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Proposed Regulations for Research with Biospecimens: Responses from Stakeholders at CTSA Consortium Institutions

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Abstract

Secondary research with biospecimens acquired through clinical care and through research is often conducted without the informed consent of individuals from whom the specimens were acquired. While such uses are consistent with the current federal regulations, surveys of the general public suggest that many individuals would prefer more information and choice regarding research use of biospecimens. The federal government issued an Advance Notice of Proposed Rulemaking (ANPRM) in 2011 that proposed a number of potential changes in the regulations governing human subjects. These proposed regulations are particularly pertinent to institutions committed to research involving human subjects – including institutions in the NIH-funded Clinical and Translational Science Awards (CTSA) consortium. In this study, we reviewed public responses by CTSA-funded institutions and CTS-affiliated organizations and groups regarding the proposed changes in the ANPRM with respect to research with biospecimens. Our results indicate that the majority of responses to the ANPRM from CTSA institutions were not supportive of the proposed changes. While many responses acknowledge a need to change current research practices regarding biospecimens, the proposed changes in the ANPRM received only limited support from this subgroup of academic research institutions.

Keywords

biospecimens; informed consent; ethics

INTRODUCTION

Biospecimens are utilized in a wide range of biomedical research projects. Following the use of biospecimens in research protocols that authorized their initial collection, biospecimens are often retained for future research uses. Further, biospecimens for research are often acquired from clinical sources when the residual specimens are no longer necessary for their original clinical purpose. Biospecimens also may be obtained specifically for a biobank for future research uses that may not be fully anticipated at the time of collection. The ethical and regulatory challenges that arise in the use of biospecimens are due primarily to the use

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of these resources in times and locations that are remote from their acquisition. The potential for future, unanticipated uses of research and clinically acquired tissues creates challenges for the role of informed consent in guiding those uses. Accordingly, the ethical and regulatory debates regarding research with biospecimens turn primarily on questions about how much information and control the individuals from whom specimens were obtained should have over the future uses of their specimens.

The literature demonstrates that most individuals are supportive of research in general and willing to provide biospecimens for research purposes [Brothers et al., 2011; Hull et al., 2008; Kaufman, 2009; Kaufman et al., 2012; Murphy et al., 2009; Simon et al., 2011; Vermeulen et al., 2009]. However, these same surveys also demonstrate that people want to know whether research is being conducted with their biospecimens and many individuals want some choice over the purposes for which their tissues will be used. Current practices are not consistent with these expectations. The federal regulations permit research on tissues without the informed consent of the source individuals in several situations. The definition of human subjects stipulates that research using de-identified tissues (or data) does not constitute human subjects research [Department of Health and Human Services, 2009]. The Office for Human Research Protections (OHRP) has clarified that this applies when the tissues or associated data are not readily identifiable to investigators using the biospecimens, even if the specimens are coded and identifiable by someone else who holds the key to the code [Office for Human Research Protections 2008]. Thus biospecimens that are banked in an identifiable fashion can be distributed to investigators in a coded fashion and, as long as the receiving investigators cannot readily identify the individuals from whom the materials were obtained, they are not conducting human subjects research. The fact that biospecimens can be used in this way for secondary research may not be addressed in the original consent process by which the specimens were obtained. That is, the regulations permit specimens to be used for purposes that are entirely different than the original research purpose for which the individual consented. In other contexts, projects may be considered exempt under 46.101(b)(4) or investigators can request a waiver of the requirement to obtain informed consent. If an institutional review board (IRB) finds that the four waiver criteria are met under 45CFR46.116(d), research can be conducted on identifiable biospecimens or records without the informed consent of the source individuals. In this context, the two most relevant waiver criteria are a determination about whether the research confers no more than minimal risk and whether obtaining consent for secondary uses would be impracticable.

Research with biospecimens often involves the use of relatively large numbers of samples that have been acquired over years and perhaps from geographically diverse locations. Therefore it is often considered impracticable for investigators to re-contact and obtain consent from individuals for additional research with their biospecimens. Further, the risks associated with tissue-based research are typically low and IRBs can justifiably consider such research to be no more than minimal risk. The net effect is that an unknown but potentially large proportion of secondary research with biospecimens acquired through research and clinical sources is conducted without the specific informed consent of the individuals from whom they were obtained.

