INTERNATIONAL SOCIETY FOR BIOLOGICAL AND ENVIRONMENTAL REPOSITORIES

To:

Jerry Menikoff, MD, JD
OHRP, 1101 Wootton Parkway, Suite 200,
Rockville, MD 20852

Date: 11/24/2015

Re: Comments on Notice of Proposed Rulemaking for Revisions to the Common Rule - ID number HHS– OPHS–2015–0008

Dear Dr. Menikoff,

The International Society for Biological and Environmental Repositories (ISBER) appreciates the opportunity to submit the following comments on the Notice of Proposed Rulemaking for Revisions to the Common Rule, ID number HHS-OPHS-2015-0008.

ISBER is an international organization addressing the technical, legal, ethical, and managerial issues relevant to repositories of biological and environmental specimens (see www.isber.org for additional information). Although not restricted to repositories and biobanks involving human biological materials, the great majority of ISBER members focus on the management of biobanks and repositories of human tissues and associated data procured for research purposes, either directly or indirectly (e.g. from clinical specimens procured for non-research purposes). ISBER membership and expertise in the area of human specimen biobanks is extensive and longstanding, and representative of the best practices in the field. ISBER's Best Practices for the Collection, Storage, Retrieval, and Distribution of Biological Materials for Research, that were published in Biopreservation and Biobanking, April 2012, reflect the collective experience of its members and have received broad input from other biobank professionals. ISBER's membership is global and includes thought leaders worldwide with expertise in bioethics and policy issues related to biobanks. With this expertise, we believe ISBER is in a unique position to provide input on the proposed Rule.

ISBER appreciates the opportunity to comment on the Notice of Proposed Rulemaking (NPRM) to modernize, strengthen, and make more effective the Federal Policy for the Protection of Human Subjects. We agree with the major goals of the proposed Rule to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators. However, while some of the proposed changes will help further these goals, others will significantly impede important research, particularly low-risk projects involving the use of human specimens and associated data for research.

We strongly agree that informed consent should be obtained when it is known at the time specimens are collected that they will be used for research and it is possible to do so. However, we are greatly concerned about the impact on important research using archived clinical specimens collected after the compliance date for which it was not possible to obtain consent or waive consent under the new, very stringent waiver criteria. ***As explained further below, the end result will be missed opportunities in answering important research questions critical***

to the health and welfare of patients and the public and lost lives or increased morbidity resulting from delays in such research.

Impact on Important Research Involving the Use of Residual Archival Pathology or Other Specimens Collected During the Course of Routine Care

ISBER is greatly concerned about the impact of the proposed Rule on important research involving the use of residual pathology or other biospecimens collected during the course of routine health care. These specimens have been used in the development of tests to predict response to therapies for breast cancer; the isolation and characterization of the 1918 flu virus; and the identification of helicobacter pylori as a cause of gastric ulcers, which also has been linked to the development of stomach cancer. Many of these important findings were obtained from the use of previously existing archived collections for which informed consent could not be obtained.

The NPRM now proposes requiring consent for nearly all research involving human biospecimens, (regardless of identifiability). In addition, the criteria for a waiver or alteration of consent have been changed so that a waiver of consent for research involving biospecimens will occur only in very rare circumstances. Specifically, the two new waiver criteria that have been added for research use of biospecimens (in addition to the other criteria for a waiver specified in the Rule) are:

(1) There are compelling scientific reasons for the research use of the biospecimens; and

(2) The research could not be conducted with other biospecimens for which informed consent was obtained or ***could be obtained***.

As indicated previously, ISBER strongly agrees that consent should be sought whenever it is known that specimens will be used for research and it is possible to do so. However, there will be many situations after the compliance date where research is not foreseen when specimens are collected during the course of routine care in hospitals and clinics and when it is not possible to implement institution-wide procedures to obtain broad consent. The requirement for consent with only a very narrow waiver provision is likely to have a significant impact on the use of human specimens that are collected during the course of routine care, especially the use of clinical archival specimens, for which research use was not initially envisioned or for which it was not possible to seek broad consent for future use. In addition, in practice, IRBs are unlikely to grant any waivers. Furthermore, efforts to re-contact patients to obtain a research consent for residual specimens collected during the course of routine care are usually not successful. Often, patients cannot be located because they may move out of the hospital system or re-locate. Additional concerns are the biases that will be introduced that may result in harms to patients if research on treatments reaches incorrect conclusions. Furthermore, certain minority or other underserved populations may be excluded from important studies if sites at which archival specimens are located are not able to implement institution-wide broad consent processes.

