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

Re: Docket Number HHS-OPHS-2015-0008, Notice of Proposed Rulemaking: *Federal Policy for the Protection of Human Subjects,* published in the September 8, 2015 *Federal*
*Register* (80 FR 53933)

Dear Dr. Menikoff:

The University of North Carolina at Chapel Hill welcomes the opportunity to provide feedback on the Notice of Proposed Rulemaking (NPRM) published in the September 8, 2015 Federal Register (Docket ID number: HHS-OPHS-2015-0008, *Federal Policy for the Protection of Human Subjects* (80 *Federal Register* 53933 The University of North Carolina at Chapel Hill is an academic institution committed to research excellence and to the highest levels of human subject protections in that research The University of North Carolina at Chapel Hill ranked eighth among leading private and public research universities for the level of federal funding ($623.24 million) devoted to research and development in all fields during fiscal 2013, and research funding for fiscal year 2014 totaled $792,729,006.

We commend the federal agencies for proactively and thoughtfully engaging in this review of the Common Rule and human subject research regulation. We believe that it is possible to meet the agencies' goals to modernize, strengthen and increase efficacy of human subjects protections with regulations that are reasonable, evidence-based, and that reflect the needs and values of all those engaged in the research enterprise. Certain of the proposals contained within the NPRM are an important step in that direction.

We concur with the overarching principle of calibrating the level of review to the level of risk and support the idea that, if done well, such an alignment would maximize protection for human research subjects, while also reducing undue burden on institutions and investigators. However, based on our analysis of certain proposed provisions, we conclude that the processes outlined in the NPRM may actually increase complexity and the workload of institutions and investigators involved, rather than create a system in which the burden of regulation diminishes according to the level of risk to subjects. Additionally, as outlined in this letter, we have serious concerns about the feasibility of some specific proposals and the lack of clarity in some of the specific revisions proposed in the NPRM.

**New "Exclusions" and Revisions to Exemptions**

We endorse the first set of six exclusions of activities that are deemed not research. However, as indicated below, we have concerns about the additional four categories. As noted in the NPRM, there is no information outlining how decisions about what is excluded will be made and how differences in such decisions amongst collaborators would be handled. Therefore without further details, at this time, we cannot support such a determination process for the additional four exclusion categories.

If investigators are to be empowered or required to make their own exempt and exclusion determinations, it could be done, but it is important to ensure that is done properly. There should be consistency across institutions utilizing a mandated decision tool. That said, it is vital that the NPRM assures that additional recordkeeping requirements do NOT accompany the decision tool as this would undermine the stated goal of decreasing administrative and regulatory burden. The lack of a published, vetted decision tool as part of this NPRM is deeply troubling if the use of such a tool is to be required under a forthcoming final rule, because it does not allow institutions to make a measured, rationale assessment of the proposed process.

**Definition of Human Subject and "Broad Consent"**

We do not support the inclusion of biospecimens in the definition of human subjects because it appears to narrowly address an area of current government focus without appropriately calibrating proposed requirements with the balanced objectives of protecting human subjects and facilitating valuable research. Further, it does not recognize the adequate protections currently in the Common Rule.

The discussion in the NPRM seems to indicate that biospecimens cannot be rendered non-identifiable. While there is no doubt a biospecimen can be used to identify an individual, both the specimen where the identity of the individual is unknown and information where the identity of the individual is known are required to do so. Further it seems more likely and technically much easier to identify individuals from other linkage data rather than from biospecimens. However, if OHRP believes biospecimens cannot meet the standard of not-identifiable, then this is best addressed through a clear guidance rather than a change to the Common Rule.

We acknowledge the important concerns raised by the public regarding autonomy and note that a central component of autonomy is that an individual have the opportunity to make an informed decision. We respectfully find that the "broad consent" concept proposed in the NPRM is neither informed nor meaningful. Meaningful, informed consent requires an engaged dialogue, as well as individuals who appreciate the importance of, and dedication required for, obtaining that meaningful consent. While the NPRM points to literature regarding the public's desire to agree with use of their biospecimens, the NPRM provides no evidence that the process it envisions would meet public expectations.