The mismatch between the expectations of the public for knowledge and, potentially, more choice regarding the use of their specimens and data in research and the routine IRB approval of such research without the knowledge or specific consent of those individuals has created concerns over current research practices with biospecimens and associated data [Hayden, 2012; Tomlinson, 2013]. Public concern is illustrated by two lawsuits against the state newborn screening programs in Minnesota and Texas [Lewis et al., 2011]. These lawsuits arose over the practice of saving residual newborn screening bloodspots after the completion of clinical testing for a variety of purposes, including research. Parents were not

made aware of this practice and had not been asked for their permission for research with their child's residual sample. The popular book, *The Immortal Life of Henrietta Lacks* by Rebecca Skloot, also raises the issue of consent for research with biospecimens to greater public awareness[Skloot, 2010]. The book portrays the development of the HeLa cell line from tumor tissue acquired from Henrietta Lacks in 1951 following a clinical procedure, but without the permission of Mrs. Lacks or the knowledge of her family after her death. The book conveys the sense that Mrs. Lacks and/or her family members were harmed or wronged by not being informed or compensated for the contribution she made to biomedical science. Nisbet and Fahy found that the consent issues raised by the Skloot book dominate the articles about the book in international media [Nisbet and Fahy, 2013].

In July 2011, the Department of Health and Human Services (DHHS) issued an Advance Notice of Proposed Rulemaking (ANPRM) with preliminary proposals to change the federal regulations governing human subjects research in a number of way [Department of Health and Human Services, 2011]. One section of the ANPRM addressed research with biospecimens and the nature of individual decision-making with regard to this type of research. The purpose of the ANPRM is to present proposals for public comment, after which a Notice of Proposed Rulemaking may be issued toward a final step of enacting new regulations.

A basic change DHHS proposed in the ANPRM with respect to Biospecimens would be to require informed consent for the use of specimens acquired from both research and clinical sources [Emanuel and Menikoff, 2011]. The proposed rule stipulates that the consent form in the clinical context could be brief and open-ended, that is, the consent need not include a specific description of potential research uses of the specimen. Further, a consent document would not need to be signed each time biospecimens are collected. Further, in the research context, it would no longer be appropriate to de-identify specimens and then use them for purposes that were not covered in the original research consent process. The ANPRM proposes that these changes would only govern specimens collected after the effective date of the new regulations. With strict data security measures in place and with the consent of tissue sources as described, the ANPRM proposes that research with biospecimens would require only limited IRB oversight. The ANPRM asks for comment on 74 questions, seven of which pertain directly to research with biospecimens.

We are currently conducting an NIH-funded study of the policies and practices of Clinical and Translational Science Award (CTSA) -funded institutions regarding human subject policy and procedures in biospecimen-dependent research. The CTSA consortium consists of 61 US institutions that are funded by the NIH to conduct innovative clinical and translational research [Clinical & Translational Science Awards][<https://www.ctsacentral.org/>]. We are seeking to understand the range of practices for these institutions and address the question of whether differences in policies or practices inhibit the conduct of multi-center investigations. The proposed changes in the ANPRM would substantially change the regulations governing this type of research. We therefore decided to evaluate the response of CTSA institutions to the ANPRM with respect to biospecimen-dependent research. The results provide insight into the attitudes of a number of leading US academic research institutions regarding the proposed changes in the regulations.

METHODS

The Office for Human Research Protections published the Advance Notice of Proposed Rulemaking, *Human Subject Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay and Ambiguity for Investigators* on July 25, 2011 in the Federal Register (page 44524, volume 76, No. 143). We conducted a search of all public

responses following the close of the comment period. The search was conducted on [regulation.gov](http://www.regulation.gov) for the term “HHS-OPHS-2011-0005”.

The search returned 1125 items, 1123 of which were public submissions. All 1125 comment documents and associated attachments are in the public domain and were downloaded from the website for this review. Documents without substantive responses to the ANPRM questions, such as requests for comment period extensions, were excluded from further analysis. Inclusion criteria for further analysis included: 1) CTSA funded or affiliated institutions or groups, and 2) the responses addressed one or more of the ANPRM questions in Table I. CTSA funded institutions were identified through the CTSA website [Clinical and Translational Science Awards]. A number of institutions submitted several responses from different entities within the institution. Because each of these entities offered a potentially different perspective on the issues, we chose to include in our analysis the responses from all institutional entities within CTSA institutions. For example, responses from an institution’s school of public health were included even though the school of public health per se was not the primary recipient of an institution’s CTSA award. Responses on behalf of research administration at the University of Utah were submitted by one of the authors of this report (JRB).

