope of human subject research governed by the Common Rule. Greater clarity would likely result in better compliance by affected individuals and entities.

It is important to mitigate the impact of redefining research on biospecimens on cancer registry-based research and other studies using de-identified archival tissue. The National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) registries have been a source of biospecimens for cancer research for decades. Registry-based biospecimen studies have recently become more practical and valuable, with the expansion of electronic networks for pathology and medical record reporting and new methods for application of next-generation sequencing and other molecular techniques to formalin-fixed paraffin-embedded specimens. Although the proposed changes to the Common Rule would allow such research if broad consent were obtained at the time clinical samples were drawn, clinical samples are collected at community hospitals, surgical centers, and pathology labs and it is unclear that these institutions will uniformly adopt broad consent into their existing clinical consent process. Given the increasing value of archival specimens for precision medicine research, we suggest the Administration develop an implementation strategy to encourage hospitals and surgical centers across the U.S. to obtain broad consent for future research use of archived clinical samples for registry-based research subject to appropriate safeguards.

Ideally, individuals would provide broad consent for secondary research use on their clinical samples at the time the sample was taken. However, in the event that consent is not obtained or is limited in scope, it is important to recognize that researchers not in possession of biospecimens can satisfy consent requirements with separate consent documents. For example, for over 60 years, the Society has been conducting large, nationwide prospective studies designed to better understand the causes of cancer so that we may ultimately prevent it.[1] In the case of our Cancer Prevention Study-II (CPS-II) Nutrition Cohort, the Society obtained broad consent directly from subjects to obtain biospecimens from the participants in order to get biospecimens from their clinical providers, registries or wherever samples were stored. We ask the Agencies to affirm that a subject can provide broad consent to a researcher to use their previously collected biospecimens including biospecimens held in various repositories, registries, or institutional storage regardless of whether the institution holding the biospecimen obtained broad consent at the time the specimen was collected.

Changes to the Informed Consent Process

We are pleased to see the efforts by the Common Rule Agencies to improve consent forms so that subjects can fully comprehend the nature of any applicable research, use and/or disclosure of their data. The tremendous complexity of our health care system results in many people struggling to complete tasks essential to their health, such as understanding their care, navigating various parts of the system, and making informed decisions. Such decisions would

[1] American Cancer Society. (2015). *Prevention Studies for a Cancer Free Tomorrow.* Retrieved from http://www.cancer.org/research/acsresearchers/acspc-043792

include whether or not to, consent to the use of their biospecimens in human subjects research.[2] The problem is not anecdotal: in 2003, the U.S. Department of Education conducted a study on the health literacy rates of the general U.S. population and reported that only 12 percent of Americans had "Proficient" health literacy, while more than 75 million Americans displayed "Basic" and "Below-Basic" health literacy.[3] As recent research suggests, this issue is further prevalent among minority groups in the U.S., which have a disproportionate percentage of individuals within the "Below-Basic" category when compared to the white ethnic category.[4] We offer suggestions below to further assist the Agencies in their efforts to improve the understandability of consent forms.

Reaching Older Patients: Because the risk of developing cancer increases with age, any research seeking participation from older patients must take into account how they use and process information. According to some research, 71 percent of adults over aged 60 have difficulty using print materials; 80 percent have a difficulty using documents or charts; and 68 percent have difficulty interpreting numbers and performing calculations.[5] For this reason, the National Institutes for Aging has developed specific guidelines and examples for communicating information in print form to older Americans. We recommend the Common Rule Agencies consider these standards to ensure participants fully understand and agree with such use by making consent forms as clear, concise, and written in terms they can easily comprehend.[6]

Eliminating Language Barriers: We recommend the Common Rule Agencies consider adding a requirement that consent forms be provided in the language of the participant. In many instances, English may not be the native or preferred language of individuals being asked to provide consent. For example, there are roughly 54 million Latinos living in the United States, representing approximately 17 percent of the total population. At a minimum, consent forms should be available in Spanish, but also in other languages where appropriate based on the trial population. Even further, by 2044, more than half of all Americans are projected to belong to a minority group (any group other than non-Hispanic White alone); and by 2060, nearly one in five of the total U.S. population is projected to be foreign born.[7] The increasing diversification of the nation's population underscores the need for consent documents to be provided in the preferred language of the patient where appropriate.

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[2] Health literacy is defined as the degree to which individuals have the capacity to obtain, process and understand basic health information needed to make appropriate health decisions and services needed to prevent or treat illness. U.S. Department of Health and Human Services, Health Services and Resource Administration. *About Health Literacy*. http://www.hrsa.gov/publichealth/healthliteracy/healthlitabout.html

[3] Kutner, M., Greenberg, E., Jin, Y., and Paulsen, C. (2006). *The Health Literacy of America's Adults: Results From the 2003 National Assessment of Adult Literacy* (NCES 2006–483). U.S. Department of Education. Washington, DC: National Center for Education Statistics.

