October 25, 2011

Jerry Menikoff, M.D., J.D.
Office of Human Research Protection
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Dear Dr. Menikoff:

Thank you for the opportunity to provide input in response to the Advanced Notice of Proposed Rulemanking (ANPRM) entitled Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators (Notice Number HHS-OPHS-2011-0005), published in the July 26, 2011 Federal Register (76 FR 44512).

Attached please find a joint response to the ANPRM from the Association of American Universities (AAU) and the Association of Public and Land-grant Universities (APLU). Should you have any questions or require more information, please do not hesitate to contact Carrie Wolinetz at AAU (202-408-7500, carrie_wolinetz@aau.edu) or Jennifer Poulakidas at APLU (202-478-6040, JPoulakidas@aplu.org).

Thank you again for your consideration of our recommendations.

With best regards,

Dr. Hunter R. Rawlings III
President
Association of American Universities

Peter McPherson
President
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AAU-APLU Response to ANPRM on Human Subjects Protection
October 25, 2011

The Association of American Universities (AAU) and the Association of Public and Land-grant Universities (APLU) welcome the opportunity to provide feedback on the Department of Health and Human Services (HHS) Advanced Notice of Proposed Rulemaking (ANPRM) titled, "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators." AAU and APLU together represent most of the major public and private research universities in the United States, all of which are engaged in research affected by the proposed revisions in human subjects research regulations contained in the ANPRM.

First and foremost, we applaud HHS for proactively and thoughtfully engaging in this review of the Common Rule and human subjects research regulation. Too often regulations represent reactions to adverse events; this ANPRM presents a rare opportunity to focus, in a positive way, on a very important common goal: to ensure the highest standards of protection for volunteers who participate in research studies that ultimately benefit society through improvements in health, enhancements of living standards, advancements in knowledge, and/or economic progress. AAU and APLU believe that it is possible to meet that goal with regulations that are reasonable, evidence-based, and that reflect the needs and values of all those engaged in the research enterprise: scientists, institutions, regulators, funders, and the human research subjects themselves. The proposals contained within the ANPRM are an important first step in that direction.

As a general principle, we strongly support the intent of the proposals in the ANPRM to streamline and improve regulations that obstruct that which they aim to regulate: ensuring the protection of people participating in research studies. However, in consulting with those in our institutions who have great expertise in the day-to-day operations of human subjects protections, we encountered serious concerns about the feasibility of some specific proposals or the lack of clarity in some of the specific revisions proposed in the ANPRM. We see these as problems of implementation that emphasize why the stakeholder consultation process embodied by the ANPRM is so critically important. We offer these collective critiques and concerns over the specifics of the ANPRM in the spirit of support for revision of the Common Rule and to facilitate this effort to achieve an ideal system of regulations for protecting human research subjects.

Many of our member universities will be submitting detailed responses to the ANPRM, based on their own experiences and expertise. As Associations representing a broad range of institutions, we have focused our response primarily on areas of great consensus and concern.

Ensuring risk-based protections: AAU and APLU embrace the principle of calibrating the level of review to the level of risk and support the idea that, if done well, such an alignment would maximize protection for human research subjects put at risk, while also reducing undue burden on institutions and investigators. However, we conclude that the process outlined in the ANPRM may actually

increase complexity and the workload of institutions and investigators involved, rather than creating a system in which the burden of regulation diminishes as the level of risk does.

We support the idea of identifying minimal risk research that does not need to undergo Institutional Review Board (IRB) review [Questions 1-9; 14-20]. However, the details of the process outlined in the ANPRM are problematic. First, minimal risk must be carefully defined, and the process should recognize the potential need for local input when, for example, one is gathering sensitive information or involving a vulnerable population. We support the definition proposed by the Council on Governmental Relations (COGR) in this regard.

