December 22, 2015

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

Dear Dr. Menikoff:

Thank you for the opportunity to provide input in response to the Notice of Proposed Rule Making (NPRM) entitled, "Federal Policy for the Protection of Human Subjects," Docket ID HHS-OPHS-0008 published in the Federal Register on Tuesday, September 8, 2015 (FR 80-173).

Attached please find a joint response to the NPRM 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 contact Lizbet Boroughs at AAU (202-408-7500, Lizbet.Boroughs@aau.edu) or Genevieve Croft at APLU (202-478-6040, GCroft@aplu.org).

Thank you again for your consideration of our recommendations.

With best regards,

Hunter R. Rawlings III
President
Association of American Universities

Peter McPherson
President
Association of Public and Land-grant Universities

December 22, 2015

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

FROM: **Association of American Universities**
Contact: Lizbet Boroughs, Lizbet.Boroughs@aau.edu, (202) 408-7500

Association of Public and Land-grant Universities
Contact: Genevieve Croft, GCroft@aplu.org, (202) 478-6040

Subject: Common Rule NPRM Comment Letter from the Association of American Universities (AAU) and the Association of Public and Land-grant Universities (APLU);

RE: Docket ID HHS-OPHS-2015-0008

The Association of American Universities (AAU) and the Association of Public and Land-grant Universities (APLU) welcome the opportunity to comment on the Notice of Proposed Rulemaking (NPRM), "Federal Policy for the Protection of Human Subjects," Docket ID HHS-OPHS-0008. AAU and APLU together represent most of the major public and private research universities in the United States, all of which are engaged in human subject research affected by the proposed rule. Many of our members will submit detailed institutional responses to the NPRM, based on their own experiences and expertise. As associations representing institutions that perform a broad range of research involving human subjects, we focus our response primarily on areas of considerable consensus and concern to our institutions.

We applaud the Office for Human Research Protections (OHRP) effort to update the Common Rule to improve efficiency in the management and conduct of research and the protection of human subjects. We concur with OHRP's conviction in the foundational principles of the Belmont Report, and furthermore emphasize that justice and beneficence merit equal consideration alongside autonomy. These principles ensure that all populations benefit from high quality and safely conducted human subject research. At the same time, administrative burden across the research enterprise has grown appreciably due to a significant increase in regulations and reporting obligations promulgated by federal agencies and a lack of harmonization among those regulations. Human subject protection policies and regulations are among the most frequently

cited causes of the increased administrative burden and cost associated with research. We are pleased that the NPRM seeks to streamline some requirements.

We offer our collective critiques of specific proposals in the spirit of helping the Office conduct a thoughtful and timely revision of the Common Rule, and to aid the development of an optimal system of regulations for protecting human research subjects.

In consulting with experts in our institutions who are engaged in the daily operations of human subject protections, we identified three serious concerns with the NPRM:

1. the proposed inclusion of biospecimens within the definition of "human subject";
2. the feasibility of some specific proposals regarding exclusions, exemptions and waivers; and
3. a lack of clarity in other specific proposed revisions.

We conclude generally that some proposed changes will reinforce research participant protections and reduce unproductive administrative burdens and their associated institutional costs. Unfortunately, many other proposed changes will not advance research subject protections and will likely create obstacles, and in some cases barriers, to research participation, thereby limiting human subject research involvement and jeopardizing the benefits of such research to individuals and to society.

We would like to highlight our support for the comments submitted by the Council on Governmental Relations (COGR), which express concern that the 262-page NPRM "reads like an Advanced Notice and may result in a final rule that, depending on the tools developed, options chosen, and direction taken, has the potential to substantially increase the cost and administrative burden of implementing the Common Rule revisions with little benefit for the protection of human subjects." We encourage the Office for Human Research Protections (OHRP) to engage stakeholders to further develop NPRM elements highlighted in our comments and either issue a separate ANPRM for these sections or develop detailed guidance letters before moving to a final rule.

Among our strong concerns, the NPRM relies heavily on tools which have yet to be developed and terms which are not defined. We cannot comfortably support proposed changes to the Common Rule which rely on these pending determinations:

- a proposed fundamental, yet undetermined, change to the definition of human subject;
- an undeveloped broad consent template;
- an undetermined "list" of explicit exclusions from the Rule;
- a to-be-developed Secretary's List of "minimal risk" research;
- an undeveloped tool to determine research exemptions; and
- undetermined and undeveloped data protection requirements, including "HIPAA alternatives" and "data security determinations."

