RESEARCH
UNIVERSITY OF MICHIGAN

January 5, 2015

Jerry Menikoff, M.D., J.D.
Office of Human Research Protection (OHRP)
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Subject: Common Rule NPRM Comment Letter from the University of Michigan; Docket ID HHS-OPHS-2015-0008

Dear Dr. Menikoff,

On behalf of the University of Michigan's Human Research Protections Program (HRPP), we are submitting the following comments on the Notice of Proposed Rulemaking (NPRM), "Federal Policy for the Protection of Human Subjects," Docket ID HHS-OPHS-2015-0008. Following our letter with general comments, we have included an appendix with direct responses to the 88 questions embedded in the NPRM.

The University of Michigan's HRPP oversees a large volume of human research with more than 6000 projects subject to oversight by a U-M IRB. U-M is committed to maintaining high standards for our HRPP while supporting and encouraging the streamlining of our IRB processes and procedures. U-M was an early advocate for utilizing flexibility within the federal regulations, and our IRBs piloted nationally recognized demonstration projects for reducing administrative burden with non-federally supported projects. Across the country, there have been many lessons learned from utilizing flexibility and conducting demonstration projects to reduce administrative work that does not improve protections in human research, including having knowledgeable staff issue exempt determinations, creating new categories of exemptions, and issuing two- or three-year approvals for non-federally supported studies. From this vantage point, we are concerned that OHRP and other federal agencies involved in the drafting of the Advance Notice of Proposed Rulemaking (ANPRM) and the current NPRM did not make more of an effort to reach out to the research community to test the proposed changes against real-life situations before issuing the notices.

We are also concerned that several of the proposed changes will not advance protections for human subjects and will increase administrative work for investigators, IRBs, and healthcare delivery systems resulting in new barriers to research that will jeopardize benefits to individuals and society. We have particular concerns about the following sections:

- OHRP's suggested change to the definition of human subjects;
- The proposed but not-yet-developed template for broad consent;

4080 Fleming Administration Building, 503 Thompson Street
Ann Arbor, Michigan 48109-1340
T: 734 764-1185 F: 734 763-0085
research.umich.edu

- The yet-to-be-developed Secretary's List of "minimal risk" research;
- The not-yet-developed exemption tool(s);
- The proposal to mandate single IRB of Record; and
- The undetermined and undeveloped proposed data protection requirements including "HIPAA alternatives" and "data security determinations".

It is unreasonable to ask U-M and other similar institutions to comment on the parts of the NPRM that use undefined terms or that reference criteria, lists, and decision tools that are not yet developed. To honor the intent of the Administrative Procedures Act, the current NPRM should not be the basis for an interim final rule, but rather a new NPRM should be issued with those items finalized. Furthermore, the Regulatory Impact Analysis (RIA) is based on old data and seemingly arbitrary assumptions that do not fit common practice, as referenced below.

We acknowledge that there are parts of the NPRM we support, as they align with other efforts to reduce regulations that waste researcher time and research dollars and do not add to the protection of human subjects, including the elimination of continuing review for minimal risk research and the expansion of the current exemption categories. Yet, even for the proposed changes that we see as positive, there are additional points OHRP should consider when issuing a revised NPRM, as described in the sections below with detailed comments.

Proposed Changes to the Definition of Human Subjects and Treatment of Biospecimens

We do not support the NPRM's proposal to include non-identified biospecimens in the definition of a human subject. We believe the current practice of excluding non-identified biospecimens from the regulations is appropriate, as the risk of re-identification of these specimens is extremely low. We believe the current definition of human subjects research in the Common Rule should be retained with the clarification that if the identity of the person whose biospecimens was obtained becomes readily ascertainable by the investigator, the research would be subject to the Common Rule. This would accommodate the use of new and emerging technologies utilizing genomics.

The proposed requirement for broad consent for future research associated with the NPRM's newly proposed definition would hinder research and substantially increase the cost and administrative workload while not enhancing human protections. Broad consent, as described in the NPRM, would simply serve as a kind of "rubber stamp" for use of specimens. The RIA describes this as a five-minute process, which is in contrast to the time generally dedicated to explaining consent for research studies. It is likely that routinizing such a consent process will render it meaningless.

We echo the Secretary's Advisory Committee on Human Research Protections' (SACHRP) suggestion that public education and awareness of research practices and the value of research would better serve the public than a blanket broad consent. We also agree with their recommendation that appropriate policies for data sharing, including limitations and sanctions for unauthorized re-identification would be a far more effective way of improving public trust.

We also are concerned that the new requirement for obtaining and tracking consent for biospecimens that are currently routinely collected from various sources, including small

hospitals and clinics, will result in the loss of important biospecimens from a diverse population, as only large, well-supported institutions will be able to develop the administrative structure needed to track broad consent. Thus, biospecimens from populations currently already underrepresented in clinical research will likely become even less available to scientists, undermining one of the major principles of the Belmont Report: justice.

It is worth noting that the NPRM's RIA assumes that institutions will develop a centralized process for obtaining and documenting broad consent. The cost of developing this kind of system at U-M would far exceed the estimated costs in the RIA. Staff, who are logistically in a position to do this sort of across-the-board consenting, are generally trained and focused specifically on clinical care. At large medical centers like our own, to meaningfully carry out the broad consent process to respect and facilitate the autonomy of individual specimen donors, literally hundreds of employees would need extensive training and periodic retraining in research ethics. Significantly, we calculate that every procedure that involves any tissue collection should take a minimum of 10 – 15 minutes of additional staff time to be able to even attempt to make the process meaningful. Otherwise, the entire Belmont principle of honoring autonomy in a consent process is significantly diminished. With millions of unique patients and their associated procedures presenting annually at major medical centers (e.g. at UMHS we currently have one million patients), this would substantively congest intake and medical triage at points-of-service. Consent may not even be possible for emergency department visits.

Additionally, it will require millions of dollars to build and support the necessary IT and infrastructure required to keep track of the consents and their associated ten-year expirations, as well as managing the opt-outs and declined consents, which will be needed to avoid inadvertently harassing those who have said they are not interested. It is important to respect the decisions of our patients who have said they are not interested in research with their biospecimens, but this broad consent effort does not effectively represent the most efficient procedural efforts and will substantively increase health care costs where there is very little or no patient risk.

Further, to effectuate the rule, full identifiability must be maintained on all patient materials that would otherwise simply be discarded so that it can be determined if permission was obtained for the specimens (which would otherwise be deidentified) to be used in research. This will increases the risk of information breaches.

We believe treatment of biospecimens is best covered through clear guidance which can be adapted to evolving technologies rather than to changes in the Common Rule. In addition, we strongly disagree with the NPRM proposal limiting the ability of IRBs to issue waivers of informed consent for biospecimen research. We believe that responsible use of this valuable research resource is in the best interest of our society's future healthcare, and that thoughtful decision-making by knowledgeable IRBs can serve to better protect human subjects from objectionable uses of their biospecimens.

Finally, we wish to note that the NPRM proposes a federally mandated "broad consent for future research use" but does not supply draft language for this consent; we are therefore unable to provide meaningful comment on its usefulness. If a broad consent for future research will be

required, we can offer the example of the consent template (https://medicine.umich.edu/medschool/research/office-research/biorepository/informed-consent) developed for inclusion of biospecimens in our U-M central biorepository.

Continuing Review

We enthusiastically support the elimination of continuing review for minimal risk research qualifying for expedited review. For several years, U-M has extended IRB approval for two years for non-federally funded studies, and we have had no concerns and had no significant findings when these studies underwent internal audit. From this experience, we conclude that there is little value in the current system requiring annual review of minimal risk research studies. Furthermore, we would argue that the final rule should also eliminate the requirement for researchers to provide an annual certification regarding the status of the study.