With respect to the questions of whether providing a definition of biospecimen and a clearer definition of identifiable private information in the regulation would be helpful, we think not and believe if clarification is needed it is best accomplished through guidance which would dynamically allow the definition to be modified as our understanding of biospecimens and identifiable private information evolves. As definitions and current thinking further mature, it is vital for IRBs to retain flexibility in decision making. With regard to the questions related to non-identified biospecimen broad consent implementation and burden to investigators and institutions, we believe the proposed regulatory changes will result in significant unfunded costs and burden for investigators and institutions. As other institutions have clearly explicated, we believe the cost estimates in the NPRM are inaccurate underestimates based on incomplete information or flawed assumptions and methodology.

**Waivers of Consent**

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 ability to protect subject safety and autonomy and ensure ethical human subject research. For research involving biospecimens or identifiable private information, we believe that that IRBs should be entrusted to grant a waiver of consent based upon whether, (as suggested by SACHRP), scientific validity would be compromised if consent were required, ethical concerns would be raised if consent were required, a scientifically and ethically justifiable rationale exists for why the research could not be conducted with a population from whom consent can be obtained. In exercising this experienced discretion, IRBs could continue to ensure that the granting of waivers not be determined solely by considerations of convenience, cost, or speed.

In general, we do not 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, with regard to whether or not the waiver criterion regarding "practicably" at ___.116(d)(3) should be explicitly defined or otherwise clarified, we concur that additional clarification and guidance would be helpful. As above, we believe the provision of further definition and clarification would best be addressed through guidance rather than through revisions to the regulations to enable a dynamic and flexible regulatory regime that might better keep pace with the ever evolving research landscape. We agree with the clarifications regarding the definition

and application of “practicably” provided by SACHRP and urge that this guidance be adopted by HHS and the other Common Rule agencies.

With regard to the proposed differences between the criteria for waiving informed consent for the research use of biospecimens versus identifiable private information, we are not in favor of such differentiation. While we support increased protections for biospecimens, we believe the potential risks related to the research use of identifiable private information are at least as great. For this reason, the protections and waiver criteria should be equivalent for the research use of both types of materials/data.

IRBs should be allowed to exercise discretion, informed by agency guidance, on a study-by-study basis to determine when a waiver of consent for use of biospecimens would be appropriate and such authority should be included in the regulations. We disagree with the presumption that waivers should be granted sparingly as there are instances when a waiver of consent would be appropriate, and IRBs should not be limited in their ability to balance the rights of subjects with the benefits of research by prohibiting an IRB to waive consent.

We feel it is crucial that IRBs be allowed to grant waivers for secondary research use of information or biospecimens. Where an IRB required consent for the original research, it should continue to be at the IRB’s discretion to determine if consent for the secondary use of information or specimens can be waived, and the regulations should allow an IRB to determine if the original consent is appropriate for the secondary use relevant to risk or benefit as appropriate for the individual study.

It is our opinion that investigators are more likely to avail themselves of those provisions within the NPRM under which certain research can be conducted without specific consent, e.g., the exemption at § ___.104(e)(2), rather 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 affecting 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, leaving important research specimens untapped. Approval of the secondary use of identifiable private information is a decision which should be made by the IRB based on the circumstances and nature of the research proposed. An “open-ended” consent may well be rejected by a participant, while consent for a narrower use, e.g., additional research of the same nature or for the same purpose, is likely to be given. The reality is that there are significant costs, time and effort involved in implementing and maintaining a tracking system for obtaining broad consent and little incentive for doing so if a participant’s refusal to give broad consent is considered a refusal of consent to use for all other research purposes.

We believe 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 and would not serve the goal of research institutions and federal sponsors to foster the sharing of knowledge. IRBs are best

situated to assess and balance the benefits and risks of re-disclosure on a project-specific basis, and to review the individual plans for safeguarding information and biospecimens for a given study. Institutions should be given the option to implement local policies designed to protect the security of the biospecimens and identifiable private information within the research portfolios of their institution, consistent with agency guidance and the principles of human subject protection with which they are well versed.