While de-identified specimens collected prior to the compliance date are grandfathered in, this does not solve the problem. As explained below, the consent requirement with a very narrow waiver provision would hinder many important, low-risk retrospective studies involving the use of pathology specimens. New prospective studies would have to be initiated, many of which may take years to complete because of the need for long term follow-up, delaying the development of new diagnostic, prognostic and markers of response to therapy resulting in lost lives and lost opportunities.

Logistical Difficulties and Resource Requirements of Obtaining Institution-Wide Consent for Research in the Clinical Setting

It is difficult to know in advance which specimens collected during the course of routine care will be used for future research. Therefore, in order to make sure that clinically collected materials such as pathology or other residual specimens can be used for future research that is not yet envisioned, hospitals and clinics will have to implement institution-wide approaches to obtain broad consent from all patients seen at the hospital or clinic. The resource requirements and logistical difficulties of obtaining broad consent in the clinical setting are significant, as previously discussed by the Secretary's Advisory Committee on Human Research Protections in their comments to the HHS Secretary on the Advanced Notice of Proposed Rulemaking (2011) and others more recently in the literature (Botkin, 2015). Obtaining consent in a clinical setting is often logistically difficult because there can be multiple different entry points within a single hospital system. In addition, systems will need to be established and maintained to track the consent for all specimens that are collected in the course of routine care. Given these resource requirements and logistical challenges, it is unlikely that many hospitals and clinics would be able to implement institution-wide practices for obtaining broad consent.

It is not clear who will pay for the cost of seeking consent for the future research use of specimens collected during the course of routine care. The costs will only be covered by grant funds when there is specific project for which specimens will be collected and/or used. Will implementing hospital-wide processes for all clinically collected specimens (many of which may never be used for research) raise the costs of health care? **The end result may be 1) increases the costs of health care in a non-transparent way or 2) most hospitals and clinics will simply not implement institution-wide consent processes or 3) consent will be obtained in a pro-forma approach.**

An Example Illustrating the Impact on Important Retrospective Research Resulting in Delayed Benefits to Patients and Lost Lives

Our concerns about the impact on important retrospective research involving residual clinical specimens are illustrated in the following example:

> A researcher wishes to determine whether her research findings about a new marker of response to therapy can be extended to a certain minority population of breast cancer patients. She has determined that a small community hospital has a sufficient number of cases in the hospital pathology archives with clinical and follow-up data already available. The biospecimens were collected 5 years after the compliance date for the new Rule. However, the hospital did not envision this research at the time the pathology specimens were collected and did not have the resources to implement a process to obtain consent for all patients seen at the hospital for the research use of all residual specimens collected during the course of routine care. Efforts to re-contact the study subjects to obtain consent are not likely to be successful because patients often move in and out of hospital systems and cannot be located. In spite of these challenges, the research will not meet the criteria for a waiver under the new waiver criteria in the NPRM because a new study could be initiated prospectively in which **consent could be obtained**. Even though de-identified biospecimens could be used for the research with minimal risks to subjects, the research would not be permissible without a new consent. Because of the difficulties of recontacting the patients, the existing biospecimens, that already have the needed 5 years of clinical follow-up data, could not be used. The researcher would have to initiate a new, more expensive prospective study to consent new patients. Patients would be inconvenienced and put at some minimal risk to begin a new study. Perhaps more importantly, the researcher would have to wait at least 5 years to get the necessary clinical and follow-up data. ***This would delay patients from any benefits of the research by at least 5 years and at considerable additional costs.***

This example used a small community hospital and minority subpopulations. However, other types of hospitals and clinics will be affected. Due to resource limitations, non-academic hospitals and clinics will not implement a consent process from all patients. As a result, some populations served by these institutions may be excluded from important research (such as the underserved, economically disadvantaged or minority populations). This may result in research findings that may not be generalizable to those populations. This is a major justice issue and could result in actual harms to individuals to those groups if those groups are not included in the initial studies.