Our Associations have significant concerns, however, about the proposed process for managing informational risk contained in the ANPRM. The ANPRM seems very narrow in its consideration of informational risk relative to the unauthorized disclosure of sensitive data and its lack of recognition that all informational risks are not the same. To the first point, we do not believe HIPAA represents the best model to prevent breaches of confidentiality or inappropriate disclosure or reidentification. The HIPAA Security Rule was not designed with research in mind and would prove extremely burdensome to implement in a research setting without commensurate protection of human subjects. To the latter issue, there is tremendous breadth in the types of research conducted in our laboratories and as part of classroom teaching, and a resulting diversity of data sensitivity, yet the ANPRM uses only identifiability as the standard for calibrating risk. We do not believe this allows for an adequate assessment of the risks involved and would result in both over- and under protection of research involving informational risk.

The change to category 2 of the exemption criteria is generally positive, but we can envision problematic exceptions – such as surveys involving illicit activity or immediately after a traumatic event. Furthermore, automatic "excusing" from IRB review is a good idea in theory, but HIPAA data security and information protection standards are not necessarily the right model for addressing the excused category. AAU and APLU prefer maintaining some form of "exemption." If research truly poses minimal risk and does not need to be reviewed, then we suggest allowing institutions to not review it, rather than creating an entirely new, parallel system of registration and retrospective auditing. We support the suggestion by COGR to expand and clarify the current exempt categories using a panel of experts and the creation of unambiguous tools and processes to aid investigators in self-identifying exemption status. In addition, we support broadening or expansion of category 5 type exemptions to capture more activities, such as public health programs or program evaluation, that do not pose risk to human subjects but for which regulatory requirements can contribute significantly to institutional burden. [Question 26] AAU and APLU do support the proposal to eliminate ongoing review for studies that have been through the expedited review process.

It is our view that retrospective audits do not protect human subjects and create more problems than they solve [Questions 21-22]. Although the ANPRM states that the retrospective audit "is intended

to encourage institutions to use the regulatory flexibility proposed for the Excused category of research," we are concerned that liability issues and lack of detail about the process would have the opposite effect. For example, what happens when an audit reveals something is amiss, and who is accountable for both the problem and the solution? How frequently would random audits need to be conducted? Moreover, establishing a mechanism for conducting retrospective audits, dealing with issues uncovered by these audits, managing liability concerns, and tracking proposals not submitted would create an entirely new and significant burden on institutions.

We support the proposal in the ANPRM to clarify the Common Rule to exclude quality improvement or quality control studies, for example in health care settings, or internal program evaluations [Question 24].

Regarding Question 29, while we think it might be useful to measure when an IRB is engaged in activities that go beyond the requirements laid forth in the regulation, we do not believe transparency itself should be the underlying principle. Such analysis could prove useful in identifying weaknesses in the regulation or providing institutions feedback that could help improve efficiencies. However, taken out of context, such information could be used to compare the human subjects protection programs at institutions in such a way as to incentivize unnecessary overcompliance and increase regulatory burden and delay without a commensurate increase in protections afforded human subjects.

Finally, we strongly support the creation of national IRB biomedical and social/behavioral sciences application forms. Currently, IRBs and institutions develop their own forms, a practice that is inefficient, non-portable, and wasteful without enhancing protections for human subjects. It creates a plethora of forms and a regulatory environment in which variability is the enemy of quality. A standardized application would be particularly helpful in multi-site trials or for institutions that are new to human subjects research and are in the process of setting up an IRB.

Streamlining IRB review of multi-site studies: AAU and APLU concur with the ANPRM's assertion that the involvement of multiple IRBs with multi-site studies "can take many months and can significantly delay the initiation of research projects." Therefore, we support the designation of a single IRB of record for multi-site studies and believe such a model is more cost effective [Questions 30-34]. In fact, when central IRBs are used currently it seems to work fairly well. However, we believe that this is an area in which the government needs to proceed thoughtfully and work to create regulations with as little ambiguity as possible, cognizant of liability concerns, local context considerations, and personal or institutional conflicts of interest issues.

