



October 26, 2011

The Honorable Kathleen Sebelius
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Jerry Menikoff, M.D., J.D.
Director
Office of Human Research Protections
1101 Wootton Parkway
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Rockville, MD 20852

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

Dear Secretary Sebelius and Dr. Menikoff,

The American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), and the Association of American Cancer Institutes (AACI) are pleased to provide comments in response to Department of Health and Human Services (HHS) Advance Notice of Proposed Rulemaking (ANPRM), "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators." AACR, ASCO, and AACI are the nation's leading professional and scientific organizations representing cancer researchers, oncology care professionals and cancer centers. The AACR is the world's oldest and largest scientific organization focused on every aspect of high-quality, innovative cancer research and representing more than 34,000 scientists, clinicians, survivors, and patient advocates. ASCO represents more than 30,000 physicians and health care professionals involved in cancer clinical care and research from all oncology disciplines and subspecialties. AACI comprises 95 leading cancer research centers in the U.S., including National Cancer Institute (NCI)-designated centers and academic-based cancer research programs that receive NCI support. We appreciate the opportunity to comment on the important changes under consideration by HHS.

General Comments

The AACR, ASCO, and AACI recognize the profound importance of protecting individuals who choose to participate in cancer research, and we strongly support efforts to strengthen those protections where necessary and appropriate within the Common Rule. Overall, we believe the majority of the changes proposed in the ANPRM represent meaningful reform and should move forward to rulemaking. We welcome the opportunity to comment on the additional details in the draft rule.

Before we enumerate the specific topics we believe should proceed to rulemaking, we want to raise two overarching concerns related to the ANPRM's provisions on privacy standards and biospecimen research. With regard to privacy standards, we strongly disagree with the decision to include the Health

Insurance Portability and Accountability Act (HIPAA) Privacy Rule standards in the Common Rule because it fails to rectify the current fragmented and overlapping regulation of research. We believe that HHS should not miss the opportunity to implement a *single, uniform* set of criteria for meaningful protections to ensure the privacy of information in research. To that end, we urge the Secretary of HHS to take a leadership role over the agencies that are under HHS authority and develop a *single* approach to HHS regulation of research (see detailed discussion below).

In addition to our deep concern about applying the HIPAA Privacy Rule standards to the Common Rule, further discussion and deliberation are warranted before moving forward with the proposed changes related to pre-existing data and de-identified biospecimen research. We believe that the proposed changes are not sufficiently calibrated to the low level of risk posed by de-identified biospecimen research at the present time, when limitations of science and technology and a lack of publicly available genomic data on individuals largely impede re-identification. This issue merits more intense scrutiny before making the dramatic proposed changes to the rules governing this valuable research (see detailed discussion below).

For both topics, we suggest that HHS consider holding public stakeholder meetings to examine these issues in greater depth before proceeding to development of a proposed rule. Given the complexity of these two issues, it is critical that the perspectives of both researchers and patients are fully heard in this process.

Aside from these two topics, we support the department moving forward with rulemaking on the other provisions highlighted in the ANPRM and are eager to examine the details in the draft rule. Specifically, we generally support rulemaking to promote the following policies¹:

1. Requiring data security standards calibrated to the identifiability of the information collected (see detailed discussion below)
2. Applying the Common Rule to all studies conducted at HHS-funded institutions (see detailed discussion below)
3. Developing a central website for harmonized, electronic reporting of adverse events and unanticipated problems (see detailed discussion below)
4. Providing greater regulatory specificity regarding consent forms to make them shorter and clearer (see detailed discussion below)
5. Supporting a single IRB of record for multi-site trials (see detailed discussion below)
6. Establishing consistent Common Rule guidance across federal agencies (see detailed discussion below)
7. Eliminating annual continuing review for studies in which investigational interventions are complete
8. Eliminating annual continuing review for research eligible for expedited review
9. Updating the minimal risk research list
10. Establishing the default assumption that research eligible for expedited review is minimal risk
11. Establishing more clear cut criteria for determining if a study is “exempt”
12. Creating a registration process and audits, in lieu of administrative review, for “excluded” research (see detailed discussion below)

¹ Note: The bulleted topics are in order of the HHS table entitled “Regulatory Changes in ANPRM: Comparison of existing rules with some of the changes being considered, available at <http://www.hhs.gov/ohrp/humansubjects/anprmchangetable.html>.

