January 5, 2016

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

Dear Dr. Menikoff:

Washington University in St. Louis (WU) is a private educational, research and clinical institution with a long-standing commitment to the discovery of new knowledge and its translation for the public’s benefit. Our research program engages faculty, staff, students and trainees in a variety of research activities and training programs across many disciplines. The WU FY15 research portfolio of $613M includes $457M of funding from federal sources which includes growing clinical and behavioral research programs in which human participants are a critical part of our success. We have long been committed to the protection of the rights, privileges and protections of our human participants and to the ethical and objective conduct of research. This commitment includes a strong belief in the principle of informed consent. We appreciate the opportunity to provide our comments in response to the Notice of Proposed Rule Making for the Federal Policy for the Protection of Human Subjects.

The stated goals of the NPRM to strengthen and modernize the regulations protecting human subjects and to decrease administrative burdens are praiseworthy and necessary. Given the impact on our research community, we felt it was imperative to share the proposed rule with our faculty, who have extensive experience in conducting research with human participants and with biospecimens. We sought their insights to better inform our responses, and these discussions with our faculty and administrators resulted in our conclusion that while some portions of the NPRM do further these goals other sections are presented without sufficient detail or are dependent upon yet to be developed forms, rules or instruments effectively precluding our ability to provide informed comment. Other sections of the NPRM appear to be at odds with the stated goals and actually create new burdens or barriers to research that will limit benefits to patients, reduce research productivity and increase cost without improving upon existing protections for human subjects.

The document is unnecessarily complex and hard to interpret. We discovered that it was extraordinarily difficult to educate our faculty on the elements of the NPRM. For example, a key element of the proposal describing the 10 year provision for the broad consent, were frequently misunderstood by our faculty. In many other areas, ambiguity was such that
reasonable individuals came to differing interpretations of the same language. We are concerned that these communication challenges arise from a Proposed Rule that is overly complex, confusing and, if enacted as written, will result in institutions such as WU struggling to implement and assure compliance. Because of these issues with clarity and completeness, we strongly urge you to rewrite the Proposed Rule as a more concise, organized and clear document and republish it as an NPRM for a second comment period.

The following summarizes our major responses to the Proposed Rule, which are explained in more detail in subsequent paragraphs.

- We strongly oppose expanding the definition of a human subject to cover investigations with non-identified biospecimens.
- We oppose the Broad Consent process as complex, costly and a barrier to research that fails to meaningfully enhance participant protection. Instead, we propose a requirement for increased transparency for human research participants to better understand the value of use of their biospecimens in research.
- We oppose the proposed transition provision requirement to de-identify all previously collected biospecimens, including those for which full consent or an IRB approved waiver of consent has been obtained.
- We support revisions to exemptions, although the section on the use of a yet to be developed and tested exemption tool is vague and incomplete.
- We support the use of single IRB in cooperative trials, where appropriate, but do not believe this should be mandated as part of the Common Rule.
- We support the extension of the Common Rule to many clinical trials but believe the extension should not include trials that are not greater than minimal risk.
- We support the use of shortened and simplified consent forms but note that no examples or directions are provided for us to assess as part of this response letter. Failing to provide such examples diminishes the substance of this section.
- We believe the NPRM grossly underestimates the cost and burden of implementing the proposed rules and grossly overestimates the savings.

Expanding the Definition of Human Subject to Cover Research with Non-identified Biospecimens

Comments from the faculty at WU indicated that this is the most controversial section of the NPRM and the one that our faculty believes has the greatest potential to limit important research without meaningfully improving the protection of human subjects. Simply stated, de-identified specimens are not human subjects. One of the rationales for this proposal seems to be that participants want to control use of their specimens. In our experience, human research participants want to support research and a more transparent and robust notification process will produce a better understanding of the impact research has on the treatment of diseases that affect them and other members of society. The proposal emphasizes the principle of respect for persons over the principles of beneficence and justice to the point that appropriate balance is lost.
The NPRM proposes two alternatives to the inclusion of all biospecimens under the definition of a human subject. While these are more limited in scope than the general proposal, they depend upon technical definitions that are likely to change in the foreseeable future. We do not support either alternative, as they will limit important research without enhancing participant protection.

In summary, we strongly oppose expanding the definition of a human subject to non-identifiable biospecimens, and propose that secondary use of such biospecimens continue to be outside the scope of the Common Rule.