First and foremost, regulation and guidance must clearly delineate the responsibilities of the IRB versus those of participating institutions related to the review and conduct of research. There is concern over the ANPRM proposal not to relieve "any site of other obligations under the regulations

to protect human subjects." The proposed rule must be very clear in outlining Office of Human Research Protection (OHRP) compliance requirements for the IRB of record versus those for the site participating in the study.

AAU and APLU believe the regulations would be well served by examining the best practices of institutions that use a single IRB for multi-site investigations. Our institutions identified a number of these practices, most of which have the effect of limiting the risk to the institution of record. Although there has been periodic criticism of independent or professional IRBs, the review of multi-site studies is one area in which they have proven to be particularly useful, since they can assume the liability more ably than a single, nonprofit research institution.

Some institutions that have used independent IRBs have found it useful to develop criteria to "certify" the IRB as competent. Such criteria could be used to "certify" any IRB, institutional or independent, that wishes to serve as the IRB of record. Development of such criteria would likely have the collateral effect of reducing both the number of IRBs and "IRB shopping"; the former because small entities involved in multi-site studies but no other independent research would no longer need an independent IRB, and the latter because all IRBs qualified to serve as the single IRB of record would have to meet the same standards.

Improving informed consent: Without question, the current informed consent process is far from optimal. The length and complexity of the Informed Consent Document is highly problematic. Rather than improving the understanding of research participants of the actual risks they are facing and clarifying to what they are consenting, the document can have the opposite effect. AAU and APLU applaud the intent of the proposals to return the informed consent process to a system that provides meaningful information and protections to research subjects, and memorializes them in a succinct, comprehendible document. Many of the ANPRM's proposals are very focused on the Informed Consent Document itself. [Questions 35-40] While written consent is important, and provides written information to subjects to which they can refer later, the Informed Consent Document ultimately provides protection mostly to the institution and researcher involved, rather than to the research participant. The Informed Consent Document itself is only a part of the informed consent process, which should involve a dialogue between the subject and conductors of research. The most critical element of informed consent is that the subject is made aware of the risks involved in the research. [Questions 41-44]

The ANPRM objects to the "boilerplate" that institutions include to "protect themselves from lawsuits," yet it suggests that a template form – what amounts to a federally generated boilerplate – be used instead. While we do not support a one-size-fits-all form, it would be helpful for the regulation to include clearer guidance on what should or should not be included in a consent form. Such guidance should focus on the types of information most needed to inform the research subject, and include, either 1) suggested lengths – without creating restrictions – in order to ensure adequate

flexibility for the myriad types of complicated studies involving human subjects, or 2) template forms that allow some institutional flexibility in adding or subtracting information. In developing such guidance, HHS should consider state laws related to informed consent. A standard consent form template might not meet some states' requirements. In addition a standard consent form for biospecimens aimed at patients entering hospitals for treatment would be helpful. However, we are concerned over the concept of providing "consent categories" for "specified types of research." It would be too easy to pillory politically sensitive types of research, such as embryonic stem cell research or sexuality research with such an approach [Question 50]. We also believe there is value, in many cases, of maintaining an ongoing relationship between the subjects and the researcher, which a universal consent form might discourage.

Strengthening data protections to minimize information risk: Conceptually, we support strengthening the protection of research participants through protection of data. We recognize that technological and scientific advancements might increase the chances of a breach of confidentiality or information-related harm to a research subject, although we believe the probability of such a breach occurring is exceedingly small. We strongly believe, however, that the HIPAA Privacy Rule is an ill-fitting model for developing standards related to research. [Question 54] Using HIPAA standards to address informational risk is a solution in search of a problem. Rather than adopt HIPAA standards (which were not written with research applications in mind), HHS could develop new standards relevant to research and harmonize HIPAA for research purposes, rather than the reverse. However, because of the diversity of research involving human subjects, even creation of such a standard raises a host of issues. HIPAA and new health information requirements have illustrated that a one-size-fits-all approach to data or information protection is problematic, and that would seem to be even more the case for research. In addition, if the creation of a national data protection standard for research diminishes the role of the IRB in considering information risk, who is responsible for ensuring the standards are followed? Would previously collected data be grandfathered into such a process and if so, how would this affect continuity of research?