**Issues related to Secondary Use of Biospecimens or Identifiable Private Information**

In § __.101(b)(2)(ii), additional protections for publicly available information even if it is sensitive are not warranted beyond those already existing under the Common Rule. However, the research community does need a clear and unequivocal definition of what represents identifiable information (such as the 18 identifiers defined by HIPAA or the personally identifiable information as defined by OMB and referred to in Question 3 of the NPRM).

In § __101(b)(2)(iv) the exclusion seems to represent more of a "bookkeeping" change of shifting the oversight from 45 CFR 46 (Common Rule) to 45 CFR 160 and 164 (HIPAA). It should be noted that this exclusion will not significantly reduce the impact for the investigator or IRB as oversight of these activities will still likely sit with the IRB; however now in the IRB's role as the institution's research privacy board under HIPAA.

The broadening of the definition of information from "existing" to "has been or will be acquired" is a welcome change as it eliminates a component of the previous exemption category 4 that was open for open subjective interpretation and unnecessarily complicated the research process.

In regards to the concept of "prior notice" for the exemption of identifiable secondary information § ___.104(e): there is not enough information or detail in the NPRM to allow IRBs to consider what prior notice really means, what it should include, or how IRBs or researchers will be required to document or verify that prior notice was given. Would a HIPAA notice suffice? What about researchers in the social and behavioral sciences who don't have this functionality and want to share non-research information? Without clear guidelines, implementation of this exemption will be complicated. For example, is placing a sign in the middle of an inner city ER that information gathered about effectiveness of HIV or asthma education may be used for research acceptable notice? Also, we cannot discern the difference between the information referred to in categories § __.e(2) and § __.f(2), as it seems by definition information that is being used secondarily for research had to be stored or maintained after its original use for this purpose.

Similarly, if the exempt categories in § __.104(f) (data/specimen repositories and secondary use) require use of the expedited review procedure to determine that a project meets regulatory approval criteria at § ___.111(a)(9), then conceptually it would be more appropriate to include them on the expedited list rather than defining this as

exempt research. The current concept of exempt projects is that they are not subject to regulation; the new rule imposes a regulatory review requirement. In addition, these projects would not qualify for self-determination by investigators because they require an IRB review. Per § __.109(f)(1)(iii), continuing review is not required for these projects "requiring limited IRB review" (as well as other projects undergoing expedited review).

Although section § __.105 is not concerned with secondary use per se, a requirement of secondary use of identifiable data in § ___.101e(2) and f(2) is that the safeguards for information protection in § ___.105 be followed. Unfortunately it refers to unspecified measures to be published in the future or to apply safeguards provided by HIPAA or other federal regulations/agencies.

In § __.116(e) the provision indicating that an IRB cannot waive consent for either the storage or maintenance for secondary research use, if an individual were asked to consent and then refused, will result in increased administrative burden and a reduction in participant rights. As a result, the process of documenting refusal becomes a paradox that researchers and administrators will have difficulty implementing. Furthermore, it is not typical to document dissent during a consenting process without the appearance of harassing the potential participant and/or violating the potential participants' autonomy to decline providing information to researchers that documents their decision not to participate.

**Mandated Single IRB for Multi-site Studies**

The biomedical research landscape has evolved dramatically, and research with human subjects has become an increasingly complex endeavor in which multi-center, rather than institution-based research is increasingly the norm. In light of this shift, it is reasonable to consider whether an alternative structure for research review better safeguards the rights and welfare of research participants and lessens unnecessary administrative burden. Indeed, we fully understand the interest in reducing inefficiencies associated with multiple IRB review motivating the proposed mandate that studies involving multiple institutions rely on a single IRB for review.

However, while the use of a single IRB can be a beneficial approach for *some* multi-site studies, we believe that a mandated single IRB review for all cooperative research is a not realistic option at this time. Many factors influence whether the use of a single IRB serves the interests of greater efficiency, reduced costs, and stronger protections for subjects. Such factors include the number and types of institutions involved, the study design, the degree of risk created for subjects (e.g., minimal risk or greater than minimal risk), the nature of the study team, and the resources available for investigators and local sites.

