



October 25, 2011

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Office for Human Research Protections (OHRP)
Department of Health and Human Services
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Rockville, MD 20852

**45 CFR Parts 46, 160, and 164
21 CFR Parts 50 and 56**

Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators

Advanced Notice of Proposed Rulemaking

Dear Dr. Menikoff:

On behalf of the American Medical Informatics Association (AMIA), I am pleased to submit these comments in response to the above-referenced advanced notice of proposed rulemaking (ANPRM). AMIA is the professional home for biomedical and health informatics and is dedicated to the development and application of informatics in support of patient care, public health, teaching, research, administration, and related policy. AMIA seeks to enhance health and healthcare delivery through the transformative use of information and communications technology.

AMIA's 4,000 members advance the use of health information and communications technology in clinical care and clinical research, personal health management, public and population health, and translational science with the ultimate objective of improving health. Our members work throughout the health system in various clinical care, research, academic, government, and commercial organizations.

As health care professionals and informaticians, many of our members practice in institutions subject to the Common Rule and some are involved in health services and other research that uses health data. AMIA is deeply interested in regulations that pertain to all forms of health research, including research that makes use of protected health information (PHI), limited data sets (LDS) and de-identified data, as defined by the Health Insurance Portability and Accountability Act (HIPAA), for such purposes as health outcomes analyses, epidemiology studies, health quality assessments, comparative effectiveness research (CER) and other

information-based research. We believe the potential revisions to 45 CFR Parts 46, 160 and 164 and 21 CFR Parts 50 and 56 discussed in the ANPRM would be significant for the health research and informatics communities, and we are pleased to provide the comments to follow.

We thank the Department of Health and Human Services (the Department, HHS) the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) for issuing this advanced notice of proposed rulemaking, which discusses a wide range of possible regulatory reforms. AMIA strongly supports the two goals articulated by the Department in the ANPRM: (1) to enhance the protection of research subjects and (2) to improve the efficiency of the research review process.

To accomplish these goals, seven broad areas of possible regulatory reform are considered in the ANPRM. Below AMIA provides comment on issues raised, questions asked and proposals made across these seven topic areas. Our response, (organized and numbered by section to mirror the presentation of the ANPRM,) focuses on biomedical and health sector information-based research, (such as health services research); it does not aim to cover implications of the ANPRM for social and behavioral research, educational tests, surveys, focus groups, and so on.

II. Ensuring Risk-Based Protections

This section discusses a variety of potential changes to the current three tiers of review of research studies: *review by a convened institutional review board (IRB)*, studies eligible for *expedited review* and categories of studies *exempt* from IRB review.

We note first that the ANPRM does not provide any new guidance regarding one of the initial tasks of the IRB: determining which studies involve “more than minimal” risk. Rather, the ANPRM leaves in place the construct that the IRB should evaluate physical or psychological risk in the context of “the probability and magnitude of harm or discomfort” *greater than that encountered in daily life*. AMIA is concerned that, when using this vague definition today, IRBs display significant inconsistency in determining which studies may involve “more than minimal” risk. We believe this variability in determining the basic question of the level of risk posed by a research study serves neither patients nor researchers well, and we urge the Department to consider additional guidance on this key issue.

The ANPRM proposes that research involving more than minimal risk would continue to require *review by a convened IRB*, and – with the proviso noted above that the Department should issue additional guidance concerning the determination of “more than minimal” risk – AMIA supports this position. While the Common Rule currently requires that such more than minimal risk studies also require continuing (at least annual) review by a convened IRB, the ANPRM proposes that continuing review would generally not be required after all subjects in the study have completed any study interventions, and the only remaining procedures are standard-of-care procedures that are used to obtain follow-up clinical information and/or the analysis of the research data. The ANPRM suggests, and AMIA agrees, that after the interventional portion of a study is completed the only research risks to subjects would relate to privacy and confidentiality concerns, which the ANPRM would deal with by establishing mandatory data security and information protection standards. Recognizing that IRBs are often overworked and under-resourced, and believing that continuing review of studies in which the degree of risk is minimal

once a risk-bearing intervention has been completed is unnecessary, AMIA strongly supports this proposed change.

Currently, a study is eligible for *expedited review* if the type of research appears on a list published by HHS and the research is found by a reviewer (generally a single reviewer) to involve no more than minimal risk. The ANPRM proposes: that HHS regularly update the list of categories of research eligible for expedited review; create the presumption that studies that use only research activities that appear on the HHS list are indeed minimal risk, unless a reviewer documents a contrary determination; eliminate the requirement of routine annual review; and streamline the documentation submission requirements for such minimal risk studies. AMIA supports these proposed changes.