**Broad Consent**

We join our faculty, who have extensive experience with consenting research participants, to oppose the use of a broad consent process for the use of all biospecimens for the following reasons:

1. Broad consent does not provide true protection of an individual’s autonomy interest but rather an illusion of such. By definition, the broad consent will be so vague and generic that it cannot provide a meaningful informed consent for the participant. The processes implemented would likely be highly routinized with limited ability to convey any substantive information about the possible research uses of the biospecimens or provide any opportunity for discussion. Even if implemented in a more meaningful way, it is impossible for the participant or the investigator to anticipate the nature and extent of future uses further questioning the significance of such consent.

2. Requiring broad consent for clinically obtained samples will reduce the number and variety of biospecimens available for research. Patients come to the hospital for clinical care. These are patients who are often in pain and worried about their health outcomes and not in a frame of mind to give a broad consent full consideration, or distinguish it from other consents they are asked to sign. Coupling consent for research with the provision of clinical care may unduly influence the patient to sign out of concern that a refusal may affect subsequent treatment. We are concerned that the timing of the Broad Consent may result in an environment in which an individual may not be able to fully comprehend and provide informed consent that is actually consistent with their individual beliefs, values and goals.

We are also concerned that the Broad Consent and the associated tracking requirements may cause difficulty for some smaller or resource constrained facilities from participating in the collection and transfer of biospecimens. If such facilities opt out of this type of research activity, we worry biorepositories may not then reflect the true diversity of our patient populations. If this happens, research results will not be generalizable to these diverse populations, thereby limiting benefits for improving health outcomes. This is particularly problematic as we move forward with initiatives such as the precision medicine initiative, in which having a full understanding of the diversity of the population is essential.
3. Obtaining Broad Consent will be costly and difficult, if not impossible, to operationalize in many environments. Health care entities that do not routinely conduct research, particularly in small and rural hospitals, will not be able to take on this responsibility, and will not be able or willing to invest the personnel and resources necessary to implement such a system. Major academic centers will need to hire and train large numbers of skilled workers to obtain Broad Consent and develop and maintain complex IT tracking systems. This unfunded mandate is costly, complex and at risk for failure. What if a patient signs a Broad Consent with one doctor but not another or in one health system but not in another? The creation of large databases of who did and did not sign Broad Consent will place patient confidentiality at greater risk as any database can be compromised. No outside funding will be available to support these activities, thus, pulling dollars from already scarce research funds.

4. As we already mentioned, the proposal for re-consent at 10 years is widely misunderstood as a requirement to stop using any samples collected during this time. Further confusion exists as to whether the samples need to be destroyed if re-consent is not obtained. Our faculty believes 10 years is an arbitrary number unrelated to any information or data supporting the protection of participants.

As an alternative approach, we support requiring a more robust and transparent notice to the participant providing information about the research use of clinically obtained biospecimens. This could be accomplished by providing patients with a notification of research practices at their initial and subsequent contacts with the institution, as well as increased public education and awareness campaigns. Information to be provided might include a general description of the types and scope of research performed at the institution, whether data and/or specimens might be more broadly shared and a point of contact for additional information requests. We do not support an opt-out provision as this would also require implementing burdensome tracking methods and would likely reduce the number and variety of specimens available for this highly beneficial, minimal risk research. We believe this approach appropriately respects individual's dignity by informing them of the potential uses of their excess biospecimens while balancing the public good achieved by facilitating important research.

In summary, the proposed requirement for Broad Consent does not enhance participant autonomy and creates a costly, complex system that will have a high failure rate and will limit the accumulation of biospecimens critical for research that will benefit individuals and society. The appropriate balance of the competing ethical principles can be better struck by alternative approaches.

**Explicit Exclusion of Activities from the Common Rule**

With a few caveats, we support the creation of excluded activities to better clarify which of these activities fall outside of the Common Rule. In our experience, many of these exclusions provide much needed clarification to areas that have been interpreted inconsistently. In particular, our faculty strongly agrees that oral history, journalism, biography and historical scholarship focused on the individual be excluded to remove the current regulatory burden from these types of activities. However, we strongly urge OHRP
to supplement each of these exclusions with clear guidance and examples to prevent misinterpretation. For example, with regard to oral history, journalism, biography, and historical scholarship it is not clear if these are strict limitations based upon academic discipline or examples of a type of research activity that is excluded. Language clarifying this should be included in the final rule to make this point clear. Finally, we ask that the terms used in these exclusions be carefully reviewed before the final rule is released. Terms such as “accepted practice” and “public health surveillance activities” need further definition to make the rule clear and unambiguous.