Ethical Considerations

In addition to the practical implications of the proposed Rule on important retrospective research and impact on patient lives and public health, we find the proposed Rule problematic from an ethical standpoint. The NPRM seeks input on whether the proposed changes within the NPRM strike a reasonable balance among the core ethical principles of the Belmont Report, i.e., respect for persons, beneficence and justice. In our view, the proposed requirements with regard to biospecimens do not appropriately balance respect for persons (embodied as the ethical principle of autonomy and implemented in the consent requirement) with the other ethical principles of beneficence and justice. While we agree that autonomy is an important principle, the NPRM gives too much weight to autonomy with regard to biospecimens over the ethical principles of beneficence and justice, by requiring consent to use biospecimens (even those that are de-identified) for research except under very limited circumstances. As explained previously, this requirement will have a serious negative impact on important retrospective studies involving the use of residual specimens collected during the course of routine care, particularly archived clinical specimens, and does not allow autonomy to be balanced with the social value of research that will ultimately lead to improvement in medical care and health of the public. **Respecting autonomy at the expense of patient lives is a significant ethical concern.**

Differential Treatment of Biospecimens and Data

Throughout the NPRM, biospecimens and data are treated very differently. Biospecimen research is subject to more stringent requirements than research using clinical/phenotypic information, as well as whole genome sequence data.

For example, the definition of human subjects has been expanded to include "obtains, uses, studies, or analyzes biospecimens", but genomic data is not included. Another example is the requirement for consent for research on human specimens, even when de-identified, but research on de-identified data (which may include genomic data) does not require informed consent. Moreover, the NPRM allows for oral consent, when certain conditions are met, for the use of private identifiable information but requires written consent for research using biospecimens.

A compelling rationale has not been provided for this differential treatment of specimens and data. Research using clinical and genotypic or phenotypic data potentially have a much greater risk than research using biospecimens. While the NPRM points to surveys that suggest that people want to be asked about the use of their biospecimens, surveys also suggest that they want to be asked about the use of their medical record data. Again, this differential treatment of biospecimens and data is not justified.

Overreliance on Broad Consent

The NPRM places too much reliance on broad consent and not enough attention to governance and oversight of research on biospecimens. While a broad consent should be permissible in appropriate circumstances, it should be used in conjunction with mechanisms to ensure that specimens are used in ways that are ethically appropriate (Grady, 2015), especially since it is unknown at the time the specimens are collected what new technologies they may be used for in the future. For example, without IRB review subpopulations might be stigmatized by certain research approaches or findings.

Impact on International Collaborations

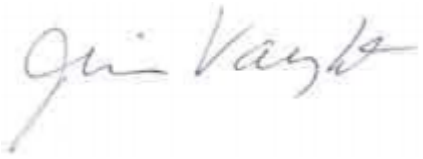
Finally, ISBER is very concerned about the impact on international collaborations. Our understanding is that many countries require IRB or comparable review before researchers may access specimens from biobanks (Rothstein, 2015). However, when a broad consent is used for the future research use of specimens, the NPRM only requires IRB review if research results are to be returned. Thus, many countries may not find the regulations adequate for their participation in research collaborations.

Recommendation:

In order to address ISBER's concerns, we recommend that IRBs continue to be able to waive consent for the research use of de-identified archived clinical specimens using the criteria of the current Common Rule. If this is not possible, we recommend that Alternative Proposal A be adopted rather than the primary proposal. While Alternative Proposal A is not an optimal solution, it is far preferable to the primary proposal because this choice will reduce the impact of the proposed changes on research, medical advances and human lives, and more closely balance autonomy with beneficence.

On behalf of ISBER

Jim Vaught, ISBER President 2015-2016



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Rothstein, Mark unpublished data presented at Public Responsibility in Medicine and Research Annual Meeting, 2015.