13. Broadening the exempt category for studies that involve competent adults
14. Enabling general, open-ended consent for future research in situations in which researchers choose to obtain and record identifiable information (see detailed discussion below)

Detailed Discussion on Select Topics

Privacy Standards for Research

As noted above, engaging the Secretary of HHS would provide the opportunity to design privacy standards that specifically address the secure use of information in research, as is recommended by the Institute of Medicine (IOM) in its 2009 report.² If a single standard is implemented as the IOM report recommends – rather than preserving separate regulatory authority under the Common Rule and HIPAA Privacy Rule, HHS could establish clear and consistent standards across all research. The importance of the privacy of health information and the value of health research to our society demands more comprehensive, transformative change than is envisioned in the ANPRM.³

De-identified Biospecimen Research

As noted above, we have serious concerns with the treatment of biospecimen research in the ANPRM. Although biospecimens and genomic information are all identifiable at some level, the ability to connect de-identified biospecimens to their original contributors is extremely limited at the present time. We are concerned about immediately applying the ANPRM proposal to categorize “all research involving the primary collection of biospecimens as well as storage and secondary analysis of existing biospecimens as research involving identifiable information.” Rather than proceeding with this proposal today, we recommend a more measured approach that could be calibrated to the level of risk associated with the ability to re-identify previously de-identified biospecimens. In the longer term, particularly in cancer research and treatment, the proliferation of personalized genomic data and the growth of increasingly sophisticated technology means it will become easier to re-connect a previously de-identified biospecimen or data set with the patient or research subject. Therefore, we believe that immediately putting in place strong data security protections and meaningful penalties for re-identification while laying a more gradual groundwork for obtaining consent is the direction in which this policy should be headed.

The time to develop a stepwise strategy to address the growing risk associated with re-identification is now, but we do not believe that it is commensurate with today’s risk to immediately adopt a proposal to consider all biospecimen-based research inherently identifiable. Biospecimen research is critical to our ability to link genetic aberrations to specific cancers and translate our increased knowledge of cancer biology into molecularly-targeted treatments for cancer patients. While the privacy of information is equally important, we need to develop policies that will ensure privacy without significantly compromising this type of research. As organizations representing research professionals, we are eager to work with the Secretary of HHS, the Office of Human Research Protections (OHRP), and patient advocacy groups to devise a policy strategy to address this important issue.

² Institute of Medicine. *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research*. Washington, DC: National Academy Press; 2009.

³ Note: We are distinguishing between the HIPAA Privacy Rule and the HIPAA Security Rule. We believe the Privacy Rule provisions should *not* be applied, while standards based on the Security Rule requirements are reasonable to implement.

With respect to the proposed consent rules for pre-existing data or biospecimens, first and foremost, we support the HHS proposal that the application of any new rules must be done prospectively. To retrospectively require consent for use of biospecimens that are in current use for research would have a serious detrimental effect on translational research. The medical community has millions of biospecimens already banked, and it would be tragic to lose the ability to work with these samples. In the field of cancer, our successes in molecularly-targeted cancer therapies would not have been possible without these specimens. Continued use of existing specimens will help provide the baseline data on disease progression, enabling assessment of outcomes in a shorter timeframe than observation of trial participants allows.

Data Security and Protections (point #1 above)

We support the adoption and enforcement of mandatory data security and information protection standards for health information. Enforcing current policies and implementing stricter penalties for violations have the most potential to protect patients from misuse of data about their health. The IOM embraced this approach in its 2009 report on enhancing the privacy of health research.

We support the requirement for strengthened data security protections for health information. Standards based on the HIPAA Security Rule (as distinct from the HIPAA Privacy Rule) make the most sense. Indeed, many institutions are already complying with the Security Rule. We also support the concept of calibrating the level of security to the sensitivity of information. Ultimately, strong data security coupled with enforcement of strong penalties for illegal data release may be the best way to ensure adequate protection of health information. Again, we support the approach of the 2009 IOM study recommendations on this issue.