Today, six categories of studies are, technically, *exempt* from IRB review altogether. To provide one example, if the subjects of the study cannot be identified, either directly or through linking identifiers, by the investigator, the study qualifies for exemption. Unfortunately, in our view, since the Office for Human Research Protections (OHRP) has issued guidance recommending that some type of review of these exempt studies be conducted, most institutions have imposed such a requirement. Thus, practically speaking, in many institutions the exempt level of review is under-utilized.

In order to ensure that protections more appropriately match risks when IRBs review research, HHS proposes a number of changes to current practice. These include establishing mandatory data security and information protection standards for identifiable information and rules protecting against the inappropriate re-identification of de-identified information in order to minimize informational risks and thereby eliminate the need for IRBs to review informational risks of the research. In our observation, few IRBs have expertise in assessing informational risks – including the capacity to assess data security practices, the likelihood of information breaches (and the impact of current breach reporting requirements), actual risks of re-identification of individuals, and the like – and so AMIA strongly supports the goal of getting IRBs out of the business of evaluating informational risk as part of their normal review.

As outlined in the ANPRM, investigators and institutions would be subject to HIPAA Privacy and Security Rule standards, (if they were not already,) and OHRP would harmonize Common Rule definitions of “identifiable” information, “limited data sets” and “de-identified information” to be consistent with HIPAA. Because these data security and information protection standards would, in fact, extend to studies currently exempt from IRB review (exempt at least in theory), the ANPRM proposes to move away from the concept of exempt; “*although still not subject to IRB review, these studies would be subject to the new data security and information protection standards... and in some cases informed consent would be required. Given that these studies would no longer be fully exempt from the regulations, they could more accurately be described as “Excused” from being required to undergo some form of IRB review....*”

Again, because IRBs typically do not have expertise in information privacy or security, getting them out of the business of reviewing studies for informational risk would be a highly salutary result for many kinds of studies, including the information-based studies many of our members conduct. We do remain concerned that risk-averse institutions may not recognize a body of

excused studies any more than they currently recognize studies that are clearly ‘exempt’ under the Common Rule, especially in light of the ANPRM’s suggestion that *excused* studies be ‘registered’ and randomly ‘audited’. In fact, we think this last requirement is an example of OHRP making a proposal (that certain studies be *excused* from review) and then providing guidance to institutions that will result, practically, in undoing the regulation, with those studies being ‘registered’ and ‘audited’ by the very IRBs that we agree should not be in the business of reviewing them. AMIA urges OHRP to clarify that, while institutions have an obligation to track (even to ‘register’ and ‘randomly audit’) excused studies, such activities should be undertaken by an institutional compliance office or any other entity within the institution but not the IRB. We make this suggestion not to create still more regulatory barriers to information-based research, but to clarify our strong interest in reaffirming the role of IRBs as scientific and ethical review bodies, and to discourage the increasing use of IRBs as enforcers of regulatory compliance.

Studies excused from IRB review would include those making secondary use of identifiable data and biospecimens, if new consent requirements are satisfied. In proposing individual consent for the research use of data – including for the use of limited data sets, and even de-identified data – the ANPRM would go far beyond HIPAA requirements. In our view, this introduction of individual consent is ill-advised and poorly thought out. Specifically, the ANPRM seems inconsistent in suggesting that individuals should have to give consent for new use of limited data sets or de-identified information when such data was originally collected for (other) research purposes, but not need to provide consent when the underlying data was collected for non-research purposes (such as clinical care). If not having consent disallows the use of data for secondary research once the data are anonymized or de-identified, why would the use of such data be allowed when it was not originally collected for research, though there would be no indication that the individual ever gave consent for any research use?

In effect, having rightly argued that mechanisms other than IRB review should be used to protect subjects from informational risks, the ANPRM proceeds to distrust those mechanisms (of de-identification and limited data sets and information security and data protection standards) and falls back on what we believe would too often be ‘uninformed’ consent. Instead, AMIA believes that in regard to information-based, non-interventional research the Common Rule should be harmonized with current HIPAA requirements, which do not call for individual consent for the use of limited data sets or de-identified data.

In discussing informational risks, the ANPRM cites “an increasing belief that what constitutes ‘identifiable’ and ‘de-identified’ data is fluid...” and suggests that “...much of what is currently considered de-identified is also potentially identifiable data.” To address this issue, we commend to the Department the findings of a study commissioned by the ONC¹ and summarized in a forthcoming paper by Dr. Daniel Barth-Jones, which suggests that the risk of re-identification is only about 0.22%.