We support the continued exclusion of quality improvement and quality assurance activities from IRB oversight. These activities are essential functions of any responsible health care and/or research environment. However, as written, the current exclusion would appear to forbid the collection of any outcome data that measures the effectiveness of the QA/QI intervention, even if determining the effectiveness is not the primary aim of the study. Furthermore, minimal risk interventions, such as comparing the effectiveness of two different types of hand cleanser, would be subject to IRB oversight with no meaningful participant protection provided. We urge that the final rule contain greater clarity as to the types of activities that would be specifically excluded and consider excluding minimal risk interventions that are designed to test the effectiveness of such interventions.

We do not support dividing the excluded list into explanatory groupings under which the exclusions have been categorized. While beneficial from a descriptive standpoint, this artificial separation will only serve to confuse interpretation as has been evidenced in the reading of the NPRM. The categories should be removed and all exclusions listed under one heading. The explanatory text could be included in a preface to the exclusions as a whole.

Proposal to Extend the Common Rule to All Clinical Trials
We support the rationale for extending oversight to all clinical trials and close the “gap” on some trials that may currently not be subject to regulation. However, it is important that this not be extended to those studies where no additional protections are required. One of the major goals of the NPRM is to match the level of scrutiny to the level of risk for a participant in a research project. We believe that extending oversight to studies that involve only minimal risk, and, in particular, to behavioral minimal risk studies is not appropriate. We support the Council on Governmental Relations’ (COGR) proposal of including only studies that represent more than minimal risk in this expansion.

Revisions to Informed Consent Requirements to Limit Content, Create Appendices, Add Elements, and Require Posting to a Public Website
Our faculty experiences with consents indicate that there is too much information provided for the average person to easily understand. Therefore, we strongly support the idea of reducing the amount and type of information that is standard in current consents. Unfortunately, no examples are given nor is any advice provided as to how to achieve this goal. Templates that provide information at an appropriate reading and health literacy level for all participants are critically needed. However, it appears that many of the current struggles about consent documents have not been addressed and instead have been relegated to appendices. We anticipate that many sponsors will be resistant to the changes
proposed and that difficult negotiations will continue to slow the review process and reduce the effectiveness of this proposed rule.

There are many questions yet to be resolved with regard to a new consent document. For example:

- What information is considered necessary for an average person to make an informed decision?
- What information will be placed in the appendices?
- Will information in the appendices be limited or specific?
- Will the participant be required to read and/or sign the appendices?
- Should the researcher explain the information in the appendices?
- Are IRB's obligated to review all information in the appendices and any subsequent changes to them?

Depending on the answers to these questions, whether or not the use of an appendix or appendices reduce and simplify information provided to subjects remains to be determined.

Our faculty and administration have a few additional suggestions for consent forms.

- We do not support continuing to mandate inclusion of the risks of standard of care drugs or procedures in any area of the consent. This information further obscures the difference between the research intervention and standard clinical care, making it more difficult for the potential participant to decide whether to enroll in the study.
- Contractual terms between the institution and sponsor with regard to who pays for participant injury and the conditions for payment should be prohibited in the consent or appendices. It is well-established that the subject is not a party to the contract between the sponsor (whether federal or commercial) and the awardee, yet the consent is used to document and burden the participant with unnecessary information regarding injury payments.
- We support the revisions to the elements of consent and the additional elements of consent with one important exception. We strongly disagree with the requirement to provide an option for the subject or the representative to consent, or refuse to consent to investigators re-contacting them to seek additional information or biospecimens or to discuss participation in another research study. Several years ago, Washington University specifically removed such language from all of our consents due to the confusion it caused with both research subjects and investigators. How is this tracked when a subject could say yes to one researcher and no to another? What happens when researchers on a project change? Is the option specific to the study, to a researcher, to a particular hospital or institution? What if the participant changes his or her mind or might want to know about a future research project that is not even conceived at the time they say no to future contact? How are children’s decisions tracked or do their parents choose? Do children then need to be re-contacted when they become adults? The current IRB
review process sufficiently protects participants through scrutiny of identification and recruitment methods without making this onerous and unachievable tracking infrastructure a regulation. Rather, the regulations should focus on those requirements that truly add protection to human subject without overloading the research community with minimally useful regulatory burden.