Extension of Federal Regulations (point #2 above)

Consistent protections for research participants should be in place regardless of how the particular studies in which they participate are funded. Ultimately, it may be easier for institutions to apply a single standard. We agree, in theory, that the Common Rule should be extended to all research (including not federally-funded) being conducted at a domestic institution that receives federal funding; however, greater clarity is needed regarding how such an extension would be implemented. Extending the Common Rule may have a significant impact on institutions that receive large amounts of money from non-federal sources, so how an extension would impact these institutions in the short term should be taken into consideration.

Harmonized, Electronic Reporting of Adverse Events and Unanticipated Problems (point #3 above)

We strongly support changes to the current system of reporting adverse events in research that would simplify and consolidate the reporting of information that is already required to be reported. Such action would help eliminate confusion around reporting, ensure that data are directed as the regulations require, improve the safety of research participants, improve communication and information sharing across federal agencies, and allow quicker identification of and responses to risks from experimental interventions. It also would reduce the burden on researchers to enter events multiple times through multiple, and different, portals.

Improving Informed Consent (point #4 above)

We strongly support efforts to clarify, simplify, streamline and standardize consent forms by specifying appropriate content for consent, prohibiting certain content, limiting the length of various sections,

reducing “boilerplate” language, and making standardized forms available that meet the new criteria. When written consent is necessary, consent forms should help the potential participants focus on the risks and benefits associated with the investigation and put them in context. For example, the standard cancer treatment on a trial (whether it comprises the baseline of care to which the investigative therapy is added or whether it is the comparator treatment) also comes with significant risks. These standard risks should be distinguished from the risks associated with the investigative agent because the patient would most likely receive the standard treatment if they chose not to participate on the trial. It is important that consent forms assist with placing benefits and risk of participation into the proper context.

As discussed below, the consent form should also allow subjects to consent to use of their data for unspecified future research, allowing opt-in or opt-out for certain, limited categories of research. Language that is aimed at a layperson understanding has improved potential to optimize comprehensibility and clarity. In addition, we support the proposal to reduce or eliminate legalistic or scientific language that can be intimidating to participants and even discourage participation in studies.

The research community would benefit from specific language and templates for consent forms; thus it would be most useful for the department to develop or point to specific examples of language that meet the standard for grade-level and readability as well as templates for different types of research. The department can draw on experts in the field to help develop these resources. In addition, since this has been an area where institutional review boards (IRBs) tend to spend a lot of time and effort, it would be helpful to set the expectation that HHS language and templates should be used, thereby reducing variability and providing assistance to IRBs. The NCI and the NCI Clinical Trials Cooperative Groups have laid important groundwork in developing a model consent template for NCI-funded trials. We urge OHRP to build on these successful efforts.

We also agree with the ANPRM that the criteria for waivers of informed consent should be clarified, as well as criteria for when future research use of data collected for non-research purposes would require informed consent. Any new rules should be applied prospectively.

Streamlining IRB Review of Multi-Site Studies (point #5 above)

As stated above, we agree with the proposal that all domestic sites in a multi-site study should rely on a single IRB as the IRB of record for the study. Multi-site studies are growing in number and importance as we discover the biological basis for subpopulations of what were previously thought of as single cancer types. In cancer clinical trials, we have significant experience with use of central IRBs in both adult and pediatric settings.

As noted in the ANPRM, the NCI Clinical Trials Cooperative Group Program relies on adult and pediatric central IRBs as the IRBs of record to streamline review for Cooperative Group studies. Acceptance of the NCI central IRBs has grown significantly over time, which has helped enable consistent protocols and processes across Cooperative Group trial sites and has resulted in cost savings to the system. This success points to the feasibility and benefits of centralized review. Because of this, we support mandating use of the central IRB specifically for NCI Cooperative Group studies.

Generally speaking, for centralized review to work, participating institutions must agree to the approach and process, must be willing to delegate to the single IRB of record the ability to act on its behalf; and the selected IRB must commit to open, regular communication with participating institutions to ensure

all parties are kept informed. Constraints on the single IRB of record should be taken into account, such as the workload of the IRB and its capacity to handle the reviews in a timely manner.

