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October 26, 2011

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

RE: HHS-OPHS-2011-0005  
Enhancing Protections for Subjects and Reducing Burden, Delay and Ambiguity  
for Investigators

Dear Dr. Menikoff,

Duke University appreciates the opportunity to provide comment on the Advance Notice of Proposed Rulemaking entitled "*Human Subjects Research Protection: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators*" (ANPRM). Duke University commends HHS for taking on the revision of the Common Rule regulations. As one of the leading federally funded academic research institutions in the country, Duke has extensive experience with the challenge the current regulations, crafted in 1981, pose for contemporary human research. However, the fundamental protections afforded by the current regulations remain of utmost importance. As regulatory changes are contemplated and enacted to reduce the burden on IRBs, researchers, institutions, and sponsors, the first consideration must be to the protection of research participants.

The ANPRM poses 74 questions covering a wide range of topics for consideration. At this time, Duke has elected to provide general commentary on several provisions. As the comment and revision process moves forward, Duke may choose to address additional topics or provide additional detail for previous commentary.

Proposed extension of regulatory scope

The ANPRM proposes to extend the application of the regulations to all research, regardless of funding source, conducted by a US institution that receives federal funding for human research. Duke does not support this extension and does not believe it will achieve the goal of extending protections to all human research participants or decreasing regulatory burden. For example, the Common Rule would still not apply to federal agencies that are not current signatories or who decline to accept the revisions; it would

still not extend to research conducted by organizations that do not receive federal funds or conduct federally sponsored research. Additionally, this proposed extension would eliminate the flexibility institutions currently have to apply equivalent protections when the existing regulations are inappropriate or impose a burden. For example, the Subpart B requirement that the research contribute to biomedical knowledge would be impossible to apply to non-biomedical research such as behavioral or social science research. It is also unlikely that the Secretary of HHS would be willing to take on making determinations required by regulation for non-federally sponsored research, such as those under 46.306 and 46.407.

#### Proposed creation of a new category of research

The ANPRM proposes extensive changes to exempt research and establish a new category of research, "excused." While Duke agrees that the existing regulations regarding exempt research could be refined, we do not agree with most of these proposed revisions and believe the proposed changes will actually increase regulatory burden. For example, it is unclear how specifically allowing investigators to determine whether their research is excused or exempt provides protection for participants or reduces regulatory burden. Duke's experience is that investigators are not in a position to make objective, unbiased determinations and often misclassify their studies as exempt when they do not meet regulatory criteria. Duke agrees with the proposed change that exempt determinations do not need to be made by IRB members or staff; however, Duke believes these determinations must be made by individuals independent of the study who are knowledgeable about the regulatory requirements and the protection of human subjects and can assess the informed consent process as mandated by the Belmont Report. Additionally, requiring institutional auditing of investigators' self-determinations and holding institutions responsible for investigators' determination will only result in greater regulatory ambiguity and impose an additional regulatory burden. The regulations should, however, make clear that exemptions apply only to research involving no more than minimal risk. In conjunction with this clarification, the definition of minimal risk as it applies to all types of research should be revised to refer to the risk of harms and discomforts ordinarily encountered in the life of the average person and not to those encountered in the daily lives of patients or others with a high level of daily risk. It should also reference experiences of the average person, not just routine medical and psychological examination as examples. Further, the regulations should clarify that the criteria of no more than minimal risk applies to children and incompetent adults as well as to competent adults.

### Proposed changes for a risk-based approach for review and oversight

In response to legitimate concerns about the variability in IRB review, and the over-review of research with no more than minimal risk, the ANPRM includes a series of proposals based on the assumption that risks of harm to research subjects in the social and behavioral sciences can be quantified and standardized so that the type of review can be prescribed by the regulations. The metric for categorizing risk in the proposed revisions is often the research methodology. However, it is not the research method, but the research topic, the setting, the population, and the questions that will be asked, as well as the interaction among these and many other contextual factors, that determine the level of risk. It is impossible to state categorically, as the ANPRM does, that every interview, survey, or focus group, regardless of the topic, poses no more than minimal risk and should be exempt. It is not possible to develop criteria to determine with specificity whether a study's psychological risks are greater or less than minimal.

Proposals for exempt and expedited research do not take into account that different risk determinations can be associated with any single research method or research topic. This has serious, if unintended, negative consequences for research subjects and for researchers. Classification of risks of harm using method as the sole measure without applying a more complex analysis would place research subjects at risk of harm. The proposed definitive list of research activities that will always pose no more than minimal risk, and therefore should be expedited, could only include a very limited set of research activities in the social and behavioral sciences. Therefore, more research will require full review.