Exclusions and Exemptions

We acknowledge and appreciate the intent of the NPRM to calibrate review based on risk, particularly as related to social science research. Unfortunately, many of the proposed exclusions and exemptions described in the NPRM are complex, difficult to interpret and will likely be challenging to operationalize. The NPRM proposes three different categories of excluded research and three different categories of exemptions involving differing review requirements with multiple types of research activities described within each. Our IRBs are able to apply the current regulatory definitions of research with human subjects and make appropriate determinations regarding the requirement for IRB oversight. Our experienced IRB staff reviewers are also able to interpret the current exemption criteria and issue determinations within a day or two of submission. Our research community has developed an understanding of these definitions and criteria, but investigators still rely heavily on the IRB staff for help to craft their studies so as to minimize risk, or to fit exemption criteria. We are also concerned that the new excluded/exempt categories described in the NPRM will make these decisions more difficult, particularly given the intent that they will be made primarily by investigators rather than by IRB members or staff. This could result in decision errors and potential risk to participants when appropriate safeguards are not applied to projects.

We suggest that rather than describing specific excluded activities within the regulation, which could be interpreted as the definitive list of activities not subject to IRB oversight, these examples be provided in guidance that can more easily be updated or clarified. Also, we are concerned that making the distinction between "low risk" human subjects research activities that fall within the exclusion categories and those that are now considered to be exempt may be unnecessarily complicated for institutions and investigators, and we recommend that these research activities continue to be categorized as exempt. We suggest that OHRP clarify and expand the definitions of the current exemption categories via guidance.

With regard to proposed exemption §_.104(e)(1) for surveys/interviews that collect sensitive identifiable information that could pose a disclosure risk to participants, we note that risks associated with such research are not limited to breach of confidentiality that can be mitigated by strong data security procedures. Participants may be asked to share information regarding illegal behaviors, immigration status, or other sensitive information that could be subject to compelled disclosure, for which an IRB may currently require the protections offered by a National

Institutes of Health (NIH) Certificate of Confidentiality. IRB review often addresses concerns that extend beyond privacy, such as recruitment strategies or research settings. IRBs also consider the burden of research on participants by considering possible psychological risk associated with interviews on sensitive topics and assess the necessity for collection of such information as related to scientific goals. Many survey/interview projects seek permission from participants to link their data to government or other data sources that may pose risk through re-identification. Given all of these considerations and the current value added by comprehensive IRB review in these cases, we recommend that research described by this exemption instead be included on the list of research activities to be considered via expedited review. Additionally, we recommend that the proposed exemptions at §_.104(f) that include a requirement for limited IRB review also be included on the Secretary's list of expedited review categories, as the added requirement seems inconsistent with the concept of exemption.

The NPRM notes that OHRP plans to develop a web-based decision tool for use by investigators to determine whether research meets the criteria for exemption. Given the complexity of some of the new proposed exemption categories, we question whether this is feasible, and we cannot provide meaningful comment on the use of such a tool without seeing it. We note that the Human Subjects Committee of the Federal Demonstration Partnership (FDP) has developed a prototype Exemption Wizard for the current federal exemptions, but found that there were difficulties with its implementation, including objections from investigators about having to complete the tool and still register with the IRB, which is proposed in the NPRM. U-M already uses a smart form logic in our electronic IRB application, which provides a similar experience to the Exemption Wizard while maintaining a record of completion within our IT system. We encourage OHRP to partner with the FDP and experienced IRBs to develop and pilot new tools to accurately dovetail with real-world infrastructure rather than attempting to develop these independently.

Extension of Common Rule Oversight to all Clinical Trials

We oppose the proposal to extend the Common Rule to all clinical trials. By policy, U-M already extends the same human subjects protections to all research conducted by our faculty, staff, and affiliates, regardless of funding source.

From the perspective of behavioral researchers, we find that the terms "intervention" and "behavioral health-related outcomes" used in the NPRM are not clearly defined. We are concerned that changes proposed in the NPRM would create unnecessary administrative work for social and behavioral research without enhancing human research protections.

We oppose the requirement for posting informed consent documents for clinical trials online. It is unlikely that this will serve as a tool for improving consent. Since the informed consent process may involve other components in addition to the consent form, we are also concerned that posting only the consent form (especially during an ongoing clinical trial) might be misleading, and result in confusion, apprehension, and resistance to participate in research, thus hindering our ability to make advances in medicine and treatments. As an alternative, we encourage development of a working space to post informed consent templates to inform best practices and development of effective and understandable language.

Single IRB of Record

The University of Michigan regularly engages in collaborative research and always strives to avoid duplicate review. We have signed hundreds of IRB authorization agreements both accepting the role of IRB of record and ceding that role to other institutions. We have master agreements with several commercial IRBs for multi-site clinical trials where U-M is a participating site. We also have agreed to create research networks where U-M assumes responsibility for multiple sites (for as many as 60 participating sites). This experience puts us in a good position to comment on the NPRM's proposal to mandate single IRB review for all U.S. institutions engaged in multi-institutional research.

In general, U-M supports the concept of relying on a single IRB for most multi-site clinical trials. However, we do not support a mandate for a number of reasons, primarily because we do not believe that the single IRB model is appropriate for all types of cooperative research. It is best suited to clinical trials where an identical protocol is implemented at all sites. The single IRB model is less appropriate for studies that are designed for collaboration across several institutions with each institution having a discrete role based on local expertise or resources. For example, in a collaborative study, one institution may conduct all participant interventions, one institution may have special diagnostic equipment for biospecimen analysis, and another may be best equipped to serve as the data coordinating center. In these cases, IRB review at each institution providing each separate function would offer the best research oversight and human subject protections.

Given that there are significant costs in staff time to negotiate and establish collaborative agreements for using a single IRB review model, the process is most efficient and useful when there is a plan to run more than one study through the same single IRB. For example, U-M has established master agreements with a few institutions to join networks of researchers who plan long-term collaborations and multiple cooperative research projects. We might utilize these agreements for five or more projects within a year. Since the master agreement spells out all roles and responsibilities for IRB review, we can streamline the ceding of the review for these projects. With the proposed NIH policy for mandating that all clinical trials funded by the agency use a single IRB model, we anticipate that U-M will be compelled to establish collaborative agreements for each new NIH award subject to the policy, which would not be efficient. It is our experience that it can take several months to establish these agreements, when our median turnaround time for standard U-M IRB review is significantly shorter.

Further complicating and adding to the study review timelines are ancillary review processes (e.g., conflict of interest, investigational pharmacy, biosafety and radiation safety) that are required at each local institution, as well as State-specific requirements, which may warrant additional local review and site-specific changes to the informed consent process. These efforts are not diminished by a single IRB effort.

The IRBs at many research organizations are not appropriately staffed or equipped to administratively support the review of studies involving a significant number of sites and the proposed changes will require a massive and costly restructuring of current systems. Indeed, U-M is currently attempting to reconfigure our electronic IRB application system to more efficiently accommodate work with small hospitals and physician practice plans. Moreover, because individual study teams generally are not staffed to provide the needed regulatory

oversight for these sites and additional resources are necessary for single IRB of record arrangements, we are exploring the possibility of providing services through a central office. We are, however, concerned about the costs associated with developing and maintaining this service and its possible impact on direct costs in research budgets. These costs may result in limitations to the number of sites that can participate, which could ultimately have a negative impact on research progress.