The focus of our larger project is institutional policies and practices regarding human subject protections in biobanking. Therefore, responses to the ANPRM from individual investigators or commentators were not evaluated. Accordingly, we excluded responses from single individuals who did not indicate that their response represented a stakeholder group within the CTSA, such as research administration, the IRB, or a research center.

Each comment was read in full by two of the authors (JRB, RA) and the elements relevant to the proposed changes in biospecimen related research were abstracted, including answers to questions 47, 48, 49, 50, 52, and 53. Responses to question 51 were excluded from analysis because this question relates to specimens collected overseas and is beyond the scope of the current project. The ANPRM requested specific responses regarding the acceptability of the proposed changes in the regulations. Therefore the large majority of responses were explicit in their support for, or opposition to, the proposed changes.

RESULTS

We identified 62 set of responses to the ANPRM in general from 33 different CTSA Consortium institutions. Therefore 33 of 60 CTSA institutions (55%) chose to submit responses on the ANPRM. Twenty-six of the CTSA institutions (48%) submitted specific responses to the proposed changes to the biospecimen regulations (Table II).

Multiple sets of responses were submitted from several institutions. In addition, two sets of responses were submitted from CTSA affiliated entities including a joint statement of 33 Principal Investigators from CTSA institutions, and a joint statement from the CTSA Clinical Research Ethics Key Function Committee. The statement from the Office of the President of the University of California system was included for analysis because all University of California universities with medical schools are CTSA institutions. Overall, 38 sets of responses from CTSA funded institutions or CTSA affiliated organizations or groups to the biospecimen proposals were included in this review. These responses ranged from brief comments to detailed analyses. Only six institutions submitted responses on all of the questions regarding biospecimens.

A majority of responses from CTSA funded institutions did not express support for the proposed changes regarding the requirement for informed consent for future uses of biospecimens obtained in research or clinical care. Of the 38 sets of responses, 26 (68%)

stated explicit opposition to these changes. There was broad consistency in the opposing responses to the effect that biospecimen research is productive and important and that current regulations adequately protect source individuals. The risks associated with this type of research were perceived to be low. There also was broad consistency in the opinion that the proposed changes in this domain would be complex and burdensome, particularly with the management of an informed consent process in the clinical environments of large academic health centers and the maintenance of databases of individual choices regarding use of specimens. In response to question 49 regarding the use of a standardized consent form, seven institutions offered support for such a form while eight opposed such a change. Several who opposed a standardized consent form argued for continued flexibility in how consent is obtained. With respect to public education about biospecimen research, two institutions supported public education campaigns by the federal government to enhance public understanding.

Responses from one institution's CTSA organization are typical:

... [W]e strongly oppose the proposed change requiring specific consent for research use of de-identified biological specimens – and possible requirements for re-consent prior to each subsequent study: the burden on investigators would be enormous, the benefit to sample donors minimal, and much important research would never be performed.

Responses from a dean of a school of public health are also generally characteristic of a number of commenters who recognized the need for some changes but were not supportive of the proposed changes in the ANPRM:

... [Our institution] generally agrees that there is a need for greater public education about the nature and scientific value of future research uses, and recommends tightening protections to prevent unconsented re-identification of data and biospecimens. At the same time, however, [our institution] is opposed to the idea that all or nearly all such future research uses must be conditioned upon subjects' "general consent for future research uses."

We identified three responses (3/38 = 8%) indicating support for the proposed changes with respect to informed consent. The most substantive was provided by an institutional center for bioethics. This group states that unanticipated future research analysis should not be permitted without consent as a way of promoting "trust, transparency and stewardship." They support the acquisition of consent at the time of surgery or biopsy for future research on residual clinical samples with a notification that all future uses cannot be predicted. With respect to a standardized consent form, the bioethics center stated, "A standardized, general consent form to permit future research on biospecimens and data would be highly desirable, but only if it has been validated by direct research with prospective participants. Use of biospecimens and data should always be opt-in so that personal choices about privacy and risk are honored."

However, a comment from the same institution's deans for research and the school of medicine indicates a different point of view from the same university.