Certainly it is difficult to disprove a *belief* that de-identified data is “potentially re-identifiable” but when even sophisticated statisticians can successfully re-identify with a probability of slightly better than 2 in 1,000, we believe that a proposal to require consent from thousands or

¹ P.K. Kwok, M. Davern, E.C. Hair, D. Lafky. Harder Than You Think: A Case Study of Re-Identification Risk of HIPAA Compliant Records. Joint Statistical Meetings. Miami, FL Aug, 2, 2011.

millions of de-identified patients (who, of course, cannot be known as specific individuals by a researcher) would represent an extraordinary burden on research and provide no substantive additional protection to any individual. Again, AMIA suggests that in regard to information-based, non-interventional research the Common Rule should be harmonized with current HIPAA requirements, which do not call for individual consent or IRB review for the use of limited data sets or de-identified data.

The ANPRM states that because “it is possible to extract DNA from a biospecimen itself and potentially link it to otherwise available data to identify individuals”, individual consent should be required for all uses of biospecimens. While AMIA would not object to a suggestion that researchers always have the option to seek consent, we are again concerned about both the logic asserted here and the impact on research uses of biospecimens if this blanket consent requirement were adopted. First, absent what Dr. Barth-Jones calls the “perfect population register” (in this case, a database of 7 billion DNA samples associated with specific individuals) the notion that a biospecimen is theoretically identifiable seems to us a potential concern, but not so compelling as to justify new and burdensome consent requirements, which all too often may be submitted to IRBs (IRBs that we agree are not suited to assessing informational risks) for waiver. Again, AMIA believes that mechanisms other than consent will be more effective for protecting subjects from informational risks and assuring the security of biospecimens and the privacy of the individuals from whom they were derived. In any case, the application of consent requirements to the use of de-identified biospecimens is, in our opinion, an issue that deserves much further study.

III. Streamlining IRB Review of Multi-Site Studies

Today the Common Rule does not require local IRB review by each institution engaged in a multi-site research study. However, most Common Rule-regulated institutions do not recognize the use of a ‘central’ IRB and typically a local IRB for each institution independently reviews the research protocol, informed consent documents, and other materials, sometimes resulting in hundreds of reviews for a single study. The ANPRM seeks public comment on a proposal to mandate that all domestic sites in a multi-site study rely upon a single IRB as the IRB of record for that study.

While indicating that the Office for Human Research Protections (OHRP) would cease the current practice of enforcing compliance with the Common Rule through the institutions engaged in a multi-site project even when a central IRB was used, (a counter-productive approach that has exacerbated the problem that OHRP now wishes to solve,) the ANPRM does note that institutions would not be relieved of any other obligations to protect human subjects under existing regulations, and “institutions could still choose, for their own purposes, to conduct additional internal ethics reviews, though such reviews would no longer have any regulatory status in terms of compliance with the Common Rule (and could be discouraged).” Again, we see OHRP encouraging one thing – the use of a single IRB for multi-site studies – only to turn around and suggest the opposite, that “internal ethics reviews” could still be pursued by each site/institution. As we did before, AMIA suggests that OHRP should clarify that such “internal

ethics reviews” could be carried out by an institutional compliance office or any other entity within the institution but not by the IRB. If IRBs are to fulfill their primary function of protecting the rights and welfare of human subjects, they should not also be enlisted as internal mechanisms by which institutions police regulatory compliance or contain legal/financial liabilities.

IV. Improving Informed Consent

Under Common Rule and FDA regulations, investigators generally must obtain and document subjects’ informed consent to participate in research. At least eight specific elements – including descriptions of risks and benefits, alternative procedures or treatments, the availability of compensation or medical treatment if injury occurs, a statement that participation is voluntary and the subject may withdraw at any time, etc. – must be included in the informed consent. Many observers have noted that informed consent documents have become excessively long and legalistic, often stretching to 15 to 30 pages in length, and that the high reading levels required for the documents make it very difficult for subjects to have a full understanding of relevant information about the study.

The ANPRM indicates that HHS is considering modifications to the Common Rule that would: prescribe the appropriate content of informed consent forms with greater specificity; restrict content that would be inappropriate; limit the acceptable length of various sections of consent forms; prescribe how information should be presented in the form; reduce ‘boilerplate’; and make available standardized consent form templates, “the use of which could satisfy applicable regulatory provisions.” AMIA supports the drafting of more specific guidance regarding ‘appropriate’ and ‘inappropriate’ content for informed consent forms and, especially, the availability of “standardized” consent form templates.