Rather than move ahead with the NIH policy and the NPRM-proposed mandate for single IRB review, we strongly support the SACHRP recommendations that DHHS should:

- Fund research evaluating the advantages and disadvantages of single IRB use in domestic multi-site research;
- Collect and disseminate data regarding its own experience with the use of single IRBs for grants that have been mandated to use a single IRB (e.g., the NeuroNEXT multicenter trial) or for those grants where it has been voluntarily utilized;
- Support meetings with the research community where issues regarding the use of a single IRB can be discussed in a public forum;
- Evaluate concerns related to the cost of utilizing a single IRB and put forward a proposal that would cover the cost of both single IRB review and local review without reducing dollars to the researcher; and
- Find mechanisms to encourage investigators and institutions to voluntarily utilize single IRBs as part of their grant submissions until such a time that there is sufficient data to support a single IRB mandate. This could be accomplished by providing incentives such as awarding additional dollars to those grants that agree to utilize single IRB arrangements.

We strongly urge OHRP to abandon the mandate for use of a single IRB as a component of the Common Rule and to work with the community to test models.

Expansion of Scope to Cover Unaffiliated IRBs Not Operated by an Institution Holding a Federalwide Assurance

U-M supports the proposal to add a provision at §_.114(b)(1) that would explicitly give Common Rule departments and agencies the authority to enforce compliance directly against unaffiliated IRBs that are not operated by an assured institution. Previously, OHRP proposed such a change and it received widespread support, but it was never implemented.

Data Security and Privacy

Regarding the proposal in the NPRM to impose yet-to-be-developed data security and privacy protections, we are unable to comment on this, as no specific standards are presented. From our experience, we know that HIPAA standards do not fit for all cases of human research and we would discourage the broader application of HIPAA or HIPAA-like standards.

At U-M, IRBs can seek assistance from institutional data security consultants to assess data security plans for more than minimal risk research to assure protections are calibrated to the risks of the research and guided by institutional data policies. We find this to be an efficient and effective practice for addressing data security and privacy protections. We recommend that OHRP issue guidance regarding these protections rather than imposing additional regulations.

Waiver of Consent

As noted above, we strongly urge OHRP to retain the current practice that allows IRBs to determine when a waiver of consent for use of biospecimens is appropriate. Where consent is required by an IRB for the original research, that IRB should have the discretion to grant a waiver of consent for the secondary use of that information or those specimens. We agree with previous recommendations from SACHRP and others that the current waiver process addressed at 45 CFR 46.116(d), as implemented through thoughtful review by the IRB, provides better protections for human subjects than broad consent.

Transition Provisions

We feel strongly that research with biospecimens collected prior to the implementation of a revised Common Rule should not be subject to the provisions proposed in the NPRM. We agree with the Association of American Medical Colleges and others that recommend deleting the requirement proposed in the NPRM that research involving biospecimens collected prior to the regulation compliance date be allowed only if the individually identifiable information is removed. Again, we strongly believe this would impede research without adding protections for human subjects.

Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

We support clarifying and harmonizing regulatory and agency guidance, but we do not see how the recommendations in the NPRM would accomplish this. Under the proposed rule, federal regulatory and funding agencies would seek "consultation" before issuing new rules, but still be allowed to impose additional requirements. This would not prevent agencies from issuing regulations and guidance that would be inconsistent with or duplicate requirements of other agencies and would thus continue the present state of confusion. Joint issuance of regulations and guidance would be much more efficient and would help to reduce unnecessary administrative work.

Regulatory Impact Analysis

U-M participated in the drafting of the comments provided by the Council of Governmental Relations (COGR), and we agree with the fundamental point made by COGR, that "Many of the NPRM's cost estimates are based on inappropriate assumptions and opaque methodology." As documented in the COGR comments, the estimates of the salary rates presented in the NPRM for institutional officials, IRB members and staff, and investigators are far below the national average for these roles. We are concerned that although OHRP estimated extremely high costs associated with the implementation of the proposed rules, they did not do due diligence to estimate the actual costs to institutions, which will be significantly higher. Likewise, the anticipated benefits of the new proposed rule appear to be grossly overstated.

We would urge the Office of Information and Regulatory Affairs to require OHRP to revise the estimates of costs and benefits before allowing any of the proposals in the NPRM to move forward.

Summary

In summary, we believe that many of the proposed changes to the Common Rule do not meet the intended goal of enhancing protections for human subjects and streamlining the research review process. Parts of the NPRM are incomplete and other parts confusing. Several of the proposed changes have potential to impede important research from moving forward. The estimated costs of the proposed changes are prohibitive and have been greatly underestimated while the benefits are overstated. We urge OHRP to withdraw this NPRM and create a new NPRM to address only those elements that would actually improve the current system, such as eliminating continuing review for minimal risk research and expanding categories of exempt and expedited research.

Sincerely,

Lois Brako, Ph.D.
Assistant Vice President for Research – Regulatory and Compliance Oversight

Addendum: Responses to Common Rule NPRM Questions

1. Public comment is sought on whether the proposed changes will achieve the objectives of (i) decreasing administrative burden, delay and ambiguity for investigators, institutions, and IRBs, and (ii) strengthening, modernizing, and making the regulations more effective in protecting research subjects.

Response: Several of the proposed revisions that would increase burden, delay, ambiguity, and cost, and result in a loss of valuable research without increasing protections for human subjects. These include expanding the definition of a "human subject" to include biospecimens; the proposed requirements for consent for all biospecimens regardless of identifiability, restrictions on the use of consent waivers; mandatory data security provisions; mandatory reliance on a single institutional review board (IRB) for multi-site studies; and the inclusion of non-federally funded clinical trials under the regulations for the subset of organizations which receive federal grants.

We strongly urge OHRP to eliminate from the proposed regulations the highly controversial proposals related to biospecimens, cooperative research, and expanding coverage to non-federally funded clinical research. Research involving biospecimens will be significantly impeded and billions of dollars will be reallocated from research to compliance without adding to the protection of human subjects.

We do, however, believe the proposed change to eliminate continuing review for minimal risk studies will ease the burden on investigators and IRBs. We support this change, but do not support the proposed requirement for annual certification by investigators.

2. Would providing a definition of biospecimen be helpful in implementing this provision? If so, how might the definition draw a line between when a biospecimen is covered by the Common Rule, and when processing of biological materials (e.g., to create a commercial product used for treatment purposes) has sufficiently altered the materials so that they should not be subject to the regulations? Would only covering biospecimens that include nucleic acids draw an appropriate line?

Response: We agree with comments from CoGR that "inclusion of biospecimens as a "special" or "protected" class of material is problematic for many reasons. First and foremost, biospecimens are not "human subjects." Second, from a security perspective, we are not aware of any instances in which researchers have violated confidentiality or other non-disclosure agreements in order to re-identify individuals' de-identified specimens that resulted in any harm or loss of privacy for the subjects involved." We strongly recommend that the changes proposed for research with biospecimens be reconsidered.

3. To what extent do the issues raised in this discussion suggest the need to be clearer and more direct about the definition of identifiable private information? How useful and appropriate is the current modifier "may be readily ascertained" in the context of modern genomic technology, widespread data sharing, and high speed computing? One alternative is to replace the term "identifiable private information" with the term used across the Federal Government: Personally identifiable information (PII). The Office of Management and Budget's 45 concept of PII refers to information that can be used to

distinguish or trace an individual's identity (such as their name, social security number, biometric records, etc.) alone, or when combined with other personal or identifying information which is linked or linkable to a specific individual, such as date and place of birth, mother's maiden name, etc. It is acknowledged that replacing "identifiable private information" with "PII" would increase the scope of what is subject to the Common Rule. However, the practical implications of such an expansion, other than the need to ensure that the data are security stored and otherwise protected against disclosure, may be minimal. Public comment is requested on the advantages and disadvantages of such a change.

Response: The current definition is adequate and should not be replaced with personally identifiable information. IRBs should continue with their current practice of assessing the risk related to unintended disclosure of private information and assuring that appropriate safeguards are in place.