[Our institution] strongly opposes the requirement to obtain consent for the research use of all biospecimens as it will severely impede medical advances. We believe that the societal benefits from access to biospecimens outweigh the slight privacy risks of potential re-identification. In addition, we doubt that obtaining a general consent for future research for clinical specimens will be a meaningful process, and we believe that the mechanisms for tracking who has opted out over

long periods of time will not be robust enough to ensure that the original decision is regarded as accurate.

Another institution's center for genomics and health quality offered a supportive opinion regarding uniform consent for use of biospecimens:

We support the proposal that written informed consent be obtained prior to the submission of samples to a biorepository. As the ANPRM notes, current practice allows samples to be submitted to a biorepository without knowledge of the person from whom the sample was obtained. Empiric data suggest that this policy would have little support from the public.

An institutional IRB was the third organization that offered what we interpreted to be a cautiously supportive view of the proposed consent changes:

Guidance from OHRP would be useful to assist PIs and IRBs in developing and implementing appropriate 'blanket' language in ICDs to allow for future use of the biospecimens, in a manner that does not unnecessarily burden researchers with additional tracking requirements.

An institutional clinical research program offered a mixed review of the proposed changes regarding consent.

Our clinical investigative community is quite divided on this proposed change. Many do not support this change and urge HHS to carefully consider this proposed change in light of four different considerations: ...

On the other hand, those clinical researchers who favor this position point to the fact that most other international research communities in Europe and Asia have already migrated to this position.

There were a limited number of responses to Question 50 regarding the best method to obtain informed consent. Several institutions noted the variability inherent in this type of research and suggested that a uniform approach to informed consent is not feasible. For example, one University responded:

There is no best method; as there are an infinite number of options. Any proposed method must take into account the feasibility/practicality of actually complying with participants' choices.

Responses to Question 52 were uniformly supportive of only a prospective application of any new regulations in this domain. We identified 12 responses to Question 53, all of which indicated that the number of potential participants in biospecimen related research is not the only factor that should determine the practicability of re-consent. There was consistent support in these responses for the current waiver criteria.

DISCUSSION

Our results demonstrate only limited support in responses from CTSA institutions that chose to comment on the proposed changes in the regulations regarding biospecimen related research.

Further, the responses in this vein often indicated strong concerns about the direction proposed in the ANPRM. However, it is interesting to note that the two most clearly articulated statements in support of the proposed changes in consent were from a bioethics and a health policy program. While the responses to questions in the ANPRM do not offer a detailed analysis of these complex issues, we would characterize the emphasis in these comments as on respect for individual choice, sensitivity to public expectations about

choice, and a need to maintain public trust in research. The responses from those that opposed the changes tended to emphasize the low risk of research in this domain and the practical problems of instituting a meaningful informed consent approach.

Of course, we do not conclude that the proposed changes are inappropriate simply because they are opposed by a number of CTSA-funded research institutions. The concept of informed consent itself was opposed by many in the research community five or six decades ago. Surveys of the public clearly indicate that many individuals want more information about use of their tissues in research. However, it is also possible that members of the general public are not fully informed of the benefits of research and/or overestimate the risks associated with this type of research. The general public also may underestimate the difficulties in obtaining meaningful informed consent in this context. Would a more fully informed public accept research on biospecimens without informed consent, assuming strong safeguards are in place? We cannot say. Yet, at the same time, public opinion should not be the sole determinant of public policy. Public opinion, professional opinion, ethical analyses, and practical realities all must be carefully considered in crafting appropriate regulations.

This study has several limitations. We did not perform a comprehensive survey of CTSA institutions. More than half of the CTSA funded institutions chose not to comment on the biospecimen proposals so conclusions cannot be drawn about the attitudes of those institutions on these questions. It is possible that only institutions with strong concerns about the proposals chose to comment. Further, we focused our analysis on institutional entities affiliated with CTSA institutions. Inclusion of all responses on the ANPRM or responses from all academic health centers would have provided a broader picture of current attitudes on the proposed changes to the regulations. Finally, one of the authors (JRB) submitted a set of responses representing the University of Utah research administration that were not supportive of the proposed changes in this domain. This perspective could have biased the data analysis although, as noted, most commenters were explicit regarding their support or opposition to the ANPRM.