We explain our concerns in much more detail below.

Proposed Changes to the Definition of Human Subjects

We commend OHRP for reviewing the definition of a human subject. Examining this topic is warranted as technology evolves. However, we oppose the proposed inclusion of biospecimens within the definition of human subject and believe that this proposal does not recognize the adequate protections of the current Common Rule.

In calling for the inclusion of "biospecimens" in the definition of human subject, the NPRM seems to indicate that biospecimens inherently cannot be rendered non-identifiable. While there is no doubt that a biospecimen can be used to identify an individual, accomplishing this requires both the specimen where the identity of the individual is unknown and a specimen where this identity is known. We are currently unaware of any biospecimen repositories where specimens are linked to individual identities that are openly available to researchers. We are also not aware of any instances where researchers or others are nefariously attempting to identify individuals from biospecimens. Identifying individuals from de-identified social media, health, finance, employment, and other data seems far more likely, and would be technically much easier.

If OHRP posits that biospecimens cannot meet the standard of non-identifiable, then this concern is best addressed through clear guidance which can be adapted as technologies evolve rather than a change to the Common Rule.

The NPRM attempts to provide some practical exceptions to this new provision by carving out some activities that use biospecimens, such as validation of certain (but unspecified) tests and assays, quality assurance and control activities, and proficiency testing. Including this new exclusion category at §_.101(b)(3)(i) is not necessary since these activities are already recognized not to be systematic evaluations designed to produce generalizable knowledge – i.e. they already are not research under the current Common Rule. We do not see the need for an exclusion category that lists activities already identified as not meeting the definition of research.

Likewise, in the proposed regulatory language adding biospecimens to coverage under the Common Rule, the proposed definition inserts "uses, studies or analyzes" at both §_.102(e)(i) and (iii) and inserts "uses, studies, analyzes or generates" at §_.102(e)(ii). These terms are part of the existing definition of "research." Including them in the definition of human subject decreases the clarity of the regulations without adding value. Therefore, these terms should be removed.

We believe that the current definition of human subject in the Common Rule adequately protects human subject autonomy and balances this principle with those of beneficence and justice. Therefore, moving forward with proposals to redefine human subject is unnecessary and would be an unhelpful change in regulation. We echo the Secretary's Advisory Committee on Human Research Protections (SACHRP)[1] recommendation that the proposed change in the definition of human subject be diligently reviewed to assure that there will be no unintended consequences of such a change; and that if such unintended consequences are identified, an alternate regulatory structure that allows for Common Rule jurisdiction over de-identified biospecimens be considered.

[1]Secretary's Advisory Committee on Human Research Protections (SACHRP) comments as discussed at December 4th meeting. http://videocast.nih.gov/summary.asp?Live=17710&bhcp=1; Julia.Gorey@hhs.gov

If OHRP chooses to move forward with redefining "human subject," then, of the proposed alternatives, we find that **Alternative Proposal A** achieves the more reasonable tradeoff between the principles of autonomy and beneficence [Question 4]. Alternative Proposal A would not limit the conduct of valuable and responsible research to the same extent as the primary proposed change in definition.

However, we believe that delineation of this term is best accomplished through guidance, which would allow the definition to be modified as our understanding of biospecimens evolves. Similarly, we do not believe that defining identifiable private information in the regulation would be helpful. As our understanding of identifiable private information evolves, future modification of its delineation can be accomplished best through guidance which would allow for the application of contemporary standards.

Proposed Changes to Informed Consent, Including Broad Consent

Since we do not support including biospecimens in the definition of human subjects and this provision results only because of this change in definition, we do not support the proposed regulatory change to require consent for research involving biospecimens in all but a limited number of circumstances. We acknowledge the important concern raised by some regarding autonomy. However, focusing solely on "biospecimens" as warranting a change in the Common Rule does not consider, for example, the autonomy issues surrounding the use of images, social media, or financial, health, employment, and other data.

Further, a central component of autonomy is that an individual can make an informed decision. We observe that the "broad consent" proposed in the NPRM does not appear to reflect informed or meaningful engagement. While the NPRM points to literature reflecting the public's desire to agree to the usage of their biospecimens, the NPRM provides no evidence that the process it envisions would meet public expectations.