4. Which of the three proposals regarding the definition of human subject achieves the most reasonable tradeoff between the principles of autonomy (including transparency and level of trust) versus beneficence (as measured by facilitating valuable research)?

Response: We believe the current definition of human subjects research in the Common Rule should be retained with the clarification that if the identity of the person whose biospecimens was obtained becomes readily ascertainable by the investigator, the research would be subject to the Common Rule. This would accommodate the use of new and emerging technologies utilizing genomics.

5. Public comment is sought regarding any concerns that you have about each of the three proposals, including concerns about implementation or burden to investigators and institutions.

Response: As stated above, biospecimens should not be included in the definition of human subject under the rule. Any special considerations for biospecimens should be covered under separate guidance.

6. Public comment is sought for whether this excluded activity should simply be discussed in the text of the final rule's preamble, and guidance produced to assist investigators in making such a determination, or whether any other similar exclusions should be addressed.

Response: We support having excluded activities discussed in the text of the final rule's preamble with the issuance of guidance to assist investigators in making a determination.

7. Public comment is sought for whether biospecimens should not be included in any of these exclusion categories, and if so, which ones.

Response: We see no reason not to include biospecimens in any exclusion category. Secondary research use of non-identified biospecimens and of biospecimens collected for non-research purposes should continue to be excluded from the Common Rule.

8. Public comment is requested on whether the parameters of the exclusions are sufficiently clear to provide the necessary operational guidance, or whether any additional criteria or parameters should be applied to clarify or narrow any of these exclusions.

Response: The current descriptions of exclusions are written in a complicated and legalistic manner that will not be easily understood by investigators. Given that the NPRM proposes that investigators should be allowed to make determinations of excluded categories, the current language should be revised. Thus, if adopted as currently written, we suggest that OHRP consult with the IRB community to revise the parameters.

9. Public comment is requested on the extent to which covering any of these activities under the Common Rule would substantially add to the protections provided to human research subjects.

Response: We do not believe that covering these activities under the Common Rule would add to the protections provided to human research subject and note the following:

- Non-identified biospecimens should be retained in the exclusion category.
- The exclusion of Quality Assurance or Improvement activities should not be limited to those where the purpose is to alter the utilization of an accepted practice.
- Regarding activities considered "low risk," excluding research involving the collection or study of information that is either publically available or non-identifiable will be helpful. The exclusion requiring that an investigator receiving protected health information (PHI) from a covered entity needs to be from a covered entity as well, is unnecessary as the HIPAA Privacy Rule already covers this.

10. Public comment is sought on whether this exclusion should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, please comment on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, ability to opt-out, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: We do not support the requirement of a notice for studies excluded from the regulations. As noted in COGR's comments "If these studies are excluded from the regulation, then institutions will not have knowledge of their existence, and will have no means of assuring that such procedures are in place. If notice is a condition of conducting "excluded" research, then it is not, in fact, excluded. By its very definition, "excluded" research is not subject to requirements of the Rule. And, therefore, institutions should not be held accountable for whether an investigator gave any kind of notice."

11. Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category. If so, should documentation of any kind be generated and retained?

Response: We believe it is not reasonable to rely on investigators to make self-determinations with the complex language currently found in the proposed rule. The rule should be written in a way that will be clear to individuals not accustomed to working with laws and regulations.

A tool, as is proposed for exempt research, could assist investigators in making these decisions independently, but institutions should not be held responsible for exclusion determinations made solely by investigators. We do not believe it is appropriate to impose regulatory requirements regarding documentation or record retention for this or other excluded categories

12. Public comment is sought regarding whether some or all of these activities should be exemptions rather than exclusions.

Response:

At U-M, we distinguish between "not-regulated" activities (i.e., those that do not meet the definition of human research) from human research activities that are "exempt." We suggest that this distinction be maintained.

13. Public comment is sought regarding whether these exclusions should be narrowed such that studies with the potential for psychological risk are not included. Are there certain topic areas of sensitive information that should not be covered by this exclusion? If so, please provide exemplary language to characterize such topic areas in a manner that would provide clarity for implementing the Rule.

Response: We believe that the exclusion at §_.101(b)(2)(i) should not be narrowed but rather should be categorized as exempt.

14. For activities captured under the third element of this exclusion, do the statutory, regulatory, and other policy requirements cited provide enough oversight and protection that being subject to expedited review under the Common Rule would produce minimal additional subject protections? If so, should the exclusion be broadened to also cover secondary analysis of information collected pursuant to such activities?

Response: Yes, the other, existing statutory, regulatory, and other policy requirements provide adequate oversight and protection. Therefore, these activities should continue in the excluded category. Because of the very significant protections that these regulations provide (e.g., HIPAA), the exclusion should be broadened to cover secondary analysis. We object, however, to the exclusion requiring that an investigator who receives PHI needs also to be from a covered entity.

15. Public comment is requested on the extent to which excluding any of these research activities from the Common Rule could result in an actual or perceived reduction or alteration of existing rights or protections provided to human research subjects. Are there any risks to scientific integrity or public trust that may result from excluding these research activities from the Common Rule?

Response: We believe that excluding or exempting these research activities from the Common Rule is both reasonable and advisable. It will not reduce the rights and protections provided to human research subjects nor do we believe it will present risks to scientific integrity or public trust.

16. Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category. If so, should documentation of any kind be generated and retained?

Response: We believe it could be reasonable to rely on investigators to make self-determinations if this excluded category is clearly explained with guidance and educational materials. Since this category is excluded from the regulation, we do not believe it is appropriate to impose regulatory requirements regarding documentation or record retention for this or other excluded categories.

17. Public comment is requested on the extent to which covering any of these activities under the Common Rule would substantially add to the protections provided to human research subjects. Is there a way in which this exclusion should be narrowed? Public comment is also sought regarding whether activities described here should appear as an exclusion or as an exemption.

Response: Information that is already publicly available or has been rendered non-identifiable should be excluded from the regulations.

18. Public comment is sought on whether this or a separate exclusion should also include research involving information collected for non-research purposes by non-federal entities where there are comparable privacy safeguards established by state laws and regulations, or whether such non-federally conducted research would be covered by the proposed exemption at § _.104(e)(2).

Response: The exclusion and exemption categories as written in the NPRM are adequate with the exception that we feel strongly that research involving non-identified biospecimens should continue to be excluded from the regulations.

19. Public comment is requested on the extent to which covering any of these activities under the Common Rule would substantially add to the protections provided to human research subjects.

Response: Coverage under the Common Rule is not needed.

20. Public comment is sought regarding whether it is reasonable to rely on investigators

to make self-determinations for the types of research activities covered in this particular exclusion category. If so, should documentation of any kind be generated and retained?

Response: We agree with the comments by CoGR that "Additional clarity is needed for investigators to make these determinations. For example, clarity is needed as to whether or not data collected under this excluded category for research by federal departments or agencies can then be excluded if used for secondary research purposes by non-federal employees. It is not reasonable to require documentation for something that is not subject to regulation."

21. Public comment is sought regarding whether some or all of these activities should be exemptions rather than exclusions.

Response: They should remain exclusions.

22. Public comment is requested on whether the protections provided by the HIPAA Rules for identifiable health information used for health care operations, public health activities, and research activities are sufficient to protect human subjects involved in such activities, and whether the current process of seeking IRB approval meaningfully adds to the protection of human subjects involved in such research studies.

Response: HIPAA protections are sufficient. In situations where research disclosures or waivers under HIPAA require institutional review, current IRB practices provide appropriate protection and no additional requirements are necessary.