Further, there is a paucity of reliable empirical data on the various ways in which a single IRB can be used to provide ethical review of multi-site research, and on whether such review is better, from the perspective of subject protections, administrative costs, efficiency, and quality of review, than each site relying on a local IRB. In the absence of

sufficient evidence, we believe that a policy requiring the use of single IRBs for all multi-site trials is premature and ill advised. As in medicine, innovations in policies should be preceded by research and supported by adequate data. We understand that the NIH is currently investing in research directed at answering some of the relevant empirical questions related to the use of a single IRB, as well as alternative models for improving IRB efficiency. Accordingly, it would seem prudent to await the results of these studies prior to promulgating such a policy.

We might hope that these studies on the consistent use of a single IRB would address the many, as yet unanswered procedural questions and logistical challenges. For instance, local institutions still maintain overall responsibility and assume the liability for the work undertaken by their researchers. The scope of responsibility for the relying institution needs further clarification and the attendant risks of ceding review but retaining responsibility must be mitigated to enable institutions to feel comfortable agreeing to this new single IRB review process. Additionally, how will responsibilities for issues such as conflict of interest and post-approval monitoring be handled? These and other such issues are of great concern to institutions and need to be explicitly addressed before the adoption of a single IRB requirement.

Further, even if an institution is not serving as the IRB of record, the infrastructure necessary to adapt existing human research protection programs software systems and protocols to participate in the centralized process contemplated by the NPRM has real financial implications. Smaller institutions will have no way to recoup the costs of setting up the infrastructure necessary to administer participating in a central IRB. The final rule should avoid shifting these costs onto institutions that are already struggling with the considerable costs of research compliance. Simply put, this effort must not be an unfunded mandate. We are concerned that the NPRM does not recognize the time and effort this endeavor will entail, and presents an overly simplified view of establishing a single IRB of record.

Additionally, there are a variety of other reasons why an institution might strongly support the need for local review. Although some of these issues could possibly be addressed, as described by the NPRM, there may be situations where a local IRB review is relevant and the regulations should allow for an exemption from the policy beyond the current scope described. Examples could include well-documented local sensitivities to specific research or differing interpretations on ethical issues between partnering institutions. We believe it is important that the policy leave flexibility for exemption in the unique circumstances that will inevitably arise in a research enterprise as large and diverse as that supported by federal agencies.

**Elimination of Continuing Review**

With regard to the elimination of continuing review for those studies that qualify for expedited review, we do not support the proposed change. We believe this change does not significantly reduce regulatory or administrative burden and negatively impacts protection of subjects. However, if such an elimination of continuing review is implemented, we do NOT support the proposal that an IRB must receive annual

confirmation that the research is ongoing, no changes have been made that would require the IRB to conduct continuing review and that it still meets the criteria for expedited review. This would merely change one form of review and record keeping for another and would NOT decrease administrative burden.

**Relying on Documents, Processes or Details Yet To Be Decided**

We find it extremely problematic that several key elements of the NPRM have yet to be decided. Among others that have already been discussed, they include: an expedited procedures list that does not yet exist, a broad consent template that has not been developed, a "prior notice" concept that is not defined, a "limited IRB review" concept that is not explained, a data security standard that is not developed, and a "consent refusal" concept that is ambiguous. The relevant stakeholders of the research community, including those that will be required to comply with any forthcoming final rule, cannot meaningfully comment without the timely provision of these absolutely vital details. If the agencies' rulemaking proceeds without the opportunity for such feedback, it is at the peril of undermining their own stated goals of improving the effectiveness of the regulations in protecting human subjects and decreasing administrative burden, delay and ambiguity for investigators, institutions and IRBs.

**Conclusions**

In an effort to reduce ambiguity, the NPRM has instead reduced needed and appropriate regulatory flexibility, and in many cases it has introduced unnecessary complexity without the benefit of additional protections to human research participants. Many of the proposals are better suited to agency guidance instead of regulation. In summary, the NPRM as currently designed has not met its stated goals, We strongly urge you to carefully consider the constructive feedback you receive and utilize it to significantly revise and reframe the Common Rule in a way that has a positive impact on human research participants and the research community.

Sincerely,

Elizabeth Kipp Campbell, Ph.D., CIP

Director, Office of Human Research Ethics