Improving Informed Consent

Without question, the current informed consent process is suboptimal. The length and complexity of the many informed consent documents are problematic. Rather than improving the understanding of research participants of the actual risks they are facing and clarifying to what they are consenting, these documents can have the opposite effect. We applaud the intent of the NPRM to return the informed consent process to a system that provides meaningful information and protections to research subjects, and memorializes them in a succinct, comprehensible document. We caution that the informed consent document itself is only a part of the informed consent process, that it should provide the participant with a meaningful opportunity to ask questions about the study, and that those questions should be answered by a researcher. The most critical aspect of informed consent is that the individual be made aware of risks involved in research participation. We are concerned that the NPRM's proposed, but yet-to-be developed, broad consent template may not meet those standards.

Undeveloped Broad Consent Template

Including provisions for an undeveloped broad consent template in a notice of proposed rulemaking is problematic. Should OHRP proceed with designing such a template, it should consider the many state laws related to informed consent. A standard consent form might not

meet the requirements of some states. Developing a standard consent form for biospecimen collection and maintenance aimed at patients entering hospitals for treatment would also be helpful. However, we caution that maintaining an ongoing relationship between the subjects and the researcher can be valuable, and relying on broad consent forms might discourage opportunities to cultivate such relationships.

If OHRP still is compelled to require consent for use and maintenance of biospecimens after reviewing the comments responding to the NPRM, we believe this can best be accomplished under the existing regulations rather than by imposing new requirements. As we noted in our 2011 ANPRM comment letter, OHRP could issue guidance defining elements of consent that need and need not be included. Further, we agree with SACHRP that if the core NPRM broad consent requirement is imposed, institutions should not be required to use a verbatim template, without opportunity to modify it as appropriate based on range of future uses, subject populations, and institutional policies and procedures.[2]

Tracking Broad Consent

Beyond our concerns around obtaining appropriate consent, the costs of managing, storing, and securing records of broad consent will be significant and will require the development of new data management tools. Indeed, the task of tracking broad consent may be prohibitive for smaller, physician-led and community-based research, and therefore may limit research participation at many institutions that care for underserved populations. Creating barriers to participation from such groups will reduce the relevance and applicability of research findings. This is a serious concern: creating such barriers could reduce the inclusion of minority populations in research and consequently further limit the applicability of research findings to underserved populations. Also, the requirements of documenting and tracking consent would result in significant unfunded costs and burden for investigators and institutions without meaningfully benefiting subject protections [Question 5].

Exceptions and Exclusions Categories

Our member institutions and affiliated organizations have reviewed the NPRM and found that the provisions regarding exclusions and exemptions are particularly unclear. In our experience, organizations and individual readers have varied widely in their interpretation of these categories and the feasibility of implementing the associated portions of the rule as proposed. Many of our member institutions are submitting their own lengthy comments on this particular topic based on their unique experiences and expertise. The views below reflect the broad consensus positions of AAU and APLU on this NPRM section.

Support Risk Based Assessment for IRB Review

The current risk stratification for IRB review is complicated and confusing suboptimal. We support this National Academies of Sciences, Engineering, and Medicine's ("the Academies") statement: "Modest revisions to ensure that regulations are calibrated to the nature and risk of the particular project and that they reflect the changing nature of federally sponsored research...can

[2] SACHRP Recommended Guidance on Minimal Risk Research and Informed Consent, September 28, 2015

substantially reduce burden without compromising robust protections for participants in research."[3]

We appreciate the attempt to provide greater clarity and definition around activities to which the Common Rule does not apply and activities which are exempt from its requirements. Improving guidance to more appropriately facilitate social sciences and education research is particularly welcomed. However, we do not support the NPRM as it stands as the mechanism to provide that clarity. We instead recommend that the proposed categories serve as examples rather than an exhaustive and fully inclusive list, and believe that most, if not all, categories can be addressed through well-developed harmonized guidance using the existing regulations.

As mentioned earlier in this letter, we do not believe that quality assurance or improvement activities constitute human subject research. For example, the sharing of de-identified information between universities as part of AAU's initiative to improve STEM education should not necessitate an IRB review. We recommend further refining existing guidance on such activities if additional clarification is needed. For these and the other activities that have found their way into the proposed exclusion, we agree with the underlying NPRM justification that the activities are not viewed as human subject research.

