



January 6, 2016

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

Submitted electronically at <http://www.regulations.gov>

RE: Federal Policy for the Protection of Human Subjects (80 *Federal Register* 53931, Docket ID number HHS– OPHS–2015–0008)

Dear Director Menikoff:

The American Medical Informatics Association (AMIA) appreciates the opportunity to comment on the U.S. Department of Health and Human Services' Office for Human Research Protections (OHRP) proposed revisions to the Federal Policy for the Protection of Human Subjects, also known as the Common Rule. We offer our feedback on proposals to modernize and strengthen the regulations governing human subjects for medical research in the U.S. as part of the Notice of Proposed Rulemaking (NPRM) published in the September 8, 2015 issue of the *Federal Register*. AMIA thanks the departments and agencies for their efforts to strengthen protections for human subjects involved in research, while facilitating valuable research and reducing delay, and ambiguity for investigators.

AMIA is the professional home for more than 5,000 informatics professionals, representing researchers, front-line clinicians and public health experts who bring meaning to data, manage information and generate new knowledge across the health and healthcare enterprise. AMIA members play a leading role in advancing health and wellness by moving basic research findings from bench to bedside, and evaluating interventions, innovations and public policy across settings and patient populations.

AMIA members emphasize that human subject protections need to be modernized and simplified to meet a rapidly evolving research and data collection enterprise. Advances in technology and ease of Internet access of medical data were not envisioned when the regulations were first developed. Furthermore, the Patient Protection and Affordable Care Act and the Medicare Access and CHIP Reauthorization Act have dramatically shifted the focus of various stakeholders toward critical analyses of quality and cost in healthcare delivery, and include numerous statutory changes to the Medicare and Medicaid programs aimed at making healthcare professionals more accountable for outcomes and overall value of care. This focus includes quality reporting mandates, as well as an increased emphasis on value-of-care and comparative effectiveness research.

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Concurrent with these shifts is the rapid adoption of electronic health records (EHRs) in both ambulatory and inpatient settings. A proliferation of health information technology (IT), and related informatics applications that enable the systematic collection, evaluation and application of data have emerged as useful and practical mechanisms for enhancing the safety, effectiveness, appropriateness and overall value of healthcare. Meanwhile large-scale human genome sequencing projects have provided new insights into disease management and cures. These tectonic shifts in care delivery are leading towards the development of a learning health and healthcare system where science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.

AMIA appreciates the proposal to create categorical exclusions and exemptions of activities from having to comply with the Common Rule, with certain caveats. Specifically, we support the exclusions pertaining to:

1. Certain activities, including data collection and analyses, that are regulated under the HIPAA Privacy Rule (i.e., covered entities); and
2. Certain public health surveillance activities.

We also support the exemptions pertaining to:

1. Secondary research use of identifiable private information;
2. The storage or maintenance for secondary research use of biospecimens or identifiable private information; and
3. Research involving the use of biospecimens or identifiable private information that has been stored or maintained for secondary research use.

Despite our support for these new policies, we note that this approach, to create categorical exemptions and exclusions, is incredibly complex. OHRP will need to engage in substantive efforts to clarify how this framework should be applied by stakeholders via use case examples, FAQs, and sub-regulatory guidance. We foresee the great likelihood of asymmetric implementation and varied interpretation among stakeholders, similar to our collective experience with HIPAA.

We also note that regulators will need to monitor implementation of these policies with great detail. This should include a process to ensure exclusions and exemptions fall within the appropriate boundaries, and they are supported by protocols to evaluate these determinations. Specifically, use of the self-determination exemption tool should include some oversight mechanism to guard against conflict of interest.

Finally, we support the notion of allowing single institutional review boards (IRBs) for multi-site studies, and believe this will create much-needed efficiency gains.

AMIA stands ready to aid OHRP in this effort, as our members have a great deal of experience with

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implementing informatics tools in the research domain. Attached below are AMIA comments to select proposals. We hope our comments are helpful as you undertake this important work. Should you have questions about these comments or require additional information, please contact Jeffery Smith, Vice President of Public Policy at jsmith@amia.org or (301) 657-1291. We look forward to a continued partnership and dialogue with OHRP.