23. Public comment is sought regarding to what extent the HIPAA Rules and HITECH adequately address the beneficence, autonomy, and justice aspects for the collection of new information (versus information collected or generated in the course of clinical practice, e.g., examination, treatment, and prevention). Should this exclusion be limited to data collected or generated in the course of clinical practice? If additional data collection is allowable, should it be limited to what is on the proposed Secretary's list of minimal risk activities (discussed in more detail below in II.F.2 of this preamble)?

Response: HIPAA Rules and HITECH adequately address the Belmont Principles for these exclusions. No further restrictions or limitations are needed.

24. Public comment is requested on whether additional or fewer activities regulated under the HIPAA Privacy Rule should be included in this exclusion.

Response: No additions or deletions are required.

25. Should research involving prisoners be allowed to use any or all of the exclusions found at §_.101(b)(2) and (3), as currently proposed?

Response: Yes, all exclusions should apply to research with prisoners.

26. Are there certain provisions within the broader categories proposed at § _.101(b)(2) and (3) to which the subparts should or should not apply?

Response: No.

27. Public comment is sought regarding how likely it would be that institutions would allow an investigator to independently make an exempt determination for his or her own research without additional review by an individual who is not involved in the research and immersed in human research protection e.g., a member of the IRB Staff.

Response: We already allow investigators to independently assess eligibility and apply for an exempt determination through our IRB application smart form logic. However, we currently have a staff member review this determination for confirmation of eligibility. If a tool could be developed that would be virtually "fool proof" we would not have a problem with investigators making exempt determinations, as long as the institution would be held harmless for any investigator error. Without this assurance, we would continue to have a staff member make the final exempt determinations.

28. Public comment is sought regarding whether an investigator would be able to contrive his or her responses to the automated exemption decision tool in order to receive a desired result i.e., an exempt determination, even if it does not accurately reflect the research activities.

Response: This is impossible to answer until the tool is available to review. If ambiguous language is used in the questions, answers may be "contrived" or innocently erroneous. For us to give meaningful feedback, we would have to be able to see the tool.

29. Public comment is sought on whether it would be more appropriate for some of the exempt categories than others to rely on the exemption determination produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances.

Response: It's hard to know until a tool is available for testing.

30. Public comment is sought regarding whether relying on the exemption determination produced by the decision tool where investigators themselves input the data into the tool as proposed would reduce public trust in research.

Response: We agree with CoGR's comments that "The entire system of human subject research is based on trust in investigators along multiple dimensions. A well-designed, tested and validated tool could actually enhance the public trust. "

31. Public comment is sought regarding how likely it would be that institutions would

rely on such a decision tool to provide a safe harbor for an investigator making a determination that the proposed research qualifies for an exemption, or whether developing such a tool would not be worthwhile, and whether institutions would be able to adequately manage exemption determinations without the use of the decision tool.

Response: Under the current rules, we are able to efficiently manage exemption determinations with the use of our IRB application smart form logic. We have refined this process to provide exempt determinations in a very short time (e.g. same day or 1-2 days). Modifying this process to accommodate the use of an independent decision tool would be expensive and not efficient for U-M.

32. Public comment is sought regarding what additional information should be required to be kept as a record other than the information submitted into the decision tool, for example, a study abstract, the privacy safeguards to be employed, or any notice or consent document that will be provided.

Response: The tool should be designed in a way that it solicits all of the information required in order to make the exempt determination and includes the researcher name and title of the project. No other information should be required.

33. Public comment is sought regarding the value of adding an auditing requirement.

Response: We do not support adding an audit requirement for exempt research determination. Auditing efforts should be focused on higher risk research.

34. Public comment is sought on whether this exemption category should only apply to research activities in which notice that the information collected will be used for research purposes is given to prospective subjects or their legally authorized representatives as a regulatory requirement, when not already required under the Privacy Act of 1974. If so, comment is sought on what kind of information should be included in the notice, such as the research purpose, privacy safeguards, contact information, etc. Comment is also sought on how such a notice should be delivered, e.g., publication in a newspaper or posting in a public place such as the school where the research is taking place, or by individual email or postal delivery. Note that other requirements, such as those of the Family Educational Rights and Privacy Act (FERPA) or the Protection of Pupil Rights Amendment, may also apply. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: Exempt research should mean that the category of activity is not subject to regulation and no notice should be required by regulation. This is an area where OHRP should provided to investigators guidance to the investigator about providing basic information in a notice.

35. Public comment is sought on whether the privacy safeguards of § _.105 should apply to the research included in § _.104(d)(1), given that such research may involve risk of

disclosure of identifiable private information.

Response: As stated above, if a category of research is exempt, then it should be exempt from all sections of the rule.

36. Public comment is sought on whether this exemption category should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice, e.g., the research purpose, privacy safeguards, or contact information. Also comment on how such a notice should be delivered; e.g., publication in a newspaper or posting in a public place, or by individual email or postal delivery. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence? In many cases, it may be that individual notice or consent to all potentially affected persons before the research or demonstration commences is ordinarily impossible in the conduct of such studies. For example, if a research or demonstration project will affect all inhabitants of a large geographic area (e.g., a housing, a police patrol, a traffic control, or emergency response experiment), or all clients or employees of a particular program or organization or setting will be subject to a new procedure being tested (e.g. a new approach to improving student performance, a new anti-smoking or anti-obesity program, a new method for evaluating employee performance), would it be possible to make participation voluntary for all affected individuals, or even to identify and inform all affected individuals in advance?

Response: As stated above, if a category of research is exempt, no notice should be required and no other requirements should be added.

37. Public comment is sought on whether this exemption category is appropriate based on the recognition that alternative processes are in place in which ethical issues raised by research in public benefit or service programs would be addressed by the officials who are familiar with the programs and responsible for their successful operation under state and federal laws, rather than meeting specific risk-based criteria, or whether risk limitations should be included, and if so, what those limitations should be. Though long-standing, this exemption has never identified specific risk-based criteria, or risk limitations to bound the type of projects that may be covered. When originally promulgated, the exemption did stipulate that following the review of such projects, if the Secretary determines that the research or demonstration project presents a danger to the physical, mental, or emotional well being of a participant or subject, then written informed consent would be required. Public comment is sought on whether to limit the risk that can be imposed on subjects while using this exemption, and if so, how to characterize those limits in a clear fashion. If more than minimal risk interventions are included, public comment is sought on whether, for transparency, this should be made clear in the regulatory text.

With regard to the issue of risks encountered by participants in such research or

demonstration projects, comments are also sought regarding the argument that any and every demonstration project involving changes in public benefit or service programs (e.g., water or sewage treatment programs or pollution control programs, programs involving educational procedures, or programs involving emergency procedures related to extreme weather events, etc.) exposes those affected to possible risks of some kind. In this regard, those risks are ordinarily and perhaps always no different in kind or magnitude than those involved in simply making the change in procedures without using research tools to evaluate them. For example, health care providers could be required to perform certain sanitation reforms to prevent patient infections whether or not such reforms were first tested in practice through a research or demonstration project. It is common for all Federal departments and agencies that regulate private or public organizations to impose conditions of participation in public programs providing for safety, program integrity, financial reporting, etc. Public comment is sought regarding whether there should be conditions (e.g., an individual notice or consent requirement) imposed on such research or demonstration projects involving public benefit or service programs which might lead to significant impediments or limitations on testing and evaluation before or after being imposed program-wide. Would the effect of imposing expensive or impracticable conditions on public benefits or services evaluations be to reduce the number of such evaluations and consequently to expose program participants to increased risk through exposure to untested reforms?

Response: Additional requirements should not be imposed on exempt research.

38. Public comment is sought on whether the existing privacy safeguards for such activities, including the Privacy Act, HIPAA rules, and other federal or state privacy safeguards provide sufficient independent controls, or whether other safeguards such as the privacy safeguards of § _.105 should be applied.