We acknowledge that some activities such as those in the NPRM sections on intelligence surveillance activities and research conducted by a government agency using government-generated or government-collected data may not be considered activities not involving human subjects. However, we observe that the existing regulations at §_.46.101(i) already allow department or agency heads to waive the applicability of some or all of the regulatory provisions for specific research activities or classes of research activities so long as OHRP is notified.

Rather than developing a new "excluded" regulatory category we believe the existing regulation, combined with well-reasoned guidance using examples, should be used to define when the regulations do not apply. We believe this provides the best mechanism to protect research subjects while at the same time allowing IRBs to exercise their discretion in gauging the risks represented by the proposed activities.

Similarly, we assert the proposed changes to the existing "exempt" categories could best be addressed through guidance. We believe the changes proposed in the NPRM are unnecessary and confusing, and will only increase regulatory burden for both investigators and institutions without substantively strengthening protections for human subjects.

We are concerned about the provisions for the federal development of a "decision tool" to make exempt determinations. If OHRP's position is that administrative or IRB review no longer is required to confirm an exempt determination, then this could be accomplished by new guidance rather than codification in the rule. Many times investigators are confused about the regulatory language with respect to exempt categories, and only after careful conversation with their IRB officer do they understand how their project may fit within the human protection framework. These valuable conversations promote safe and effective research decision-making. However, if

[3] "Optimizing the Nation's Investment in Academic Research." National Academies of Sciences, Engineering, and Medicine, September 22, 2015: p. 66.

such a decision tool is to be created, we believe it would be better accomplished through OHRP partnering further with the Federal Demonstration Project[4] to develop and pilot new tools that accurately reflect real-world research, especially for research of minimal risk, rather than attempting to impose them through regulation.

Secondary Research Use of Identifiable Private Information

We appreciate the effort to clarify the secondary research use of data, including proposed exclusions, exemptions, and safeguards. While we laud the increased clarity provided in some instances, in many cases we request additional guidance to ensure that researchers and IRBs can effectively implement the rule.

Exclusions (§_.101)

Use of Private Identifiable Information

Most generally, we believe that information that is already in the public sphere, even if it may be considered sensitive, does not warrant additional protections. Thus the proposed exclusion at §_.101(b)(2)(ii) regarding use of identifiable private information is appropriate and should not be narrowed [Question 17].

We welcome the broadening of the rule to explicitly include information that "has been or will be collected," replacing "existing" in the previous Category 4 exemption. This change would eliminate a rule component that has been open for subjective interpretation and has unnecessarily complicated the research approval process.

However, we note that the exclusion at §_.101(b)(2)(iv) represents a shifting, rather than a lightening, of administrative burden. This exclusion is in effect a "bookkeeping" change rather than a true reduction of administrative burden. In moving research oversight from 45 CFR 46 to 45 CFR 160 and 164 (HIPAA), the proposal leaves the IRB responsible for review of these activities, but in its role as the institution's privacy board.

Exemptions (§_.104)

Exemptions for Secondary Use of Identifiable Private Information

When considering exemptions involving the secondary research use of identifiable private information ((§_.104(e)) [Questions 51 and 52], we are concerned that the proposed concept of "prior notice" is insufficiently developed, and we would welcome additional guidance on this matter. The NPRM does not provide sufficient detail for IRBs to consider what prior notice really means, what it should include, or how researchers or administrators must document or verify that prior notice was given. For example, would a HIPAA notice suffice? If so, then what about researchers in the social and behavioral sciences that do not typically encounter subjects in a HIPAA-style clinical setting, and yet want to share data not originally collected for a research purpose? Implementing this exemption would be complicated in the absence of clear guidelines.

[4] http://sites.nationalacademies.org/PGA/fdp/PGA_061069
http://engage.washington.edu/site/MessageViewer?em_id=93201.0

In evaluating the categories themselves, we find additional cause for confusion. If §_.104(e) regulates the secondary use of non-research identifiable private information, and §_.104(f) regulates the storage and maintenance for secondary use of identifiable private information for research or non-research purposes, then we have the following questions: does §_.104(f) regulate only repositories? If not, then why is non-research information included? This characterization muddies the waters with §_.104(e). Furthermore, we cannot discern the difference between the information referred to in the categories at §_.104(e)(2) and (f)(2). It seems that, by definition, information that is used secondarily for research had to be stored or maintained after its original use for this purpose. We request further guidance and clarification on this matter.