Sincerely,



Douglas B. Fridsma, MD, PhD, FACP,
FACMI
President and CEO
AMIA



Thomas H. Payne, MD, FACP
AMIA Board Chair
Medical Director, IT Services, UW Medicine
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Attached: AMIA Response to Select Proposed Changes to the Federal Protections of Human Research Subjects

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Expanding the Definition of “Human Subject” to Cover Research with Non-Identified Biospecimens

Under current regulations, biospecimens research, if non-identified, does not constitute human subjects research. However, this NPRM proposes to expand the definition of “human subjects” to cover research with non-identified biospecimens, which means that nearly all research on biospecimens, even when de-identified or anonymized, would require IRB approval and informed consent. The NPRM makes clear that research on non-identified *information* would remain outside the definition of “human subject research,” even if the information is derived from a biospecimen.

The NPRM presents multiple proposals for expanding the definition of “human subject” to include biospecimens. Its primary proposal is the broadest, and would apply the Common Rule generally to “the obtaining, use, study, or analysis of biospecimens...regardless of identifiability.” Alternative definitions are also presented that are more limited in scope. Proposal A would expand the definition of “human subject” to include whole genome sequencing only, and Proposal B would expand the definition to include biospecimens using a technology that is capable of producing information that is unique to an individual. OHRP identifies potential weaknesses of Proposals A and B as being temporary solutions, requiring periodic reviews and re-evaluation of technologies’ ability to produce information unique to individuals.

In discussing the proposed expanded definition of human subjects to include biospecimens, we understand that OHRP is trying to balance beneficence with autonomy in a way that accomplishes overarching goals of strengthening the efficacy of the regulations without undue burden. While some members of AMIA preferred the primary proposal, for many of the same reasons identified by the NPRM, others were concerned the primary proposal would increase burden on clinical staff to capture consent, rather than the research enterprise, where the burden more appropriately lies. Specifically, the primary proposal to get consent during the *obtainment* of a biospecimen for non-research purposes was identified as problematic, misplacing the onus of collecting consent on clinicians.

In regards to Proposals A and B, AMIA agrees with the limitations identified by OHRP, including the fast-changing nature of technology and the future likelihood of being able to extrapolate identity from previously unidentifiable biospecimens. We share the concern that these alternative proposals have the potential for confusion and asymmetric implementation, especially as rules change to accommodate advances in technology and techniques. However, concerns with implementation are not confined to the alternative proposals.

From a technology standpoint, implementing the systems and controls necessary to comply with this revision – regardless of the proposed path – will be extensive. **AMIA calls on HHS to coordinate resources meant to help the private sector develop the infrastructure needed to comply with these new proposals.** Specifically, new software and processes will have to (1) capture and store consent for each biospecimen collected, which will have implications for data entry / intake and

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database management; (2) track versioning of consent forms; (3) enable querying of consent status; and (4) enable patients to change or withdraw consent preferences. This kind of technical system and set of controls will need to fit within existing infrastructure and policies – a task that will need dedicated leadership and support from the federal government. Further, we anticipate the costs of implementing these changes will be largely unfunded, and the administration of such processes will have to come from existing grant levels. To help offset these costs, and to enable development of an efficient set of systems and controls, we call on HHS to dedicate resources (e.g. grant funding, contracts, etc.) to develop a technical infrastructure and shared resources that will enable compliance in this new paradigm.

Ultimately, AMIA supports the primary proposal to define biospecimens as human research subjects regardless of identifiability. We see this change as the most straight-forward and extensible approach, as technology, methods and use cases evolve. However, we urge OHRP to mitigate the burden of collecting consent by clinical staff by also finalizing proposals related to broad consent for future unspecified research (discussed more below). Giving patients control over their own biospecimens is foundational to the path forward, but so too is the need to streamline bureaucratic requirements so low-risk research is not constrained.

Transition Period

This NPRM proposes to delay compliance with this expanded definition of human research subjects by three years, and it proposes that such compliance be applied prospectively.