Response: Existing safeguards are sufficient.

39. Public comment is sought on whether this exemption category should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice, such as the research purpose (if authorized deception is not utilized), privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: Additional requirements should not be imposed on exempt research and no notice should be required.

40. Public comment is sought regarding what improvements could be made to the language describing the type of interventions in this exemption category so as to make clear what interventions would or would not satisfy this exemption category.

Response: The new exemption involving what is now called "benign interventions" should be renamed since the meaning of these two words commonly are used in medical procedures, but are being used here to describe social and behavioral sciences studies. We would suggest using the description "a brief, harmless, painless, and not physically invasive procedure."

41. Public comment is sought on whether it is reasonable, for purposes of this exemption, to rely on the exemption determination produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances.

Response: Again, without seeing and evaluating the tool it is impossible to answer this question. We recommend that language and questions pertaining to the proposed tool be removed from the NPRM. The proposed tool should be developed and tested in cooperation with the research community and republished separately once developed.

42. Public comment is sought on whether this exemption category should be narrowed to apply only to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: The nature of this research is such that a notice containing specified elements should not be required.

43. Public comment is sought on the concept of requiring such minimum safeguards and limitations on disclosure, as well as whether the requirements of the proposed § _.105 would constitute a broadening of IRB responsibilities rather than a streamlining of the implementation of responsibilities that many IRBs already adopted. If an institution does view this as an inordinate broadening of responsibilities, does the institution currently have in place alternative mechanisms for ensuring data security and participant privacy in a research context? Suggestions for alternative approaches to meeting public expectation that federally sponsored research safeguard their data and protect privacy are sought during this public comment period.

Response:

We do not support having exempt research subject to additional safeguards.

44. Public comment is sought regarding whether the proposed Rule's information security requirements for biological specimens and identifiable private information are highly technical and require a level of expertise not currently available to most IRBs. Do these security requirements unrealistically expand IRB responsibilities beyond current

competencies?

Response: Our IRBs currently work in partnership with IT specialists for more than minimal risk research and this relationship works well. IRBs determine the sensitivity and necessary level of protection and IT staff assess the technical requirements of the proposed safeguards. It is beyond the scope of IRB oversight to maintain continuing awareness as to the ongoing technical requirements of IT systems for HIPAA and other compliance. This is managed best by IT security professionals for more than minimal risk research.

45. Public comment is sought on whether the proposed exemption regarding the use of educational tests, survey procedures, interview procedures, or observation of public behavior (§ _.104(e)(1)) should be applied to research involving the use of educational tests with children and whether it should also be applied to research involving the use of survey or interview procedures with children. If so, for research involving children, should the permissible survey or interview topics be limited in some way?

Response: Educational testing with children is appropriate under this exemption. However, survey or interview procedures involving sensitive information should not include children under this exemption.

46. Public comment is sought on whether this exemption category should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: Notice is not necessary.

Should prospective subjects be given the explicit opportunity to opt out of such research?

Response: We don't support requiring a notice.

47. Public comment is sought on whether it is reasonable, for purposes of this exemption, to rely on the exemption determinations produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances?

Response: As stated above, we support having an IRB staff member confirm the exempt determination.

48. Public comment is sought on whether this exemption category should be narrowed such that studies with the potential for psychological risk are not included. Are there certain topic areas of sensitive information that should not be covered by this exemption? If so, please provide exemplary language to characterize such topic areas in a

manner that would provide clarity for implementing the Rule.

Response: We suggest that this category of research should not be exempt and should be subject to IRB oversight. Psychological risk is only one of the concerns that might result from research involving sensitive information collected in an identifiable manner and it is not possible to provide a list of "sensitive topic areas" that should not be included in the exemption. Sensitive identifiable data may also be subject to compelled disclosure and could pose legal, economic, or financial risks.

49. Public comment is sought on the types of research that should fall under the proposed exemption. Should the proposed exemption be available to all types of research using identifiable data collected for non-research purposes or should the exemption be available only to a more limited subset of research? For example, should the proposed exemption apply only for research using records and information already subject to comprehensive privacy and other protections in other Federal laws (e.g., records held by the Federal Government subject to the Federal Privacy Act, or records governed by HIPAA or FERPA)? Depending upon the scope of the exemption, the relationship between this exemption and the exemption proposed at § _.104(f)(2) would need to be clarified. Since a major justification for including this exemption is to reduce burden on IRBs, should the proposed exemption apply only to research for which IRBs typically waive informed consent, that is, where the research could not practicably be carried out without a waiver of informed consent, and the rights and welfare of subjects will not be adversely affected by the waiver? Finally, is there a sufficient need for this exemption at all given the other proposed exclusions and exemptions?

Response: IRB waiver of informed consent is frequently sought for this category of research. §___.104(e)(2), as written, may reduce burden on IRBs if investigators are using a decision tool to make this determination, but it is difficult to understand how the requirement for "notice" will be communicated to or implemented by entities that do not typically conduct human subject research. This is a much higher standard than under the current rule, and will make this exemption difficult to apply.

50. Public comment is sought regarding whether the proposed exemption should be limited to research in which individuals had been informed of the potential future research use of their information, and given the opportunity to opt out of having their identifiable private information used for research. If the proposed exemption should be limited in this way, what information should be included in the opportunity to opt out? If the opportunity to opt out is made a condition of the exemption category how should it be structured (e.g., how long and under what circumstances should it remain in effect) and what, if any, impact should the opt out have on other provisions of the rule, such as the ability of an IRB to waive informed consent for a subsequent research study using the individual's information? Are there other or alternative mechanisms that should be required to respect individuals' autonomy and other interests?

Response: Given that much of the information sought under such an exempt category is already subject to regulations such as HIPAA and FERPA, this requirement is not necessary. We do not support a time

limit for opt-out consent. As proposed this is very confusing.

51. Public comment is sought regarding what should constitute notice for purposes of this exemption category. Given the many different types of data that would be covered by this provision (e.g., data from private entities used for social or behavioral science research, government records for which laws already establish standards for notice, and data publicly available for harvesting from the internet), would it be possible to develop a uniform "notice" requirement? What type of notice, in terms of its dissemination and scope, should be considered to meet this requirement of the proposed exemption? With regard to the dissemination of the notice, should the notice requirement be permitted to be fulfilled through a general public notice, not specifically directed to individuals who are potential research subjects, such as the notice allowable under the Privacy Act? Would a prominent notice posted in all clinics or other relevant public places where information will be collected be acceptable? Should each individual whose data could be used receive their own notice, such as is required of direct treatment providers covered by the HIPAA Privacy Rule? With regard to the content of the notice required by this proposed exemption, what kind of information should be included in the notice, such as the types of research that might be conducted, privacy safeguards, contact information, etc.?

Response: Notice should not be required.

52. Public comment is sought on whether, on the other hand, prior notice is necessary. Is the notice requirement proposed for this exemption a meaningful and important measure to respect individual autonomy, particularly if the notice requirement could be fulfilled through a general public posting? Current practices suggest that IRBs will frequently waive informed consent for studies involving the secondary use of identifiable private information collected for non-research purposes. If the exemption were to exclude the notice requirement, but continue to require application of the data security and privacy safeguards of § _.105 and restrict the use of identifiable private information to only purposes of the specific research for which the investigator obtained the information, would the exemption better strike a reasonable balance between respect for persons and beneficence, while eliminating the current requirement for IRB review?