On a fundamental level, we question whether the proposed exempt categories in §_.104(f) are truly exempt at all. The current concept of exempt projects is that they are not subject to regulation; however, in the new rule, these categories require use of the expedited review procedure to determine that projects meet regulatory approval criteria at §_.111(a)(9). As a result, it would be more appropriate conceptually to include them on the expedited list rather than to define them as exempt research categories.

Waivers of Informed Consent

Above all, we are concerned that the NPRM's proposed provisions for waivers of consent unreasonably limit the flexibility of IRBs to appropriately and effectively exercise their mission to protect subject safety and autonomy and ensure ethical human subject research. We believe that IRBs should be entrusted to exercise judgement in granting waivers of consent for research involving biospecimens or private information. We concur with the recommendations of SACHRP[5] that such waiver determinations should be made based on whether requiring consent would compromise scientific validity or raise ethical concerns; whether there was a scientifically and ethically justifiable rationale for why the research could not be conducted with a population from whom consent could be obtained; and furthermore, that waiver decisions should not solely be determined by considerations of convenience, cost, or speed.

IRBs should not be prohibited from waiving consent. There are instances when a waiver of consent is appropriate. IRBs should be permitted to exercise discretion on a study-by-study basis, balancing the rights of subjects with the benefits of research to determine when a waiver of consent for use of biospecimens would be appropriate. This should be included in the regulations [Question 67].

We do not generally agree with those who have argued that the requirements for obtaining waivers of informed consent or waivers of documentation of informed consent are confusing and inflexible. However, concerning whether or not the waiver criterion regarding "practicably" at §_.116(d)(3) should be explicitly defined or otherwise clarified [Question 65], we concur that additional clarification would be helpful. We believe that further definition and clarification would best be addressed through guidance rather than through revisions to the regulations. We

[5] SACHRP Recommendations for Informed Consent. Attachment D. Recommendations Regarding Informed Consent and Waiver of Consent. January 10, 2013.

agree with those clarifications provided by SACHRP[6] regarding the definition and application of "practicably," and urge that HHS and the other Common Rule agencies adopt this guidance.

We do not favor the proposed differentiation of the criteria for waiving informed consent for the research use of biospecimens versus identifiable information [Question 66]. We believe the potential risks related to the research use of identifiable information are at least as great as those for biospecimens. For this reason, the protections and waiver criteria should be equivalent for the research use of both types of data. Special protections for biospecimens should not be separately developed, thereby leaving private information less protected.

We likewise believe it is crucial that IRBs be permitted to grant waivers for the secondary research use of information or biospecimens originally collected for research purposes [Question 68]. Where an IRB required consent for the original research, it should be at the IRB's discretion to determine if consent for the secondary use of that information or those specimens can be waived, and if the original consent is appropriate for the secondary risk relevant to risk or benefit as appropriate for the individual study.

In response to questions 69 and 70, it is our opinion that investigators are more likely to avail themselves of proposed provisions under which certain research can be conducted without specific consent, e.g., the exemption at §_.104(e)(2), than to seek broad consent for the use of identifiable private information. These proposed provisions are ethically sound and reduce the burden on investigators and administrators without adversely impacting participants' rights. Although well intended, the NPRM proposal to prohibit waiver of consent by an IRB, if a person has been asked for broad consent and refused to provide it, will create a disincentive for institutions to seek broad, secondary use consent. Approval of the secondary use of identifiable private information is a decision which the IRB should make based on the circumstances and nature of the research proposed. A participant may well reject an "open-ended" consent, while agreeing to consent for a narrower use, e.g., additional research of the same nature or for the same purpose. The reality is that there are significant costs, including the time and effort involved in implementing and maintaining a tracking system for obtaining and documenting broad consent. If a participant's refusal to give broad consent is considered a refusal of consent to use for all other research purposes; then there is little incentive for institutions to undertake such a tracking system.

Protection of Biospecimens and Identifiable Private Information (§_.105)

A regulatory requirement that safeguards match sensitivity of data would be appropriate, and should allow individual institutions to implement local policy that applies levels of protection calibrated to the sensitivity of project-specific data [Question 71].

The proposed limitations on the re-disclosure of biospecimens and identifiable private information obtained for research purposes to four circumstances, unless required by law, are too restrictive [Question 72]. Current standards are reasonable and appropriate. IRBs are best situated to assess and balance the benefits and risks of re-disclosure on a project-specific basis,

[6] SACHRP Recommendations for Informed Consent. Attachment A: Recommended Guidance on Minimal Risk Research and Informed Consent. July 21, 2015.

and to review the individual plans for safeguarding information and biospecimens for a given study. Institutions should have the option to implement local policies designed to protect the security of the biospecimens and identifiable private information within the research portfolios of their individual institution.