AMIA supports this three year implementation window, contingent on close monitoring of implementation experience from the field. Further, we urge OHRP to refrain from requiring compliance before three years after publication of the final rule. Revising the definition of human research subjects as proposed will create a substantial administrative burden, especially over the short term, as institutions and researchers try to understand and comply with these new requirements. It is not clear that the operational infrastructure for such compliance is in place, or how long it might take to build the necessary systems and controls. Therefore, we urge OHRP to monitor implementation of these new policies by seeking regular feedback from the field and provide periodic updates on implementation progress during the three year window.

AMIA also strongly supports the proposal to apply these changes prospectively, meaning that they would not apply to biospecimens collected prior to the effective date of the Final Rule. Nevertheless, certain ambiguities around this transition period remain. For instance, although it appears that the intent is to carve out the use of prior collections of biospecimens from the proposed changes to biospecimen research, it is not clear what standards would apply to research on stored *identifiable* specimens. The regulations indicate that grandfathered biospecimens research “need not comply with the requirements of these regulations” if the biospecimens were collected before the compliance date *and* research use only occurs using the biospecimens in non-

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identified format. We assume this means that if an institution wants to use previously collected identifiable biospecimens, then such biospecimens research would need to comply with the regulations as finalized by this rule if such research occurs after the compliance date passes. We request the final rule resolve ambiguity in this area.

Heightened Protections for Biospecimen Research

In addition to revising the definition of “human subjects” to include biospecimens, the NPRM also proposes to require heightened protections for biospecimens research that includes explicit privacy and security protections that must be applied to research involving the collection, storage, or use of biospecimens. These protections would apply to non-exempt biospecimens research and are also part of the conditions to meet the proposed exemptions related to biospecimens (discussed below). To meet these requirements, institutions would have the choice of complying with a list of safeguards to be promulgated by the Secretary of HHS or complying with certain provisions of the HIPAA Security Rule. Institutions also would be limited in how they can use, release or disclose the stored biospecimens, similar to the downstream restrictions HIPAA imposes in the Data Use Agreement context.

AMIA supports these proposed protections for biospecimen research. This support is contingent on OHRP seeking additional public comment to define the list of safeguards, and diligence is sought to ensure harmonization between such safeguards and HIPAA requirements.

Broad Consent for the Storage and Secondary Research Use of Biospecimens

As proposed under the NPRM, informed consent to storage, maintenance, or secondary research involving non-identified biospecimens (i.e., research that is distinct from the context in which a biospecimen or information was collected or generated) would not need to include all of the basic elements of traditional informed consent and would not need to be obtained for each specific study using the biospecimen. Instead, the NPRM proposes to permit that consent be obtained through “broad consent” for future unspecified research, so long as a federally-developed template for consent is used. Further, the NPRM states IRB review of the broad consent form would not be required if the template is used.

AMIA supports the proposed creation of a broad consent template. We foresee such an approach aiding in the development of a learning healthcare system by enabling more widespread secondary use of biospecimens, while providing willing participants with more autonomy than they currently have. We note the broad consent approach would codify what many institutions and IRBs have historically done through interpretation and application of the existing requirements of informed consent to the unique context of biospecimens research.

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Exclusion and Exemptions for Secondary Research Involving Non-Identified Biospecimens

The NPRM proposes to exclude secondary research involving non-identified biospecimens from the regulations in limited circumstances. If the research will not generate any new information about the individual, it will not be held to any of the requirements of the Common Rule, even though the research involves a “human subject” under the revised definition.

The NRPM also proposes two instances where certain biospecimen research would be exempt from the regulatory requirements, provided certain stipulations are met. One exemption is related to the storage or maintenance of biospecimens collected for purposes other than the anticipated secondary research on such specimens, and the second is for the secondary research use of such stored specimens. However, in order to be exempt, the research would need to meet several regulatory requirements, including:

- Apply heightened protections for biospecimens;
- Obtain broad informed consent;
- Obtain limited IRB review and approval (reviewing the broad consent process and any changes that would impact the required privacy protections).

AMIA supports the proposed exclusion and exemptions for secondary research involving non-identified biospecimens.