Protection of information and biospecimens should be based on the assumption that the vast majority of those with access to these resources are using them for legitimate purposes in full compliance with regulations and ethical standards. Therefore, the purpose of the regulation should be to disincentivize and punish those exceptional cases in which information or biospecimens would be misused. The system described in the ANPRM seems to take the opposite approach and would create a system of barriers for those research stakeholders who are trying to do the right thing and in a way that inhibits research progress without increased protection for research subjects. Again, we do not believe HIPAA is a good model on which to create mandatory data protection standards.

Although we understand that, in theory, contributors of biospecimens or existent data can be identified and therefore are at some potential informational risk, we have serious concerns about the change, which would forbid later use of de-identified biospecimens without written consent. Private

health information already is protected under HIPAA and may not warrant additional protections for research use. Most institutions and individual researchers lack the resources or funding to conduct the tests to identify individuals from anonymous samples or data sets, and while a risk of identifying an individual is present, it is minimal. While technological advancement may merit revisiting this issue in the next decade, we do not believe the likelihood of identification is high enough to justify the increased regulation. [Question 55-57]

We recognize and support the notion that a standard consent form or automatic waiver for biospecimens [Question 23] aimed at patients entering hospitals for treatment might eliminate this concern, but such a change would have to be contingent on the details of such a measure. For example, while in many institutions the hospital is the site of the research, the researchers themselves are not hospital employees (they are university employees, as the IRB is a university entity). In this setting, the hospital would be tasked with the implementation and cost for no return. Conversely, the investigator and IRB are tasked with implementation, without any way to control compliance.

There is perhaps more flexibility to be gained by developing broadly stated rules supported by updated guidance, allowing for ongoing technological development and consideration of unanticipated issues, and harmonizing such guidance among all federal agencies involved in human subjects protection. [Questions 58-62]

Even as we support strengthening data protections, the Associations note that much of this data already enjoys significant protections. As stated earlier, private health information, which is among the most vulnerable data related to information risk, is already protected under HIPAA. Moreover, protections already exist under federal and state requirements for many types of vulnerable information, so anything that poses a risk above and beyond that probably should not be exempt.

Data collection to enhance system oversight: AAU and APLU welcome streamlining of federal reporting requirements and generally agree that it could be a good idea to maintain a centralized database of adverse events, although no information is provided in the ANPRM on who would "own" the data or who would have access to the information. [Questions 67-70] Our experience with federal reporting systems is that the details of implementation are incredibly important in determining whether or not such systems are feasible, useful, or represent an unfunded burden on institutions. It is difficult, therefore, to respond in the abstract to a data collection system, and we look forward to seeing more detail in the next iteration of the rulemaking process. As HHS considers the details of such a system, we urge strong consideration of whether or not the information is useful to the intended stakeholders, whether or not it could be harmonized or automated with existing data sources or reporting requirements, and how the information would be used in the future to inform the regulatory process.

Extension of federal regulations: Generally speaking, we are concerned with the possible extension of human subjects protection regulations to all research regardless of funding source. Our concerns are grounded in the current extraordinary burden and cost of these regulations. [Question 71] However, AAU and APLU recognize that our institutions currently do not maintain a double standard of protection for federally-funded and non-federally funded research involving human subjects and therefore routinely extend federal requirements for training and review to all such research. Moreover, we acknowledge that a revision of the Common Rule, of which this ANPRM is the first step, if done well, could substantially reduce the burden and cost of regulation.