Specifying Data Security Standards

Regarding the NPRM proposal to impose data security and privacy protections from other regulations such as those under HIPAA and the E-Government Act, we observe that these standards were not specifically developed to address the extant spectrum of research data, and we do not support their broad application to the research setting. These standards are designed to address data security and privacy for activities requiring stronger protections than many research activities would reasonably require. There are fundamental differences in the data privacy and security needs of clinical trials that include an individual's health information; economic research that includes an individual's financial information; and psychological experimentation that tracks response time to blips on a computer screen. We believe the attempt to include a defined list of acceptable standards in regulation (at §_.105(b)) does not account for the heterogeneity of research that is subject to the regulations and does not facilitate the appropriate application of standards based on the characteristics of the research. We believe that the most appropriate and effective method of preventing and deterring unauthorized re-identification of subject data and biospecimens lies in regulatory, administrative, civil, and criminal penalties against investigators and entities that would seek to re-identify any de-identified biospecimens and data that have been distributed for research uses."

Regarding the Secondary Research Use of Data

Although §_.105 is not concerned with the secondary use of personally identifiable private information per se, the requirements of exemptions at §_.104(e) and §_.104(f) state that safeguards for information protection in §_.105 must be followed. Such requirements refer to unspecified measures to be published in the future, or to safeguards provided by HIPAA or to other federal regulations or agencies. It is not possible to evaluate the appropriateness of such to-be-determined protections.

Single IRB of Record

We commend OHRP's effort to streamline regulations and improve efficiency, while maintaining the effective protection of human subjects. The duplication of IRB review in multi-site trials is a substantial element of regulatory inefficiency, and moving towards single IRBs of record may alleviate possible inefficiencies in some situations. However, OHRP has failed to produce a reason for altering the Common Rule to include a single IRB mandate. Under current practice, NIH and any other sponsor can simply mandate the use of a single IRB for any study or group of studies which they fund.

We note that the administration of human subject protection involves multiple entities on a university campus – from senior research officers to compliance officers to general counsels – all of whom may have different perspectives on the impact of this policy depending on their responsibilities related to human subject research.

As discussed in our responses to the 2011 ANPRM and the "Draft NIH Policy on the Use of a Single Institutional Review Board (IRB) for Multi-Site Research" (NOT-OD-15-026), AAU and APLU, in principle, support moving towards the use of a central IRB for multi-site research studies.[7] Many of our institutions have embraced this model or otherwise participated in central IRB initiatives. However, we believe OHRP should move in a cautious, deliberative fashion in mandating such use, and must carefully consider the potential unintended, negative consequences of implementing such a mandate. We ask that you consider the following concerns.

We agree with the 2014 NIH conclusion[8] that single IRBs for multi-site studies are currently under-utilized. However, we are concerned that implementing the proposed policy as written would be disruptive and costly. As noted below, transitioning to a single IRB model can take a substantial amount of time and resources, and allowing three years for implementation is likely to be insufficient. As such, OHRP should use a phased-in approach if it chooses to implement a mandatory policy. Using the National Cancer Institute's central IRB as a pilot before requiring use of a central IRB on a larger scale may be an appropriate alternate approach.

We believe the Common Rule should explicitly state that its purpose is not to create a more complex system by promulgating a unique single IRB for every multi-site study. Managing multiple IRBs – as many as a different one for every multi-site study – would create a far greater cost and administrative burden for institutions than the current system. This would contradict the intent of the proposed policy. We urge OHRP to avoid shifting these costs onto institutions that are already struggling with the considerable and rising expense of research compliance. OHRP should explore appropriate mechanisms for alleviating such costs. For example, could a federal agency such as NIH create electronic tools or template documents that could ease the burden of participating institutions?

It takes time to set up and smoothly administer a central IRB. The most successful models of single IRBs for multi-site trials, such as those developed by the University of California system and the National Cancer Institute's CIRB, took significant time to establish. Agreements among institutions take a substantial amount of time to negotiate, particularly when individuals from many states, each subject to their own distinct state laws and regulations, are involved. Likewise, these agreements are likely to evolve, as institutions become accustomed to new relationships and joint processes and procedures. We are concerned that the proposed rule does not recognize the time and effort this endeavor will entail, and assumes an overly simplified view of establishing a single IRB of record.