Proposed Exclusions and Exemptions from the Common Rule

Under the existing Common Rule, qualifying for a regulatory exemption means that the research is not subject to the regulations’ requirements. The NPRM would change the concept of what it means to be “exempt,” attaching conditions in order to qualify, and reclassifying activities and research outside the purview of the Common Rule as excluded activities. Unlike the definition of exempt research proposed in the NPRM, excluded activities would not be expected to satisfy any regulatory requirements of the Common Rule nor undergo any institutional, administrative, or IRB review to determine whether the activity is excluded. Rather, investigators would be responsible for self-determining whether their research is excluded.

AMIA supports the development of exemptions and exclusions to the Common Rule as the most viable way to protect participant autonomy while promoting beneficence and enabling development of the learning health system. However, we are concerned that exclusions and exemptions have given rise to wide variance in interpretation in other contexts, most notably HIPAA. While attempting to accommodate categories of activity, policymakers have placed a systemic complexity onto an already complex enterprise in healthcare delivery. Years of misinterpretation and billions of taxpayer dollars have been spent complying with HIPAA

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requirements, and we are concerned that modernization of the Common Rule could engender similar consequences given the similar approach.

While we do not offer comment on all exemptions and exclusions, our recommendations are meant to help OHRP clarify the boundaries of exemptions and exclusions which will likely be subject to the most misinterpretation and misapplication. Specifically, we focus on questions raised by creating exclusions for “program improvement activities,” “quality assurance and quality improvement activities,” and the exemption of “secondary research use of identifiable private information.” Our aim is to help OHRP finalize policies that will enable the research enterprise to avoid similar pitfalls experienced by covered entities and business associates in the implementation of HIPAA.

Exclusions

A. Exclusion of Activities That Are Deemed Not Research	
1. Program Improvement Activities	
AMIA Comment:	This category seems duplicative of other categories of exclusion. Clear distinctions between the quality assurance and quality improvement activities category, as well as the exclusion pertaining to biospecimens, are not apparent.
4. Quality Assurance and Quality Improvement Activities	
AMIA Comment:	While AMIA supports this exclusion, we remain concerned that OHRP has not created a sensible pathway for activities undertaken as QA/QI to be shared broadly or incorporated into the learning health system, when QA/QI generates new insights that may be generalizable. We agree with the delineation illustrated in the NPRM of use cases that would and would not be covered by this exclusion, but the construct does not hold in instances of retrospective review or natural experiments. Specifically, we are concerned that health services research performed as part of QA/QI activities that may have broad applicability outside the institution may be stymied. We also request the final rule explicitly state formal QA/QI program rules be followed to ensure that individuals and departments don’t create their own pathways without organizational oversight.
5. Public Health	
AMIA Comment:	We understand activities eligible for this exclusion largely depend on the context in which the investigation is being conducted. Namely, if the activity is reactive it is excluded and if it is proactive or exploratory in nature it is subject to the Common Rule. If this interpretation is incorrect, we request clarification.
Although these parameters seem clear, it seems likely that there will continue to be distinctions that might best be made by providing examples. Additional contrasts between what would or would not be excluded should be provided. Examples of how activities that would not satisfy this exclusion might satisfy other exclusions, and when they should be considered for exemptions,	

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would be particularly useful.
B. Exclusion of Activities That Are Low-Risk and Already Subject to Independent Controls
General Questions for Public Comment
<p>AMIA Comment: We generally support the exclusion of activities that are low-risk and already subject to independent controls. This category represents an important opportunity to create procedural efficiencies and to harmonize federal rules. We know that transparency is an important component to building trust between participants and research, and we agree that requiring notice as a condition of this kind of exempt research strikes a good balance between autonomy and beneficence.</p> <p>We note, however, that what constitutes “low-risk” will change over time. With increased computing power and storage capacity, it will become easier to re-identify data and extrapolate information that may violate privacy. We encourage policymakers to review their working definition of low-risk regularly and with broad stakeholder input.</p>
4. Certain Activities Covered by HIPAA
<p>AMIA Comment: We believe the protections provided by the HIPAA Rules are sufficient to protect participants involved in healthcare operations, public health activities and research activities. We do not believe the current process of seeking IRB approval meaningfully adds to the protection of human subjects involved in such research studies. In fact, we believe that such requirements ultimately undermine important opportunities to improve care quality and efficacy during the course of healthcare operations.</p> <p>It is paramount that these proposed revisions allow data generated in the course of clinical practice to be excluded from the Common Rule if such activities are performed by a HIPAA covered entity. Additional data collection should also be eligible for exclusion if it is included in the Secretary’s List of minimal risk activities, proposed elsewhere in this NPRM.</p>

