Missed Opportunities and Lost Lives: Consequences of Some Proposed Changes to Regulations on Research with Human Tissues

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Archival collections of paraffin blocks remaining after the diagnosis and treatment of diseases are frequently touted as a "treasure" in the study of human diseases. If so, why are the Department of Health and Human Services and other federal departments and agencies proposing to put this treasure out of reach for much of future research?

On September 8, the Department of Health and Human Services and 15 other federal departments and agencies published in the Federal Register a "Notice of Proposed Rule-Making" (NPRM) with the goal of modernizing, strengthening, and making more effective the Federal Policy for the Protection of Human Subjects that was promulgated as a Common Rule in 1991 (1). Specifically, this NPRM proposes future changes, after a compliance date, to the Common Rule requiring consent for nearly all research on biospecimens, even when the specimens are de-identified or anonymized. While broad consent for future use is permissible, there is only a very narrow and restricted provision for an IRB waiver of informed consent. Two new waiver criteria (in addition to those for other research) are included for the use of biospecimens: 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. According to the NPRM, waivers of informed consent for research use of biospecimens are expected to be very rare, leaving much less flexibility to local IRBs.

I agree that informed consent should be sought prospectively when it is known at the time the specimens are collected that they will be used for research purposes. However, the provisions proposed in the NPRM will have a significant impact on the collection and use of biospecimens, particularly those collected during the course of routine care. While biospecimens collected prior to the compliance date would not be subject to these proposed requirements, this does not solve the fundamental problem. The problem is that when surgery is performed, it is often unknown whether the tissues remaining in the paraffin blocks (archival blocks) will be needed for future research. To ensure the use of future archival collections, as a minimum, the proposed changes in the Common Rule and other regulations would require obtaining broad

informed consent on all surgical patients from whom tissues are removed. In most medium to large medical centers, this task would involve obtaining informed consent from about 20,000 to 40,000 patients per year. In most cases, the resources for obtaining such consent will be insufficient, as is the infrastructure to maintain and follow up on such consents. Thus, many archival specimens would be ineligible for use in research unless patients were contacted for an additional consent for this purpose. Such re-contact is usually unsuccessful, as many patients move in and out of hospital systems. Re-contact may also be perceived as intrusive and an unwarranted invasion of privacy.

Currently, most translational research using archival collections is performed without problems based on a waiver of consent by the local IRBs. If this were no longer permitted except in very rare circumstances, translational research would be crippled and many advances in medical care would be delayed. This proposal would also reduce research studies focused on minorities, increase racial disparities, and introduce biases into research because only selected patients will be studied. Many hospitals, especially smaller community hospitals, will not likely have the resources to implement consent for all biospecimens collected during the course of routine care. Thus, important retrospective studies involving underserved populations seen at these hospitals could not be conducted, and these populations would be excluded from these studies. An example is presented after my recommendations.

The ethics of this proposal are also of concern. As illustrated below, the proposal will, except in rare cases, inhibit the use of many archival specimens for retrospective research studies. Hence, there is almost a complete emphasis in the proposed modified Common Rule on patient autonomy, with little consideration of the social value and benefit of this kind of research or issues relating to justice. This will result in a great decrease both in research and in improvements in medical care, leading to missed opportunities and lost lives caused by delays in the development of new responses to therapy, therapeutic approaches, and other research affecting medical care.

Many of these same concerns were addressed in the comments submitted in response to the previously proposed rules in the Advanced Notice of Proposed Rulemaking by the Secretary's (e.g., Health and Human Services) own Advisory Committee on Human Research Protection (SACHRP; ref. 1). Unfortunately, many of the same problems remain and this proposal will have the same serious adverse consequences envisioned in the prior comments.

It is important to note that two alternative proposals are presented in the NPRM. "Alternative Proposal A" requires consent only for all whole- genome sequencing studies. Of the alternative proposals presented, Proposal A, while not an optimal solution, should be considered because this choice will reduce the impact of the proposed changes on research and more closely balance autonomy with beneficence.

In conclusion, I believe that the primary proposals related to biospecimen research in the NPRM will not, in fact, accomplish one of the stated goals of this NPRM to "facilitate cutting edge research in genomics and other 'omics' such as the transcriptome and the microbiome, which

generate a wealth of data from biospecimens designed to inform the development of treatments and preventative measures for chronic diseases such as cancer." Furthermore, in my view, it does not appropriately balance the principles of autonomy, beneficence, and justice for the use of archival specimens collected during the course of routine care and will lead to missed opportunities and lost lives due to delays in important research.