Developing the infrastructure to support this effort will involve significant financial costs. AAU and APLU member institutions report that while using single IRBs for multi-site studies has the potential for long-term cost savings and reduction of burden when implemented well, reaching that point requires a substantial initial investment. These "start-up costs" include but are not limited to: the creation of electronic management systems that are interoperable among institutions; the adaptation of automated processes to multiple institutions; the communications tools necessary to link investigators and IRBs; the staff time necessary to develop agreements,

[7] AAU-APLU Response to ANPRM on Human Subjects Protection. October 25, 2011.
[8] NIH Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. December 3, 2014.

consensus documents, or standard operating procedures; and the interaction necessary to build and maintain trusting relationships among institutional officials. Even for institutions not serving as the IRB of record, there are real financial implications of participating in the centralized process in terms of adapting existing software systems and protocols.

In some cases, central IRB review does not adequately protect research subjects, and local review is most appropriate. AAU and APLU agree that there are instances where issues could be addressed through the use of ad hoc consultants or submission of additional information, and other issues could be clarified through the issuance of additional guidance. However, there may be situations in which a local IRB review is relevant and the rule should allow for an exemption from the mandate. Examples could include well-documented local sensitivities to specific research or differing interpretations on ethical issues between partnering institutions. We do not expect that these would be frequent occurrences, but we do believe it is important that the policy leave flexibility for an exemption in the unique circumstances that will inevitably arise.

In summary, we do not support a single IRB mandate, but we can accept a gradual implementation of single IRB review that includes explicit opportunity and funding mechanisms for exceptions where additional local review is most appropriate. Implementation of the proposal as written -- even with three years before implementation is required -- will result in large unfunded expenses and unnecessary disruption of research conduct without achieving significant improvements in human subject protections or the cost savings suggested by the NPRM.

NPRM Proposal to Extend the Common Rule to All Clinical Trials

Generally speaking, we are concerned about the proposed extension of human subject protection regulations to all research regardless of funding source, including non-federal funding sources (at §_.101(a)(1)). Our concerns are grounded in the current extraordinary burden and cost of these regulations. However, we 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.

Such overarching regulations are not without precedent when it comes to protecting human health and safety: compliance with the Select Agent regulations controlling dangerous pathogens, for example, is not dependent on funding source. Therefore, we do not object outright to the proposal to extend federal protections to all research. However, 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 subject 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 extending the federal regulations might have an overall effect of decreasing human subject protections by driving away some organizations from accepting any federal funding, thus removing any oversight of their work. While this would not be the case at research universities, whose partnership with the federal government is longstanding, it is quite possible for smaller entities. We do not believe that is the intent of the Common Rule revision, and would urge OHRP to consider fully the implications of such a change. Finally, the administrative component of federal Facilities and Administrative (F&A) reimbursements is capped at 26 percent for universities, and institutions already routinely spend considerably more than this. It is important that the new regulations add no additional compliance costs to institutions; ideally, they should 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 subject protection, 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, and when the varying requirements involve human subject protections, this cannot help but lead to a weakening of the system for protection of human research subjects. We generally support harmonization of definitions, interpretation, and reporting requirements across agencies regulating research involving human subjects, particularly between OHRP and the Food and Drug Administration [Questions 72-74]. We agree with comments filed by COGR in response to this NPRM 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 redundant and does not improve the protection of research subjects. Such duplicative review, which may involve an agency IRB and/or peer review panel, only serves to delay research progress.[9]

Regulatory Implementation

We are concerned that the NPRM underestimates several hurdles to successful implementation. Among those hurdles are providing adequate notice to participants and implementing the undefined process for opting out of research participation. We support the SACHRP recommendation that "HHS develop guidance explaining how to implement the notice of research practices and opportunity for opt-out process." We further agree that "the goal of offering notice and opportunity for opt-out should be to assure that the notice is thoroughly distributed, available on an ongoing basis, and is as effective and clear as reasonably possible and that opportunity to opt-out is offered in ways that allow all concerned individuals to assert their rights."[10]

We would further point out that many of this NPRM's cost estimates are based on inappropriate or flawed assumptions, or on opaque methodology. Contrary to the presumptions of the NPRM, institutions relying on a single IRB will experience little or no cost reduction over the long term;