Exemption Determination Tool

Under this proposal federal departments and agencies would develop an “exemption determination tool” or algorithm. If a person puts accurate information about their study into the tool, the tool would indicate whether the study is exempt. Institutions would be able to rely on the use of the federally developed tool as a “safe harbor” for this determination, so long as the information that has been provided to the tool is accurate. OHRP maintains that investigators still would not be allowed to make these determinations due to potential conflicts of interest.

AMIA supports development of such a tool, and we believe that institutions would benefit from such an approach. We share concerns that allowing investigators to make an exempt determination

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for his or her own research without additional review by an independent party (e.g. a member of the IRB staff) could incentivize misrepresentation/misclassification of research activities. While we do not venture a guess as to the likelihood that institutions would allow this kind of approach, or whether allowing investigators to input data themselves would lead to reduced public trust in research, we support proposals to require an “audit trail” of exemption determinations by capturing parties involved, potential conflicts of interest and specific data elements used to render the decision.

Exemptions

B. Exemptions Subject to Documentation Requirements and Privacy Safeguards	
2. Secondary Research Use of Identifiable Private Information	
<p>AMIA Comment: This exemption is likely to be one of the primary mechanisms through which rapid-cycle, large-scale learning will be conducted – an essential component to next-generation health and healthcare. AMIA appreciates the balance sought by this proposal by requiring notice to individuals and privacy safeguards, but we are concerned with a blanket prohibition on re-use of the data. While we agree that the re-use of information gathered under this exemption should be confined to the individuals and purposes outlined in the research proposal, we underscore the nature of big data analysis to generate information and knowledge in ways not necessarily anticipated by the investigator. For this reason, AMIA urges OHRP to finalize this exemption so that additional research uses of the information is allowable. In this scenario, OHRP could require that the additional research be “related” in some way to the specific research for which the investigator or recipient entity obtained the information.</p> <p>We note, however, that the ongoing success of this kind of data use will require close coordination with HIPAA regulations. OHRP should, again, work with OCR, covered entities and business associates to ensure there are no conflicts in how this exemption is carried out -vis-à-vis HIPAA.</p> <p>AMIA rejects the alternative approach that would limit the exemption to data generated by the Federal Government as it would severely limit the kinds and amount of data eligible for such an exemption.</p>	
C. Exemptions Subject to Documentation Requirements, Privacy Safeguards, Limited IRB Review, and Broad Consent	
General Questions for Public Comment	
<p>AMIA Comment: We support this category of exemption, and we believe it joins similar exemptions that are meant to enable the use of biospecimens and data for supplemental use as foundational to the modernization of the Common Rule. We are entering a new age in healthcare where the value of tissues and data may be amplified when put into the broader context of a learning health system. It will be through the supplemental use of such tissues and data that true</p>	

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innovations and discovery can be made.
Exemption for the Storage or Maintenance of Biospecimens or Identifiable Private Information for Secondary Research Use
<p>This exemption would cover the storage or maintenance for secondary research use of biospecimens or identifiable private information that has been or will be acquired for research studies other than for the proposed research study, or for non-research purposes, if:</p> <ul style="list-style-type: none"> • Written consent for the storage, maintenance, and secondary research use of the information or biospecimens is obtained using the broad consent template that the Secretary of HHS will develop, though oral consent may be sufficient under certain conditions; and • The reviewing IRB conducts a limited IRB review of the process through which broad consent will be sought, and, in some cases, whether the privacy safeguards described in this rule are met. <p>AMIA Comment: We support this exemption, if the underlying consent and limited IRB review processes are in place.</p>
Secondary Research Use of Biospecimens or Identifiable Private Information Where Broad Consent Has Been Sought and Obtained for the Storage, Maintenance, and Secondary Use
<p>This exemption would encompass research involving the use of biospecimens or identifiable private information that has been stored or maintained for secondary research use, if consent for the storage, maintenance, and secondary research use of the information and biospecimens has been obtained using the broad consent template the HHS Secretary will develop. If the investigator anticipates that individual research results will be provided to a research subject, then the research is not exempted and instead must be reviewed by the IRB, and standard informed consent for the research must be obtained. One option that has been considered would be to create a federal panel of experts to make determinations about which unexpected findings should be disclosed to human subjects in research, and what information should be given to subjects about themselves. If this alternative proposal were adopted, then it would not be necessary to have full IRB review of these protocols.</p> <p>AMIA Comment: We support this exemption, consistent with other exemptions in this category. We do not offer comment on the return of research results, except to note that important deliberations have occurred on this subject by specialty groups, such as the American College of Medical Genetics and Genomics, among others. We urge federal officials to consult these groups in an open and transparent process to develop a policy on incidental findings.</p>
Section II.B. Proposed Changes to Obtaining, Waiving, and Documenting Informed Consent
Broad Consent to the Storage, Maintenance and Secondary Research Use of Biospecimens and