V. Strengthening Data Protections To Minimize Information Risks

As noted above, the ANPRM suggests that IRBs should not be in the business of evaluating informational risk. Rather, the drafters would approach minimizing informational risk in a variety of ways. First, the ANPRM would align the definitions and requirements of HIPAA and the Common Rule. Thus, the regulations would define protected health information, limited data sets and de-identified information in the same ways and would impose the same requirements on both HIPAA-regulated and Common Rule-regulated researchers and research institutions. For all intents and purposes, both would be subject to the requirements of the HIPAA Privacy and Security Rules, including such measures as physical, technical and administrative safeguards, data encryption, information access control with audit tracing, breach reporting as required by HIPAA and/or Federal Trade Commission rules, data use agreements and contractual prohibitions against re-identification of limited data sets or de-identified information. Representing informaticians and other professionals who are committed to the highest standards of data security and protection, AMIA supports requiring all researchers and research institutions to meet standards for securing data. Further, we encourage the Department to consider establishing in regulation civil and criminal penalties against data misuse, specifically including

any unauthorized re-identification or attempted re-identification of HIPAA-compliant de-identified data.

The ANPRM indicates that these new and harmonized data security and information protection standards would apply prospectively, and solicits feedback regarding the implications of applying them retrospectively, i.e., to existing data repositories and biospecimen banks. Believing that researchers and research institutions should be fully capable of responsible stewardship of data, AMIA would support applying information security and protection standards not only prospectively, (that is, to data gathered subsequent to promulgation of a revised Common Rule,) but retrospectively as well, (meaning to data sets already held by researchers and research institutions). As suggested by our comments to the section on “ensuring risk-based protections” AMIA supports current HIPAA Privacy Rule standards for de-identification, which we believe should be adopted as part of the Common Rule.

VI. Data Collection To Enhance System Oversight

The ANPRM points out that the Common Rule requires investigators to report “unanticipated problems involving risks to subjects or others”, while FDA regulations require the reporting of “adverse events” and notes that the relationship between these two reportable events is uncertain, because the reporting requirements use different definitions, different timeframes, and different vocabularies for degrees of severity and meaning. The ANPRM indicates that HHS is considering changes to the Common Rule that would: use a standardized, streamlined set of data elements for safety reporting; implement a web-based Federal-wide portal to allow investigators to submit certain pre- and post-market safety data electronically; and harmonize safety reporting guidance. In addition, the Federal government is considering creating a central web-based repository to house the information collected across many agencies. Knowing that consistency in data reporting is crucial, AMIA supports consideration of these proposed changes.

VII. Extension of Federal Regulations

Most institutions that hold an OHRP-approved Federal-wide Assurance (FWA) already extend the applicability of the Common Rule to all research conducted in the institution, regardless of whether the research is supported or conducted by a Federal department or agency. The ANPRM suggests that this practice be formally incorporated as a requirement of the Common Rule. AMIA supports this proposal.

VIII. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

There is little doubt that inconsistent and sometimes contradictory guidance and interpretation by OHRP, the Office for Civil Rights (OCR) and the Food and Drug Administration (FDA) have contributed to the perception by researchers and research institutions that the Common Rule and HIPAA regulations significantly burden research while providing inconsistent protection of

human subject rights and welfare and privacy. Several of our previous comments have indicated that we believe OHRP has been especially inconsistent in interpreting the underlying regulation that is the Common Rule and in providing practical and meaningful guidance to covered institutions. We applaud the Department's willingness to look at this problem.

Concluding Comments

In many ways, the ANPRM is bold: in proposing to get IRBs out of the business of assessing informational risk, for instance, and in suggesting that all researchers and research institutions should be subject to data security and information protection standards akin to the requirements of the HIPAA Security and Privacy Rules. In regard to non-interventional, information-based research, AMIA believes that the policy framework provided by a revised Common Rule should encourage the use of HIPAA-defined limited data sets and de-identified data. We do not support the introduction of individual consent for either de-identified or limited data sets, and believe that requiring individual consent for the use of all biospecimens, including those that would normally be considered anonymized, deserves much further study. We strongly support requiring all research and research institutions to comply with data security and data protection standards. AMIA supports the establishment of civil and criminal penalties for any unauthorized re-identification of HIPAA-compliant de-identified data.

Pleased as we are with many of the proposals discussed in the ANPRM, AMIA remains concerned that many Common Rule-regulated institutions continue to expand the use of IRBs as regulatory compliance offices, and we strongly urge the Department to clarify the role of the Institutional Review Board as a scientific and ethics review body that should be focused on protecting the rights and welfare of human subjects, rather than the legal and regulatory obligations of the host institution.

AMIA thanks the Department for issuing this ANPRM, and we appreciate the opportunity to provide these comments.

Please feel free to contact me at any time for additional input.

Respectfully submitted,

A handwritten signature in cursive script that reads "Edward H. Shortliffe". The signature is written in black ink and is positioned above the typed name and title.

Edward H. Shortliffe, MD, PhD
President and CEO