[9]December 12, 2015 http://cogr.edu/Comments-on-Common-Rule-NPRM-and-Summary

[10] SACHRP Commentary on the FDA Draft Guidance Entitled, "Informed Consent Information Sheet; Guidance for IRBs, Clinical Investigators and Sponsors. February 11, 2015 Letter to HHS Secretary, http://www.hhs.gov/ohrp/sachrp/commsec/february11,2015lettertothehhssecretary.html

in fact, the institution taking on the central IRB role will see additional costs. The NRPM Regulatory Impact Analysis (RIA) states that the two primary areas of institutional savings will be on IRB members (faculty) and staff. The RIA presumes 100-percent cost savings in these categories for institutions that are not selected as the central IRB, for every protocol that is reviewed. IRBs that currently rely on external IRBs report that there is generally no cost savings from a staffing perspective, because each institution's staff must coordinate the external review process. On this point, there is no mechanism within the current federal F&A reimbursement model for institutions taking on this responsibility to receive additional F&A reimbursement above the 26 percent administrative cap. New expenses will simply be new, long-term losses for the institution selected as the Central IRB. No institution will voluntarily take on this role if the funding to support it is solely transitional. Furthermore, it has been our experience that federal entities frequently underestimate the costs of complying with new regulations. As an example, the financial conflict of interest form mandated in 2011 by HHS for research funded by Public Health Service grants and cooperative agreements has required considerably more full time employees and costs than was estimated by HHS.[11]

Beyond financial barriers, as highlighted by the NAS report on "Optimizing the Nation's Investment in Academic Research," harmonizing the interpretation of the same regulation across federal departments is vital to reducing uncertainty and mitigating additional unnecessary documentation by universities. The Office of Information and Regulatory Affairs (OIRA) and the Office of Science and Technology Policy (OSTP) are critical actors in the harmonization process.

Conclusions

We wish to underscore a common source of concern expressed throughout our comments: no matter how worthwhile the intent of changes to human subject protections, the effects of such changes ultimately lie in the implementation details. Several sections of the NPRM need to be further developed, clarified, or defined before proceeding to final rule. As we have delineated in this letter, there are six specific proposed changes contained in the NPRM that we believe are not adequately developed and which should be more carefully considered. There items are:

- a proposed fundamental, yet undetermined, change to the definition of human subject;
- an undeveloped broad consent template;
- an undetermined "list" of explicit exclusions from the Rule;
- a to-be-developed Secretary's list of "minimal risk" research;
- an undeveloped tool to determine research exemptions; and
- undetermined and undeveloped data protection requirements including "HIPAA alternatives" and "data security determinations."

[11] The American Association of Medical Colleges (AAMC) report, "Implementing Regulations on Financial Conflict of Interest: Results from the AAMC Conflict of Interest Metric Project" found that after the regulations were implemented, personnel administering COI-related activities at 71 institutions increased on average from 1.9 FTE employees to 2.7 FTE employees. Participating institutions also were asked in 2012 to predict the annual administration costs of their COI programs following implementation of the rule and then report what the actual annual costs were the following year. In 2012, 61 institutions estimated that it would cost an average of $289,016 annually and reported in 2013 an actual cost of $329,078. Many of the NPRM's cost estimates are based on inappropriate assumptions and opaque methodology.

We recommend that OHRP issue a separate ANPRM on these six item items and that this occur following the conclusion of this NPRM comment period.

We concur with COGR that OHRP should publish beneficial, non-controversial items in a final rule as expeditiously as possible, and at least within the next year. These include elimination of continuing review for minimal risk studies that qualify for expedited review; identification of the types of research that are excluded from the regulations, with an indication that the list is not all-inclusive as well as development of proper guidance for investigators; adding a new provision that would explicitly give Common Rule departments and agencies the authority to enforce compliance directly with unaffiliated IRBs that are not operated by an assured institution; expedited review for studies on the Secretary's List unless the reviewer(s) determine(s) that the study involves more than minimal risk; and the elimination of the requirement that the IRB review pre-award grant applications for congruency with IRB applications. We believe these revisions would appropriately reduce administrative workload for investigators and associated costs for institutions without reducing human subject protections.

AAU and APLU share OHRP's interest in strengthening protections for human subjects while reducing unnecessary regulatory hurdles for the research community. We seek to help ensure that the final rule achieves these goals.