Given the potential importance of the proposed changes, I encourage readers to review what is being proposed in the NPRM (2) and to submit comments, identified by docket ID number HHS–OPHS–2015–0008, by the **December 7, 2015 deadline** in one of the following ways:

1) To comment, go to the Federal eRulemaking Portal (http://www.regulations.gov):
    a. Enter the docket number HHS– OPHS–2015–0008 in the ''SEARCH for: Rules, comments, Adjudications or Supporting Documents" field and click on ''Search.''
    b. After the search, the Proposed Rule by HHS on 09/08/2015 will display. Click on ''Comment Now!'' and follow the instructions.
2) Mail paper, disk, or CD–ROM submissions to the following address:
    a. Jerry Menikoff, MD, JD, OHRP, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852.
    b. As noted in the NPRM, comments received, including any personal information, will be posted without change to http://www.regulations.gov.

Input from ALL stakeholders, especially individual investigators, in addition to associated scientific organizations, is necessary to ensure that important research can proceed using archived human specimens, while at the same time protecting the rights and welfare of research participants. This input should include examples from researchers of how the proposed changes would affect future use of archived specimens. Individuals who wish to provide feedback should consider the following approach:

1) The waiver of informed consent by IRBs should continue to be permitted for archival tissues using the waiver criteria in the current Common Rule.
2) If this is unacceptable, of those alternative proposals suggested in the NPRM, Alternative Proposal A should be utilized.

The following example demonstrates the potential impact on retrospective studies involving pathology specimens:

> A researcher wants to use residual prostate cancer specimens from the pathology archives from a small community hospital that were collected 5 years after the compliance date for an important study to look at new markers of response to therapy in African-American prostate cancer patients. However, the hospital did not envision this research at the time the pathology specimens were collected. Furthermore, the hospital did not have sufficient resources to implement a process to obtain consent for the research use of all residual specimens collected during the course of routine care at

that hospital. The research will answer an important research question about the response to therapy in African-American patients. It would not be possible to seek consent from all patients whose pathology biospecimens would be studied, as many patients move out of the hospital system and/or cannot be located.

In spite of these constraints, we do not think that this research would meet the criteria for a waiver under the new waiver criteria for biospecimens proposed in the NPRM because a new study could be initiated prospectively if sufficient resources were available. The retrospective research study would not be permissible, even though the biospecimens could be evaluated in a de-identified way, with few risks to study subjects. A new prospective study would have to be initiated to obtain consent from patients and collect new biospecimens, and patients would need to be followed for many years to obtain the required outcome data. This would inconvenience and put at some minimal risk the new patient populations being studied, and would be costly and wasteful of existing resources when the necessary specimens and follow-up data already exist. Perhaps most importantly, because time would be required in a new prospective study to accrue the follow-up data (sometimes 5 –10 years) delays in translating important research to the bedside would result (e.g., new markers of response to therapies), in turn resulting in lost lives, as well as missed opportunities to improve medical care. In addition, important patient populations would be excluded from research. This is not only an issue of justice, but could lead to harm to patients if results from research studies are not generalizable to all populations. While this example focuses on small community hospitals, implementing consent for all biospecimens collected by a hospital may be challenging at even well-resourced hospitals, hampering retrospective studies on archived biospecimens and requiring new prospective studies to be initiated.

Disclaimer: The interpretations represented herein are a summary of the author's personal understanding of the proposed Rule and do not represent legal analyses or opinions. In addition, the viewpoints expressed herein represent the personal perspectives of the author and not the views of any affiliated organizations.

References

1. U.S. Department of Health & Human Services Secretary's Advisory Committee on Human Research Protections (SACHRP). [cited 2011 Oct 13]. Available from: http://www.hhs.gov/ohrp/sachrp/commsec/index.html).
2. Federal Register, Vol. 80, No. 173, Federal Policy for the Protection of Human Subjects; Proposed Rules, September 8, 2015. [cited 2015 Oct 10]. Available from: http://www.gpo.gov/fdsys/pkg/FR-2015-09-08/pdf/2015-21756.pdf.

AACR American Association for Cancer Research

Clinical Cancer Research

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