Response: We agree with CoGR's response to this question - "Given that IRBs frequently currently waive consent, there is no justifiable reason to add the notice requirement. However, keep in mind that IRBs commonly function as the Research Privacy Board under HIPAA, so this may not eliminate the requirement for Board review. The data security and privacy rules should not apply to this, as data which require specific treatment, such as patient records, are already covered under appropriate regulations. If the investigator wishes to use the information for secondary research, such activities would presumably require re-evaluation for use as excluded, exempt or covered under the Common Rule and would have to follow the appropriate rules as applicable."

53. Public comment is sought as to whether this exemption would provide appropriate protections for research conducted by clinical data registries, while enabling these research activities to proceed without delay, and what should be included in guidance regarding such activities. Public comment is sought regarding the extent to which other exclusions or exemption categories would apply to research conducted by clinical data registries, such that the conditions of this exemption category would not apply.

Response: Submission of information to clinical data registries will be evaluated under HIPAA regulations, so there is no reason to apply additional requirements.

54. Public comment is sought on whether the NPRM's proposal of exemption § _.104(f)(2) is the best option, or whether there is a better way to balance respect for persons with facilitating research.

Response: Research involving the use of biospecimens that have been stored or maintained for secondary research use should continue to be exempt without consent.

55. Public comment is sought on whether and how the provision regarding the return of research results in the proposed exemption § _.104(f)(2) should be revised.

Response: It would not be appropriate or practical for the federal government to establish a panel of experts to make determinations about returning unexpected findings to subjects. We see no reason why the research cannot remain exempt if results are returned to the subject.

56. Public comment is sought on whether there should be an additional exemption that would permit the collection of biospecimens through minimally invasive procedures (e.g., cheek swab, saliva).

Response: Yes. Such minimally invasive procedures should be treated in the same regard as collecting general information. The fact that they are biospecimens should not set them apart.

57. Public comment is sought on whether research involving prisoners should be permitted to apply any or all of the exemption categories found at proposed § _.104, either if the research consists mostly of non-prisoners and only incidentally includes some number of prisoners, as proposed in the NPRM, or if the research intends to involve prisoners as research subjects.

Response: We agree with CoGR's response to this question: "The exempt categories should stand and the inclusion of prisoners be allowed in cases where the research consists mostly of non-prisoners and only incidentally includes some prisoners. If the research intends to involve prisoners as research subjects then the exemption categories in 104 should stand except in the following situations: a) Studies covered under 104(e) which involve the collection of sensitive information when subjects can be identified directly or through identifiers linked to the subjects, and b) Any collection, use and storage of

biospecimens if the final Common Rule requires an identifiable linkage between biospecimens and individuals to allow investigators the ability to document consent for all biospecimens."

58. Would it be preferable for language at § _.104(b)(2) to resemble the 2002 epidemiologic waiver criteria and state that the exemptions apply except for research where prisoners are a particular focus of the research?

Response: See the answer above in 57.

59. Is the proposed application of the exemptions to subparts B and D appropriate?

Response: Yes.

60. What topics should be addressed in future guidance on improving the understandability of informed consent?

Response: Standard-of-care information should be moved into an appendix and only the information regarding the truly experimental component should be in the body of the consent. This change could occur immediately without a change in the regulation if OHRP and the FDA issued harmonized guidance to this effect.

61. Public comment is sought on whether broad consent to secondary research use of information and biospecimens collected for non-research purposes should be permissible without a boundary, or whether there should be a time limitation or some other type of limitation on information and biospecimens collected in the future that could be included in the broad consent as proposed in the NPRM. If a time limit should be required, is the NPRM proposal of up to 10 years a reasonable limitation? Would a limitation related to an identified clinical encounter better inform individuals of the clinical information and biospecimens that would be covered by a broad consent document?

Response: Broad consent for secondary research use of information collected for non-research purposes should not be required for research that otherwise meets the criteria for exemption under 104. No additional limitation should be imposed for information collected in the future outside of limitations already imposed through other laws and regulations (e.g., HIPAA, FERPA). Biospecimens should be handled the same way as information, and broad consent should not be required for federally-supported research when the specimens were collected for other purposes. There should be no time limits imposed.

62. Public comment is sought on whether all of the elements of consent proposed at § _.116(c) should be required for the secondary use of biospecimens or identifiable private information originally collected as part of a research study that was conducted without consent because either the original research study met an exclusion or exempt category

of research, or a waiver of consent was approved by an IRB.

Response: If the secondary research meets the criteria for exclusion or exemption, then consent should not be required. If it does not meet these criteria, then whether or not informed consent is required should be determined by the IRB. If the IRB determines that consent is required, then all elements of consent should be required unless they may be appropriately waived by the IRB.

63. Public comment is sought on whether oral consent should be permissible in limited circumstances as proposed under exemption § _.104(f)(1).

Response: If consent is required, oral consent should be permissible. However, given that oral consent applies only to exempt or excluded research, it is difficult to understand how this requirement is to be documented or regulated.

64. Would research subjects continue to be appropriately protected if the definition of "legally authorized representative" were broadened to include individuals authorized by accepted common practice to consent on behalf of another individual to participation in clinical procedures? If the definition of "legally authorized representative" was broadened in this way, public comment is sought on the interpretation of "accepted" and "common" as these terms would be used in the revised definition.

Response: Yes. The definition of "legally authorized representative" should be broadened to cover anyone providing such authorization for clinical procedures. Note. Who can consent for clinical procedures can vary from state to state because it's controlled by state law.

65. Public comment is sought on how the waiver criterion regarding "practicably" at § _.116(d)(3) could be explicitly defined or otherwise clarified (e.g., what term should replace "practicably"?).

Response: The term "practicably" could be replaced with "reasonably feasible"; capable of being effective, done or put into practice so as to be feasible.

66. Public comment is sought on the proposed differences between the criteria for waiving informed consent for the research use of biospecimens versus identifiable information.

Response: The same criteria should be applied for identifiable information as for biospecimens. There should not be a different standard and IRBs should have the ability to waive consent for research use of biospecimens as they do under the current rule.

67. Public comment is sought on whether the proposal to permit an IRB to waive consent for research involving the use of biospecimens should be included in the regulations.

Response: We believe IRBs should continue to be authorized to waive consent based on the merits of the scientific knowledge to be gained, weighed against respect for individuals' rights to consent.

68. Public comment is sought on the proposal to permit an IRB to waive consent for the secondary use of biospecimens or information originally collected for research purposes, even if the original research study required subjects' informed consent.

Response: The IRB should be permitted to waive consent for secondary research under these conditions unless original research consent a) excluded the possibility of secondary research, b) informed the subject that secondary research would be limited in a way which does not include the newly proposed research, or c) contained an opt-out or opt-in section for subjects to indicate their willingness for the data or biospecimens to be used for future research.

69. Public comment is sought regarding how likely investigators are to seek broad consent for the use of identifiable private information (as contrasted with biospecimens), given that there are provisions within the NPRM that would make it easier to do such research without consent (such as the new exemption at § _.104(e)(2)). In this regard, note that 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 might create a disincentive on the part of investigators from choosing to seek broad consent for research involving secondary use of identifiable private information. Given the costs and time and effort involved in implementing the system for obtaining broad consent for the use of identifiable private information and tracking when people provide consent or refuse to do so, are the benefits to the system likely to outweigh the costs, and if so, should the broad consent provisions be limited to obtaining broad consent for research use of biospecimens?

Response: We do not support the requirement for broad consent for both information and biospecimens.

70. Public comment is sought on the proposed prohibition on waiving consent when an individual has been asked to provide broad consent under § _.116(c) and refused. In particular, how would this prohibition on waiving consent affect the secondary research use of identifiable private information?

Response: Each research project should be viewed independently. If the consent was sought in conjunction with any specific protocol, irrespective of how broad the consent was, this should not represent a prohibition on waiving consent for secondary research.

If an individual was asked to provide such consent, should the absence of a signed secondary use consent be considered a refusal?

