Jerry Menikoff, M.D.,J.D.
OHRP
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Dear Dr. Menikoff:

Washington University in St. Louis 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. The WU research portfolio of $613M at the end of our FY2015 includes $457M of funding from federal sources. Our research program engages faculty, staff, students, and trainees in a variety of research activities and training programs across a broad spectrum of disciplines. Many of our faculty members are active in programs such as peer review panels and research councils in addition to conducting their own exciting research. We are committed to the stewardship of the funds we receive from our many sponsors and to the ethical and objective conduct of research. 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 are to strengthen and modernize the regulation protecting human subjects and to decrease administrative delays.

The goals are praiseworthy and appreciated. After extensive discussions with faculty and administrators at Washington University we conclude that some sections of the NPRM do further these goals. Other sections are presented without sufficient detail or depend upon yet to be developed forms, rules or instruments so as to preclude informed comment. Finally, other sections of the NPRM appear to be at odds with the stated goals and create burdens or barriers to research that will

limit benefits to patients, reduce research productivity and increase cost without protecting human subjects. We will highlight our major responses below which will then be presented in greater detail.

- 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.
- 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 which means this section lacks substance.
- We support the proposed transition provisions with the exception of the requirement to de-identify all previously collected biospecimens, including those for which full consent or an IRB approved waiver of consent had been obtained.

- 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

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 improving protection of human subjects. The proposal lacks face validity in that non-identified specimens are not human subjects. The rationale for this proposal is that participants want to control use of their specimens. However, participants also want to support research and that will produce better understanding and treatment of diseases that affect them and other members of society. The proposal emphasizes the principle of autonomy over the principles of beneficence and justice to the point that appropriate balance is lost.

The NPRM proposes two alternatives to 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 which 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

This section of the NPRM and the previous one on the secondary use of biospecimens are closely linked but we have chosen to separate our responses for clarity. Our faculty strongly opposes the use of a broad consent process for the use of all biospecimens for the following reasons:

1. This is not a true protection of autonomy but rather an illusion of autonomy. The broad consent will by necessity be vague and generic such that it is not going to be a meaningful informed consent for the participant. The processes implemented would likely be analogous to HIPAA privacy forms which we all routinely sign while ignoring the content. 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 coming to the hospital for clinical care, and in particular those in pain or worried about their health are not able 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. Thus, the individual may not give the full consideration needed in order to determine if agreeing to this truly is consistent with their goals and values. We believe it is a near certainty that some ethnic groups, minorities and economically disadvantaged individuals will be far less likely to sign the Broad Consent. This means that research results will not be generalizable to these groups and they will not receive full benefit from future research. 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. Even 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 certain to have a high failure rate. 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 data bases 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. 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 showing it enhances patient safety.

In summary the use of a 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.

Explicit Exclusion of Activities from the Common Rule

With a few caveats, we support the addition of excluded activities to better clarify those activities that fall outside of the Common Rule. Many of these exclusions provide final 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 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, the general interpretation of __.101(b) (1) (ii) with regard to oral history, journalism, biography, and historical scholarship is that these are the only categories that can be excluded. However, we now understand these were intended to be examples. Language to this effect 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

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.
- 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 posted publicly. Requiring these documents to be posted seemingly in an effort to use "public shame" 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 are concerned that the level of safeguard 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. 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 could 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.

Changes Anticipated to Reduce Regulatory Burden

There are a number of features of the NPRM that we believe do meet one of the stated goals of NPRM which is to reduce regulatory burden. These include:

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

We are pleased to offer these comments on the proposed changes included in the NPRM.