- We also do not support the proposal to require posting of informed consents at the conclusion of recruitment. This serves no purpose in the protection of human subjects and only creates a rich environment for litigation and motivation for even more complex legal and contractual terms to be included at the mandate of sponsors. Additionally, many consent forms contain confidential or privileged information that, by contract, may not be publicly disclosed. Requiring these documents to be posted seemingly in an effort to use “public shame” to improve quality will simply not work to achieve the stated goals. Instead it will only create a new requirement for IRBs to monitor compliance with this policy, further increasing burden and cost.

Revision to Exemptions and Use of Exempt Tool
We support the exemption categories provided in the NPRM and in concept, the exemption determination tool proposed. However, because the tool has not yet been developed, meaningful comment is not possible. The use of the exempt tool does not actually reduce researcher burden. A majority of research institutions have already created short tools and processes for making exempt determinations that allow researchers to complete a brief set of questions that determine and document an exempt decision. We cannot comment on whether a yet to be developed tool and tested tool will be an improvement over other tools already in use.

New Regulations Regarding Protection of Biospecimens and Identifiable Information
This section describes the need for institutions and investigators to implement and maintain reasonable and appropriate safeguards to protect biospecimens and identifiable private information. We support the need to have such safeguards in place but urge that the level of safeguard mandated be appropriate to level of risk. We do not believe the NPRM currently provides sufficient information for an informed comment, as all of the specific measures to be required are not included. Instead it is noted that these will be published at a later time for public comment. We hope that any such list would not include requirements at the level of the National Institute of Standards (NIST) This level would be beyond that required for much of the research that is not covered under the HIPAA regulations. Standards must be calibrated to the level of risk such that there is not an unnecessary burden imposed without a real increase in human participant protection.

In summary, we agree that institutions and investigators need to maintain reasonable standards to protect biospecimens and identifiable private information. Unfortunately the NPRM does not provide clear guidance as to how it is expected that this will be achieved.

Regulatory burden and cost
We are concerned that the NPRM grossly underestimates the costs for implementation of the proposed changes and overestimates the savings that will ensue. The cost estimates
are based on salary levels that are almost 20 years old and also underestimate the time personnel will need to spend learning, implementing and disseminating information concerning the new regulations. The time and effort of senior administration to implement changes does not appear to be included in the estimates. The NPRM analysis overestimates cost savings because excluding an activity from the Common Rule does not remove it from institutional oversight but merely shifts the burden without generating savings.

Transition period
We support the transition provisions with one exception. The NPRM proposes that biospecimens collected prior to the effective date can only be used going forward if they are de-identified. This does not respect the participants who have already signed full consents to allow for identified samples to continue to be used in an identified manner for future research and for an unlimited time period, or for which an IRB has carefully considered and provided a waiver of consent. The transition would thus override the express and documented consent of research participants who in good faith contributed their samples for what they believed would be beneficial to science. Requiring removal of the identifying information would greatly reduce the value of the specimens and information that they could contribute to research. Any biospecimens with consent for current or future use with identifiers should honor the consent conditions signed by the research participant, or the prior granting of a waiver of consent by an IRB.

Changes Anticipated to Reduce Regulatory Burden
There are a number of features of the NPRM that do meet one of the stated goals of NPRM, which is to reduce regulatory burden. These include:

1. The new exempt category that includes research involving benign interventions in conjunction with a collection of data from an adult subject through verbal or written responses agrees with the NPRM stated goal of matching oversight to level of risk.

2. The new category for waiver of documentation of consent that states “If the subjects are members of a distinct culture or community for whom signing documents is not the norm so long as the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting informed consent was obtained, the requirement to obtain a signed consent form may be waived” also agrees with the NPRM stated goal of matching oversight to level of risk.

3. The proposal to eliminate continuing review for minimal risk studies is a welcome development. It should be noted that investigators will still need to answer questions about the status of the study and the IRB will need to document the information.

4. The elimination of the requirement that grant applications must undergo IRB review and approval for the purposes of certification will reduce investigator and IRB burden without diminishing participant protection.

Summary
While we applaud the efforts to update regulations governing such a critical part of our research programs, we urge OHRP to seriously consider our comments along with those of our professional associations such as the Association of American Medical Colleges, the
Council on Governmental Relations, and the Association of American Universities. We were encouraged that our faculty were committed to providing their voices to the preparation of this response and believe that it demonstrates their support of fair and reasonable regulations that truly protect human participants. It is imperative, however, that new regulations are clear, evidence based and facilitate research into health issues that are of concern to the very participants and communities the regulations are attempting to protect. We do not believe that the current Proposed Rule achieves these expectations.

Sincerely,

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