The ANPRM proposes allowing IRBs to decide the frequency of continuing review of approved research that is minimal risk. Duke supports giving IRBs the flexibility to determine the interval of approval, based on risk. We believe this will promote closer consideration of studies in order to support the approval period and decrease burden on IRBs and investigators.

### Proposed extension of HIPAA criteria to all research

The ANPRM proposes to extend HIPAA criteria to all research. The HIPAA Privacy and Security Rule includes complex security standards and extensive enforcement rules designed for health information. Because the focus of HIPAA is the release of sensitive health information, it is an inadequate model for research in the social and behavioral sciences or other research not involving health information. For example, it would require that a study collecting zip codes or email addresses comply with security standards even when the data are not sensitive and would not harm subjects if inadvertently released. If research will not reasonably place subjects at risk, it is not appropriate to require mandatory standards that would be expensive and burdensome and in some research settings impossible. Furthermore, in much research in the social and behavioral sciences, the kinds of data that can identify research subjects are setting-specific and not typically

under the purview of HIPAA. For example, in a study about the factors influencing illegal turtle bi-catch in rural communities, the age and make of a fishing boat could identify an individual. Development of regulations and guidance that support risk-based determinations is needed to ensure protection of participants and address regulatory burden.

The proposed expanded application of HIPAA assumes that all risks are informational and therefore does not address important privacy and confidentiality issues in research in the social and behavioral sciences. For example, privacy can be violated during recruitment processes, before data are collected, in the absence of multi-faceted assessments of the subjects' privacy expectations in conjunction with the research procedures.

The implementation of mandatory security standard in place of IRB review will not sufficiently protect research subjects. We do not agree that social and behavioral IRBs do not have the expertise to address data security issues, and we are not aware of data to support this contention.

The application of HIPAA standards has already resulted in a significant burden to biomedical research and will surely result in the same for non-biomedical research if these standards are applied to all research. The IOM in its report, *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research* provides recommended reforms that should provide the basis for any regulatory revisions to confidentiality. Additionally there are other state and federal regulations that address confidentiality and data security of non-health information. A reduction in burden and enhancement of participant protections can be gained through harmonization of regulations and by not imposing additional, likely conflicting rules.

#### Proposed changes related to reuse or additional analysis of existing data and biospecimens

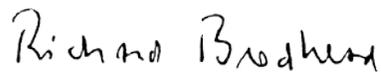
The proposed changes in the ANPRM focus on the risk of identification or re-identification of subjects that could potentially arise from analysis of their data or biospecimens. However, the proposed changes look to impose additional standards for consent or mechanisms to limit secondary use rather than establishing, clarifying or strengthening assurances or mechanisms to prevent attempts to identify or re-identify subjects or link to identifying information. Guidance is already in place to describe acceptable assurances and mechanisms for establishing and maintaining the de-identification or unlinking of data and biospecimens. Proposed prohibitions against the use of de-identified data for unanticipated research and educational purposes without prior consent would render valuable data useless and damage the practice of research, without enhancing the protection of research subjects.

Proposed requirement for a single IRB of record for multi-site studies

The ANPRM proposed establishing a requirement for a single IRB of record for multi-site domestic research. Duke agrees the current system of multiple local IRB review of multi-site research studies increases overall regulatory burden, has not been demonstrated to improve participant protection, and in some cases may actually lessen protections. However, the exact regulatory changes that are envisioned to accomplish this are unclear; therefore, it is not possible to determine whether this would increase, decrease or have no effect on participant protections, investigator burden, IRB burden or institutional burden. Clearly defining and differentiating institutional responsibilities for the review, conduct and oversight of research from IRB responsibilities is an important step. Revision or replacement of the current inter-institutional agreement process will also be required to facilitate the use of a single IRB of record and to minimize the regulatory burden on institutions. Finally, harmonization with regulations and expectations by the FDA and other agencies must accompany any initiatives to require or facilitate the use of a single IRB of record for multi-site studies—otherwise regulatory ambiguity and burden will only be increased.

In conclusion, Duke supports efforts to review, clarify and revise the regulations for the protection of human research participants. In this process it is important that the fundamental protections the current regulations afford participants serve as the starting point for change. In addition to regulatory changes, we believe that continued guidance on the application of the existing regulations would go a long way toward reducing burden on researchers, IRBs and institutions. We extend an offer to work directly with HHS and OHRP as they move forward in the process of revising the regulations and in the development of regulatory guidance.

Sincerely,

A handwritten signature in cursive script that reads "Richard H. Brodhead".

Richard H. Brodhead