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Identifiable Private Information

In addition, informed consent would generally be required for secondary research with a biospecimen (e.g., part of a blood sample that is left over after being drawn for clinical purposes) even if the investigator is not being given information that would enable him or her to identify whose biospecimen it is. Such consent would not need to be obtained for each specific research use of the biospecimen, but rather could be obtained using a “broad” consent form in which a person would give consent to future unspecified research uses. This broad consent would be sufficient to satisfy the requirements for two of the proposed exemptions discussed earlier. As is currently the case, consent would not be required for the secondary research use of Nonidentified private information, such as the research use of medical records that have had all identifiers removed.

AMIA Comment: We support the development of a broad consent process to store, maintain and use for secondary purposes biospecimens and identifiable private information. Clearly, this kind of broad consent will be necessary to enable advancement of the learning health system. Without the efficiency gains made possible through broad consent, the exemptions that are so desperately needed as part of the modernization of the Common Rule may not be preferable to the status quo.

However, the value of a model consent form will be diminished if there is not a supportive process to accompany the form. We believe both will be useful in reducing the administrative/legal burden for smaller providers who would otherwise need to develop these resources on their own. We encourage OHRP to consider developing a model broad consent process, in addition to a templated form, so institutions may have a set of underlying principles and procedures to make broad consent as meaningful as possible for participants. Further, we note that such processes should be exemplary in nature, and in no way should they be construed to mandate prescriptive requirements. Flexibility will be necessary to account for institutional variations.

Section II.C. Proposed Privacy Protections for Information and Biospecimens

First, the NPRM proposes to have the HHS Secretary establish and publish for public comment a list of specific measures that an institution or investigator could implement to satisfy the requirement for “reasonable and appropriate” safeguards. The list would be updated at least every 8 years. Second, if an institution or investigator is currently required or chooses to comply with HIPAA rules, the requirement for safeguards under the Common Rule would be satisfied.

The NPRM also proposes to include limitations for the use and disclosure of information and biospecimens. Unless otherwise required by law, institutions and investigators would only be allowed to use or release biospecimens or disclose personal identifiable private information for research purposes to other parties for the following four purposes:

1. Human subjects research regulated under the Common Rule;

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2. Public health purposes;
3. Any lawful purpose with the consent of the subject; or
4. Other research purposes if the investigator or institution obtains “adequate assurances” through the use of a written agreement with the recipient of the biospecimens of identifiable private information that the recipient will implement the level of safeguards required by this policy, obtains documentation from the recipient that the research has been approved by an IRB using this policy’s criteria for approval, and the recipient will not further release the biospecimens or disclose identifiable private information except as permitted under these four proposals.

AMIA Comment: We encourage HHS to revisit the standards for “reasonable and appropriate” safeguards more frequently than “at least every 8 years.” While we do not believe annual review is necessary, we think a more reasonable time horizon is at least every 5 years.

Second, we support the proposal to allow researchers who choose to comply, or are required to comply with HIPAA, as meeting the requirement for safeguards.

Finally, AMIA supports the circumstances under which researchers could use or release biospecimens or disclose personal identifiable private information for research purposes to other parties.