[4] "America's Health Literacy: Why We Need Accessible Health Information." An Issue Brief From the U.S. Department of Health and Human Services. 2008.

[5] Kutner, M., et al. *The Health Literacy of America's Adults*, 2006.

[6] National Institute on Aging, Making Your Printed Health Materials Senior Friendly, last updated Jan. 22, 2015, available at https://www.nia.nih.gov/health/publication/making-your-printed-health-materials-senior-friendly.

[7] Colby, Sandra L. and Jennifer M. Ortman, *Projections of the Size and Composition of the U.S. Population: 2014 to 2060*, Current Population Reports, P25-1143, U.S. Census Bureau, Washington, DC, 2014.

Making Consent Documents Less Complex: We support the Common Rule Agencies proposal to reduce the length and complexity of consent forms. In accordance with this proposed change, subjects would receive the most relevant information in a shorter consent document and all "non-essential information" would be relocated to the appendices. While simplifying and shortening the main consent document is desirable, we caution that the same comprehension and brevity standards be applied to any appendices. The proposed change was driven by consent forms that had become longer, more complicated and included issues like institution liability waivers not directly related to informing the consent of the prospective subject. Deeming some of the information as "non-essential" and relegating it to an appendix should not be seen as permission to simply reorganize the same information into a short, relevant, and comprehendible section alongside a long, complex, and tangential section. The envisioned changes should improve the relevance and complexity of the document as a whole.

In 2011, the Society supported the proposal to allow for broad consent for the future research use of biospecimens. This type of consent allows patient choice in the future use of their biospecimens without requiring that the details of that research be known when the consent is sought. Applying this consent a single time per institution, rather than each time a specimen is taken, also prevents researchers from having to repeatedly request consent from the same patients that may visit a given hospital or institution repeatedly as part of ongoing care.

While we endorse the idea of broad consent for future research, we disagree with the proposed ten-year limit on the consent and use of biospecimens. Cancer-related research often involves analyzing biospecimens collected decades earlier. For example, in the CPS-II Nutrition Cohort, which began in 1992, blood or buccal cell samples were collected from over 110,000 study participants between 1998 and 2002. A broad consent was obtained for the indefinite, long-term storage of the samples, and for the testing of the samples for future research analyses. As the biospecimen sub-cohort has matured, some participants developed certain types of cancer such as breast, colorectal or prostate cancer. Their samples, analyzed along with their matched controls that did not develop cancer, have been used in large international research consortia to identify genetic factors that increase risk for these cancers. The samples allow further study of how these genetic factors interact with lifestyle and environmental factors to better understand the causes of cancer. Our samples have contributed to large genome-wide association study consortia for the discovery of many low penetrant, common single nucleotide polymorphisms (SNPs) associated with risk of breast cancer. The resulting information is being used in risk prediction models to help identify women at high risk of this cancer.

The aforementioned example demonstrates how critical it is to have the ability to analyze previously donated biospecimens beyond the proposed ten year time frame. We believe that once a subject offers broad consent to use their biospecimens in future research, the consent associated with a biospecimen should remain valid indefinitely unless the subject actively withdraws that consent. We strongly urge the Common Rule Agencies to consider this revision to ensure medical research can continue to make scientific advances to prevent cancer, and to improve the lives of future cancer patients and their families.

Changing the Types of Research Subject to the Common Rule

The NPRM explicitly excludes several research activities from Common Rule regulations, including quality improvement and assurance studies. Both human subject research and continuous quality improvement and assurance studies by learning organizations are crucial social goods that should be facilitated, not impaired, in the interest of the public. Interventions intended to enhance adherence to accepted practices generally pose little if any risk to recipients and thus should not be delayed by IRB review or by the requirement for an overly burdensome informed consent process. In this light, we agree with the exclusion of quality improvement and assurance studies from Common Rule regulations but recommend that the Common Rule Agencies issue additional guidance in this area.

Specifically, the proposed exclusion covers activities "involving the implementation of an accepted practice to improve the delivery or quality of care or services," but does not cover the "evaluation of an accepted practice." We recommend additional clarification is provided regarding what constitutes an "accepted practice" and what types of activities are considered to have the goal of improving the "delivery or quality of care of services." Similarly, we request that the Common Rule Agencies provide additional guidance regarding the distinction between the "implementation" of an accepted practice and the "evaluation" of such a practice. Such guidance is crucial to assist affected individuals and entities in determining whether an intervention is excluded from the Common Rule as a quality improvement or assurance study.