Such overarching regulations are not without precedent when it comes to protecting human health: compliance with the Select Agent regulations controlling dangerous pathogens, for example, is not dependent on funding source. Therefore, while we do not object outright to the proposal to extend federal protections to all research, we strongly believe such an extension must be tied to an unambiguous and significantly revised regulation which fulfills the intent of a risk-based, streamlined approach to human subjects protection.

Such a new regulatory mandate must improve the clarity, consistency and transparency of the human research process while also bringing improved cost-effectiveness. In addition, careful consideration must be given to the effects such an extension would have on areas such as student research, research related to classroom education, or research on alternative ways to protect human subjects.

We are further concerned that extension of the federal regulations might have the overall effect of decreasing the overall protection of human subjects by driving some organizations away from accepting any federal funding, thus removing any oversight at all from the work that they are doing. While this would not be the case at research universities, whose partnership with the federal government is longstanding, such an effect could easily be envisioned at smaller entities. We do not believe that is the intent of the Common Rule revision, and would urge HHS to consider fully the implications of such a change. Finally, because the Administrative component of federal Facilities and Administrative reimbursements is capped at 26 percent and institutions routinely spend considerably more than this, it is important that the new regulations add no additional compliance cost to institutions and, ideally, reduce them.

Clarifying and harmonizing regulatory requirements and agency guidance: University research is funded by 25 different Federal agencies, each with a unique approach to regulatory implementation. While not all of these agencies are directly involved in human subjects protections, the point remains that unique interpretations and implementations of regulations across agencies are difficult to manage, create inefficiencies, and increase costs. Ultimately, this creates a confusing environment for researchers and institutions dealing with the compliance requirements of multiple agencies, which cannot help but lead to a weakening of the system for protection of human research subjects. AAU and APLU generally support harmonization of definitions, interpretation, and

reporting requirements across agencies regulating research involving human subjects, particularly between the Office of Human Research Protections (OHRP) and the Food and Drug Administration. [Questions 72-74] We agree with COGR that the current requirement to submit to the research agency for review and approval a protocol that has already been reviewed and approved by the institution's IRB is both redundant and unnecessary for improving the protection of research subjects. Such duplicative review, which may involve an agency IRB and/or peer review panel, only serves to delay the progress of research.

Additional suggestions to improve human research subjects protections:

Regulation Via Determination Letters: A significant contributor to the inefficiencies and burdens of the current system to protect human research subjects is OHRP's use of determination letters that focus on procedural issues, often at the expense of actually protecting research participants. Such letters are often interpreted by institutions to have the force of regulation and force the research enterprise to focus on the minutiae of process and procedure involved in compliance, rather than on the ethical and safety issues that the system was set up to address. Because compliance investigations are most often initiated by institutions themselves, this issue could perhaps be addressed in the details of the proposal to create a centralized adverse event reporting system.

Further stakeholder involvement in revising Common Rule: AAU and APLU greatly appreciate HHS providing sufficient detail in the ANPRM to allow for informed response to the proposals. In developing these comments, we hope a strong theme has emerged: no matter how worthwhile the intent of changes to human subjects protection, the effects of such changes ultimately lie in the implementation details. AAU and APLU share HHS's enthusiasm for strengthening protections for human subjects while reducing unnecessary regulatory hurdles on the research community. We seek to help ensure that the final rule achieves these goals. To that end, we urge HHS to consider stakeholder meetings or listening sessions with the stakeholder community to refine the agency's proposals before the next stage of the rulemaking process. The Federal Experts Security Advisory Panel recently utilized such a process in developing its recommendations to improve the Select Agents rule. AAU and APLU are prepared to reach out to our institutions to solicit campus experts and stakeholders to assist and be a part of such a community outreach effort. While it may seem that organizing such sessions will lengthen the timeline for developing the final rule, we believe that working with the stakeholder community in such a fashion will ultimately result in a better regulation and less contentious rulemaking process.