Our general conclusion is that the proposals in the ANPRM regarding biospecimen-based research received only limited support by CTSA institutions that chose to respond to the request for public comment. If these attitudes are more broadly shared in the research community, more work may be necessary to craft appropriate solutions to the ethical and regulatory challenges of research with biospecimens.

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Table I**ANPRM Questions Relating to Research with Biospecimens**

Question 47: Should there be a change to the current practice of allowing research on biospecimens that have been collected outside of a research study (*i.e.* “left-over” tissue following surgery) without consent, as long as the subject’s identity is never disclosed to the investigator?

Question 48: What, if any, are the circumstances in which it would be appropriate to waive the requirement to obtain consent for additional analysis of biospecimens?

Question 49: Is it desirable to implement the use of a standardized, general consent form to permit future research on biospecimens and data? Are there other options that should be considered, such as a public education campaign combined with a notification and opt-out process?

Question 50: What is the best method for providing individuals with a meaningful opportunity to choose not to consent to certain types of future research that might pose particular concerns for substantial numbers of research subjects beyond those presented by the usual research involving biospecimens? How should the consent categories that might be contained in the standardized consent form be defined (*e.g.* an option to say yes-or-no to future research in general, as well as a more specific option to say yes-or-no to certain specified types of research)? Should individuals have the option of identifying their own categories of research that they would either permit or disallow?

Question 51: If the requirement to obtain consent for all research uses of biospecimens is implemented, how should it be applied to biospecimens that are collected outside of the U.S. but are to be used in research supported by a Common Rule agency? Should there be different rules for that setting, and if so, what should they be? Should they be based on the relevant requirements in the countries where the biospecimens were collected?

Question 52: Should the new consent rules be applied only prospectively, that is, should previously existing biospecimens and data sets be “grandfathered” under the prior regulatory requirements? If so, what are the operational issues with doing so?

Question 53: In cases in which consent for future research use is not obtained at the time of collection, should there be a presumption that obtaining consent for the secondary analysis of existing biospecimens or identifiable data would be deemed impracticable, such that consent could be waived, when more than a specified threshold number of individuals are involved? (SACRP provided the Secretary with recommendations on this issue.⁸¹) If so, what threshold number should constitute impracticability? Is the number of potential human subjects the only measure of impracticability?

TABLE II

CTSA Institutions

Institution	Provided Responses on Biospecimens
Albert Einstein College of Medicine	
Boston University	*
Case Western Reserve University	*
Children's National Medical Center	
Columbia University	*
Duke University	*
Emory University	*
Georgetown University	*
Harvard University	*
Indiana University School of Medicine	
Johns Hopkins University	*
Mayo Clinic	
Medical College of Wisconsin	
Medical University of South Carolina	
Mount Sinai School of Medicine	
New York University School of Medicine	
Northwestern University	
Oregon Health and Science University	*
Penn State Milton Hershey Medical Center	
Stanford University	*
The Ohio State University	
The Rockefeller University	
The Scripps Research Institute	
The University of Alabama at Birmingham	
The University of North Carolina at Chapel Hill	*
The University of Texas HSC at San Antonio	
The University of Utah	*
Tufts University	
The University of Arkansas for Medical Sciences	
The University of California Los Angeles	*
The University of California, Davis	
The University of California, Irvine	
The University of California, San Diego	
The University of California, San Francisco	*
University of Chicago	*
University of Cincinnati	*

Institution	Provided Responses on Biospecimens
University of Colorado, Denver	
University of Florida	
University of Illinois at Chicago	
University of Iowa	
University of Kansas Medical Center	
University of Kentucky Research Foundation	*
University of Massachusetts Medical Center, Worcester	
University of Miami	
University of Michigan	*
University of Minnesota Twin Cities	*
University of New Mexico Health Sciences Center	
University of Pennsylvania	*
University of Pittsburgh	*
University of Rochester School of Medicine and Dentistry	*
University of Southern California	*
University of Texas Health Science Center at Houston	
University of Texas Medical Branch	
University of Texas Southwestern Medical Center at Dallas	
University of Washington	*
University of Wisconsin – Madison	*
Vanderbilt University	*
Virginia Commonwealth University	
Washington University	
Weill Cornell Medical College	
Yale University	
CTSA PIs Statement	*
CTSA Clinical Research Ethics Key Function Committee	*