Response: No, particularly given that oral consent is considered to be permissible.

Does this prohibition on waiving consent for the secondary use of identifiable private information create a disincentive for institutions to seek broad secondary use consent and instead seek a waiver of consent from an IRB?

Response: Yes.

Under what circumstances, if any, would it be justified to permit an IRB to waive consent even if an individual declined or refused to consent?

Response: An IRB should not over-ride the wishes of the individual for that same project.

71. Public comment is sought regarding whether particular information security measures should be required for certain types of information or research activities and, if so, what measures and for what types of information or research. Specifically, should the safeguards be calibrated to the sensitivity of the information to be collected?

Response: The data security section of the NPRM is one of the most difficult to respond to because it is so undeveloped. Patient information is already covered by HIPAA security standards, student records are already covered by FERPA, and other standards cover financial and various other types of sensitive information. There is no need for the Common Rule to regulate the security systems for these data. This section should be removed from any revised NPRM, as well as the final rule.

72. Are the proposed limitations on re-disclosure more or less restrictive than necessary? Are there additional purposes for which re-disclosure of biospecimens or identifiable private information should be permitted?

Response: Re-disclosure should be maintained at the same level and standard as exists in the current rule and does not need to be changed.

73. Will the proposed language at § _.101(j) be effective in achieving greater harmonization of agency guidance, and if not, how should it be modified?

Response: The language will not be effective. The only way to achieve true harmonization is by co-issuing policies and guidance. This needs to be addressed at a higher governmental level.

74. Is mandated single IRB review for all cooperative research a realistic option at this time? Please provide information about the likely costs and benefits to institutions. Will additional resources be necessary to meet this requirement in the short term? Should savings be anticipated in the long run?

Response: Mandated single IRB review for all cooperative research will not assure that the best IRB model is being used for all studies and therefore will not provide the best protection for human subjects. It should not be mandated, but rather encouraged where it can be appropriately applied. This can be

accomplished by creating incentives such as grant opportunities and providing dedicated funding for building infrastructure for central IRBs.

75. What areas of guidance would be needed for institutions to comply with this requirement? Is there something that OHRP could do to address concerns about institutional liability, such as the development of model written agreements?

Response: The single IRB model should be encouraged and supported with special grant funds. Guidance on model agreements is not needed. There are already many successful model agreements, but by accepting the role of IRB of record the reviewing IRB incurs extra responsibilities and costs. When funded by NIH, NIH should provide additional support to cover these costs. It would be useful for OHRP to clarify issues of institutional liability through guidance.

76. Would it be useful for this requirement to include criteria that Federal departments or agencies would need to apply in determining whether to make exceptions to the use of a single IRB requirement? If so, what should these criteria be?

Response: As noted above, single IRBs are not appropriate for all multisite research. For example, use of single IRB should not be extended beyond studies where there is an identical protocol implemented at all sites. Single IRB is not the best model for studies that are designed for collaboration across several institutions in which each institution has a discrete role based on local expertise or resources.

Single IRB is also most appropriate when there is a plan to run several protocols through the same IRB. If the single IRB model is not coupled with multiple projects, it will not save time. Applying such a policy to studies with two or more sites would be inefficient. It is important to note that social and behavioral science will not be not better served by mandated use of single IRB review. This model is more appropriate for medical clinical trials and should be restricted primarily to these types of studies, not to minimal risk research.

77. Are the exceptions proposed appropriate and sufficient, or should there be additional exceptions to this mandate for single IRB review than those proposed in the NPRM? If additional exceptions should be included, please provide a justification for each additional exception recommended.

Response: The current exceptions proposed in the NPRM are not adequate. We do not support the single IRB mandate and argue that exceptions should always be allowed. The single IRB model should be a choice, not a mandate.

78. Is three years appropriate timing to establish compliance with this provision?

Response: Three years is not enough time. Even if funding is provided, it would still be difficult to apply this model as broadly as proposed. We suggest piloting the option to conduct studies under the single IRB model through a limited number of NIH funding mechanisms where large collaborative groups already exist, similar to the NCI model.

79. How often should the Secretary's list of minimal risk activities be updated? Should advice be solicited from outside parties when updating the list?

Response: We suggest that the list be updated at a minimum of every five years. OHRP should solicit advice from the broad community whenever making such updates. We also support allowing IRBs to use expedited review for any studies that are no more than minimal risk. This would significantly reduce the administrative workload of investigators and institutions without reducing human subject protections.

80. Is this Secretarial list of minimal research activities a useful tool for the research community, or does it represent a loss of IRB flexibility in risk determination?

Response: IRBs should be allowed to determine studies that fall outside of the list to be minimal risk and eligible for expedited review.

81. What should IRBs consider when reviewing the plans for returning research results, for example, what ethical, scientific, or clinical concerns?

Response: The nature of the information should be considered if individual research results are to be returned. If the results relate to clinical conditions, then appropriately licensed healthcare professionals should be allowed to return information without restriction.

82. Is the § _.111(a)(3) and (b) focus on issues related to coercion or undue influence in research with vulnerable populations, and not other considerations related to vulnerability, appropriate? Note that this focus also appears in proposed § _.107(a).

Response: The populations and considerations as proposed in the NPRM are appropriate.

83. Should pregnant women and those with physical disabilities be included in the category of subpopulations that may be vulnerable to coercion or undue influence?

Response: No.

84. Should populations be considered vulnerable for reasons other than vulnerability to coercion or undue influence? Are the proposed categories appropriate?

Response: The proposed categories are appropriate.

85. Public comment is sought on whether there might be unintended consequences from the clinical trials expansion proposed in the NPRM in § _.101(a)(2)(i)). Unintended consequences may include an increase in burden or costs, or an inappropriate redistribution of costs.

Response: Extending the Common Rule to all clinical trials, regardless of funding source, at an institution that receives federal funding for non-exempt and non-excluded human subject research (§_.101(a)(1)) will not strengthen human subject protections as suggested in the NPRM. Most U.S. academic medical centers and institutions of higher education already review all human subject research through an IRB whether or not it is regulated by OHRP or the Food and Drug Administration (FDA).

The proposed regulation will have unintended consequences by increasing the administrative burden associated with the conduct of minimal risk behavioral and social science research that involves randomization without adding protections to the human subjects involved in these trials. Furthermore, this change will not impact the organizations, such as private hospitals, clinics, or other health-related entities that do not receive federal funds and conduct clinical trials, that likely cause the greatest concern for the public.

The proposed regulation will increase the administrative burden on both institutions and researchers, create delays in research, increase the costs of research, and potentially discourage some collaborative research. It removes institutions' ability to be flexible with how they apply the regulations without increasing human subject protections. We strongly oppose the proposed expansion. We also recommend that the definition of "clinical trial" should be limited to research studies of "greater than minimal risk" and not include "behavioral health-related outcomes."

86. Public comment is sought as to whether the criterion that the policy extends to all clinical trials conducted at an institution that receives federal support (see the NPRM at § _.101(a)(2)(i)) should be further clarified in some way. For example, should it specify a timeframe for support (e.g., within the past number of years), or a minimum monetary threshold value?

Response: This requirement should be eliminated from the revised Common Rule.

87. Public comment is sought on whether the definition of clinical trial (NPRM at § _.102(b)) should include additional explanation of what is encompassed by the term behavioral health-related outcomes.

Response: If retained, this term should be explained more clearly. However, we believe that this requirement should be eliminated from the revised Common Rule.

88. Would protection to human subjects in research be enhanced if OHRP conducted routine periodic inspections to ensure that the membership of IRBs designated under FWAs satisfy the requirements of § _.107?

Response: OHRP should not consider conducting inspections of IRB membership. This would constrain OHRP's already limited resources.