Numerous groups have looked at this issue over the past several years – including two national conferences convened by the Secretary's Advisory Committee on Human Research Protections (SACHRP). We believe the important lessons learned through these discussions are:

- **Need to Hold External IRBs Accountable** – HHS should proceed with changing its enforcement procedures to enable OHRP to hold the IRB of record that is external to the institution accountable for decisions made during the IRB review process.
- **Need for Clear Delineation of Responsibilities and Examples to Illustrate** – OHRP should also issue guidance documents that provide clear examples of responsibilities that it considers specific to the IRB of record versus institutional responsibilities associated with oversight of institutional researchers and research participants. In addition, OHRP could release examples or best practices for agreements between institutions and external IRBs of record. Over time, local institutional responsibilities related to oversight of research have been housed in the local IRB, even if the local considerations are not specifically related to IRB review. OHRP guidance on this topic would help institutions and external IRBs develop clear agreements that delineate responsibility for research review and oversight.

We believe that HHS should strongly and clearly endorse the use of a single IRB of record so that institutions know it is not only an appropriate approach, but also the preferred and default one. It is important to recognize, however, that there may be local sensitivities or concerns that merit a local IRB review. Thus, if the single IRB approach is mandated, there should be a process to “opt-out” with appropriate justification.

With respect to how the single IRB of record might be selected, one approach would be to use the IRB at the principal investigator’s institution—the primary institution—and this IRB would assume review responsibilities for the duration of the study. It is quite possible that IRBs of record will many times be an IRB of one of the participating institutions. If the study is led jointly by investigators at separate institutions, those institutions could be required to designate a primary site for the purposes of designating a primary IRB.

Clarifying and Harmonizing Regulatory Requirements and Agency Guidance (point #6 above)

We strongly support the harmonization of regulations and guidance documents that protect participants in research across federal agencies. We especially recommend that the Common Rule be harmonized with the HIPAA Privacy and Security Rules and FDA regulations, and with human subjects protections regulations administered by both the state and the federal entities that conduct or support human subjects research.

We recommend that the issue of harmonization be considered by the Secretary of HHS because there are multiple offices within the department that have jurisdiction over such protections. For example, the Common Rule is governed by the OHRP, whereas the HIPAA Privacy Rule is governed by the HHS Office of Civil Rights.

Enabling General, Open-Ended Consent for Future Research (point #14 above)

We strongly encourage HHS to adopt a template that represents a “standard, brief general consent form allowing for broad, future research.” Further, we encourage HHS to issue guidance to speed

implementation of this consent. We believe that the consent would not only provide people the opportunity to participate in research, but it also would enable greater awareness of research and has the potential to improve the quality of research databases. As mentioned above, we firmly believe this consent should be required prospectively only. Some institutions or individual departments already obtain consent for biospecimen collections; however, not all institutions are doing this. As a result, there could be significant costs and time associated with implementing standard procedures, distinguishing consent in databases, and training clinical and intake personnel. As such, we encourage HHS to solicit best practices, develop a template form (perhaps this could be done by SACHRP), and provide sufficient time to implement this provision.

In addition, we urge the Secretary to consider a stepwise approach to implement this change with regard to collection of biospecimens and data in a non-research setting. We believe the change merits additional discussion, perhaps by HHS providing more information and clarity in the context of public meetings or a Notice of Proposed Rulemaking. It is imperative that the full implications of any proposed changes are understood.

Conclusion

We offer our profound thanks for your consideration of our comments as you deliberate on these important issues. We commend HHS for initiating this ANPRM that will have a significant impact on bringing the Common Rule up to date with the practice of research. Overall, we support the ANPRM conclusion that these changes will “enhance the effectiveness of the research oversight system by improving the protections for human subjects while also reducing burdens, delays, and ambiguity for investigators and research subjects.” We are eager to provide whatever support we can offer to move this process forward.

If we can provide any additional information or assistance at this time, please contact Mary Lee Watts, Director of Government Relations for AACR at (202) 898-6499 or marylee.watts@aacr.org; Suanna S. Bruinooge, Director of Research Policy for ASCO at (571)483-1613 or suanna.bruinooge@asco.org; or Janie Hofacker, Director of Programs for AACI at 412-647-6331 or Janie@aacr-cancer.org.

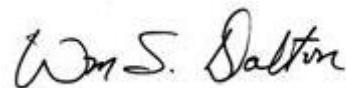
Sincerely,



Judy E. Garber, MD, MPH
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