The NPRM also includes exemptions for several research types from a number of Common Rule regulations and creation of a new tool to assist in exemption determinations. We support the NPRM proposal to create a federally sponsored, web-based decision tool to assist investigators with determining whether a proposed study will qualify for one (or more) of the exemptions. To ensure the investigator submits the appropriate information into the web-based tool, we recommend that the Common Rule Agencies require that any web-based decision tool include robust support materials to guide researchers entering information into the tool. This guidance would help ensure an accurate determination of exemption status for researchers that can provide further clarity and increase efficiency in the research process.

We applaud creating pathways that allow for decentralizing the decision that a particular study is exempt from IRB review by allowing either a knowledgeable individual to make the determination or allowing the use of a web-based decision tool for that purpose. However, we believe that even with these new pathways it is important that institutions maintain responsibility for the integrity of the process. The NPRM indicates that investigators should not independently make exclusion determinations about their own research because of potential conflict of interest, but it indicates they could use the web tool and this would be considered a "safe harbor" not subject to federal review. While such a tool might mitigate biases, it is likely that the inputs to such a tool would remain somewhat subjective and therefore still create the potential for a conflict of interest. In an effort to ensure that the tool is used correctly, we believe that institutions should retain responsibility for proper determination and documentation of exemptions. It would then be up to each institution to manage that responsibility how it sees fit. For example, some institutions could use an internal registration

and approval process, while others could use internal audits. Although institutional review and registration could make the exemption process more cumbersome, these requirements would safeguard the process from potential biases of individual investigators and/or institutions towards exempting single studies or classes of studies from IRB review due to the desire to avoid the delay involved in the IRB review process. We also recommend that if there is a material change in the research being conducted, then the exemption status would no longer be valid, until the researcher resubmits the new investigation details and receives a new exemption status. Ideally, the Common Rule Agencies would also provide guidance on what qualifies as a material change, including specific examples, to assist researchers. This approach would help prevent confusion, and thereby also lead to better compliance.

The NPRM appears to leave open the possibility for multiple online exemption-determination tools. In the interest of simplicity, we recommend the Common Rule Agencies consider developing one or a limited number of web-based decision tools for investigators. As noted in the 2011 ANPRM, a central goal of the proposed revisions to the Common Rule is to harmonize regulations across the federal agencies and departments. Disparate standards lead to compliance and administrative challenges for individuals and entities participating in government and industry-sponsored cancer clinical trials. We believe multiple tools developed across multiple agencies would be counterproductive and result in complexity that undercuts the overarching purpose of amending the Common Rule.

Ensuring Privacy and Confidentiality of Sensitive Patient Health Information

The ability to access and exchange digitized personal health information is easier now than ever before as a result of the rapid progression of sequencing technologies and the digitization of America's health care system. While this ease of exchange helps promote patient care and accelerates research, it also makes data more vulnerable to theft or being inadvertently shared. It's therefore critical that this sensitive information be adequately protected with appropriate privacy and security measures. Guarding such data, as it is being accessed or exchanged across different settings, is crucial to establishing the trust of participants in the research enterprise.

We recognize that improper disclosures of identifiable health information can occur in the research setting and agree with the NPRM's proposal that certain safeguards be implemented to protect the privacy of research subjects. In our 2011 ANPRM comments, we supported the proposal to apply the Health Information Portability and Accountability Act of 1996 ("HIPAA") Privacy Rule standards to research. We still believe the application of these standards in the research context would further protect the privacy and confidentiality of cancer patients' identifiable health information. In addition, we supported harmonizing regulations across the federal agencies and departments, and continue to do so. Many institutions and providers conduct both clinical care and medical research, so conflicting regulatory requirements on these two activities creates confusion and places a complex burden on investigators. Harmonizing the privacy and security measures with existing federal requirements, such as the HIPAA security safeguards, would allow researchers to more efficiently and effectively conduct and report their research findings, which in turn would better protect human subjects.

Conclusion

Thank you for the opportunity to comment on the NPRM addressing the Common Rule. The Society and ACS CAN remain committed to ensuring our constituents are adequately protected while raising awareness on cancer prevention and making strides in finding the cure for cancer. If you have any questions, please feel free to contact us or contact John De Carlo, ACS CAN Senior Policy Analyst at john.decarlo@cancer.org or 202-585-3216.

Respectfully,

Dr. Otis Brawley
Chief Medical Officer
American Cancer Society

Chris Hansen
President
ACS CAN