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Research Involving Biospecimens: Incorporating a Trust Model into the Common Rule

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*Research Involving Biospecimens:
Incorporating a Trust Model into the Common Rule*
by
Kristen M. Burt

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RESEARCH INVOLVING BIOSPECIMENS:
INCORPORATING A TRUST MODEL INTO THE COMMON RULE

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Kristen M. Burt

INTRODUCTION

Debate about research involving existing biospecimens has been highly visible in recent years due in part to litigation¹ and publication of books such as *The Immortal Life of Henrietta Lacks* by Rebecca Skloot.² Biospecimens by their nature may be obtained, stored sometimes for many years, and used in subsequent research activities. Biospecimens include blood, tissue, cells, and other human materials which contain genetic information.³ As technology advances, biospecimens are seen as valuable resources that can be used in research to discover new ways to diagnosis, treat, and prevent disease.⁴ However, this use can raise issues of informed consent as highlighted by the litigation filed by individuals whose biospecimens or those of their child had been used for research without permission.

¹ See e.g., *Havasupai v. Ariz. State Univ.*, 220 Ariz. 214 (2009), *Wash. Univ. v. Catalona*, 490 F.3d 667, 670 (2007), *Moore v. Regents Univ. Cal.*, 51 Cal.3d 120, 125-26 (1990), *Greenberg v. Miami Children’s Hosp. Research Inst.* 264 F. Supp. 2d 1064, 1066-67 (2003).

² REBECCA SKLOOT, *THE IMMORTAL LIFE OF HENRIETTA LACKS* (Crown 2010) (2010) (focuses on the story behind the HeLa cells, a cell line used in many research studies and that has contributed to a number of scientific advancements and raised issues such as informed consent).

³ <http://www.cancer.gov/dictionary?expand=B> (April 1, 2012).

⁴ <http://biospecimens.cancer.gov/relatedinitiatives/default.asp> (April 1, 2012).

There is a federal regulation, the Basic HHS Policy for Protection of Human Research Subjects codified by the U.S. Department of Health and Human Services Under 45 C.F.R. 46 Subpart A. Multiple federal agencies have adopted and codified 45 C.F.R. 46 Subpart A, causing the regulation to be referred to as the “Common Rule” because it is common across multiple federal agencies.⁵ This regulation applies to human subject research conducted or supported by federal agencies, requiring review and approval of an Institutional Review Board (IRB) with certain exemptions. However, the current regulation does not adequately address research involving existing biospecimens. Certain provisions of this regulation can exclude and exempt research projects that involve the use of existing biospecimens when the provision is met. This means that the issues of informed consent raised by individuals whose biospecimens used in research are not adequately addressed.

To address issues raised by these examples and others, an Advanced Notice of Proposed Rulemaking (ANPR) was published in the Federal Register on July 26, 2011 suggesting substantial changes to the human research protection regulations.⁶ While the ANPR does address some of the exclusions and exemptions that raised concern, this paper will argue that the changes proposed in the ANPR do not fully address concerns that arise when research is conducted on existing biospecimens. Instead, a model based on a trust structure should be incorporated into the human research protection regulations to better address these issues and protect the parties’ interests typically involved in secondary research involving biospecimens. The model for a trust has been proposed for research involving biospecimens to address valuable commercial research

⁵ <http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html> (May 8, 2012).

⁶ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512 (advanced notice of proposed rulemaking July 26, 2011).

where revenue may be generated by the research.⁷ The trust model has also been used in the context of when newborn blood spots are collected for clinical purposes and to permit research use on such blood spots.⁸ The trust model should be incorporated into the Common Rule.

A trust is a property model in which a settlor places property into the trust for the benefit of a beneficiary and is managed by a trustee.⁹ The terms of the trust define how the property is to be used.¹⁰ The trust model distributes responsibility and management of the property and provides checks and balances to assure that the property is used as the settlor defined in the terms of the trust. Proposing revisions to the human research protection regulation based on a trust structure balances the needs of the three parties involved in research with biospecimens: the individual providing the biospecimen, the researcher(s), and the institution that employs the researcher(s). This paper will argue that the trust model provides checks and balances needed for research involving biospecimens and will propose informed consent requirements as the terms of the trust presented to the individual providing the biospecimen as the settlor and argue for additional responsibilities as duties for the institution as the trustee and for the investigator as the beneficiary. The current structure of the Common Rule is already somewhat structured to facilitate a trust model because of the parties involved in research and informed consent requirements; however, applying the trust model in the paper highlights and divides the

⁷ See Joyce Boyle, *To Pay or Not to Pay, That is the Question: Finding an Intermediary Solution Along the Moore Spectrum*, 7 MICH. ST. J. MED. & L. 55 (2002) (establish federal commission where tissue is placed in trust and provide compensation), William Hanes, *Rejection of the Need for Informed Consent in Prostate Tissue Sample Research*, 14 Cardozo J. L. & Gender 401 (2008), Martin Harvey, *Towards a Public Human Tissue Trust*, 59 CASE W. RES. L. REV. 1171 (2009) (establishment of public tissue trust for ownership).

⁸ Denise Chrysler et. Al., *The Michigan Biotrust for Health: Using Dried Bloodspots for Research to Benefit the Community While Respecting the Individual*, 39 J. L. MED. & ETHICS 98 (2001) (Michigan Newborn Bloodspot Model (describes establishment of Michigan Biotrust based on a charitable trust model based on qualified ownership of the sample).

⁹ RESTATEMENT (THIRD) OF TRUSTS § 2 (2003).

¹⁰ *Id.* at § 4.

responsibilities of each party to indicate what changes should be incorporated into the Common Rule when it is revised.

This paper will argue that the current regulations and ANPR do not adequately address concerns raised by individual whose biospecimens are used in research and proposes a model based on a property trust structure to better address these issues. Part I will set forth the background of the current and proposed regulatory framework as it applies to research involving existing biospecimens and will introduce the proposal for a model based on a trust structure. In Part II, the current regulation and ANPR proposals will be evaluated and the trust model will be proposed for prospective collection of biospecimens. Part III will then apply the current, advance notice, and trust proposal to research using existing biospecimens. Part IV will evaluate issues that arise after research is approved, such as withdrawal and sharing of biospecimens, and argue that the trust model provides a better structure to address these areas. Overall, this paper will suggest that a trust model and specific changes to informed consent and additional review considerations based on this model are needed to address concerns raised when research is conducted on biospecimens.

I. BACKGROUND

This section will provide background on the current human research protection regulation, the ANPR proposals, and will introduce the proposal for a model based on a trust structure to be incorporated into the human research protection regulation.

A. Current Common Rule

The Common Rule applies to human subject research and is applicable to an institution when a federal agency supports the research project.¹¹ An institution may voluntarily choose to extend the oversight of the federal government by “checking the box” on the Federal Wide Assurance provided to the U.S. Office for Human Research Protections to extend the regulation to all human subject research conducted at the institution, regardless of funding source.¹² While the ANPR proposes to extend the applicability of the Common Rule to any domestic institution that receives federal funding,¹³ an evaluation of this change is beyond the scope of this paper and as a result, this paper assumes the applicability of the Common Rule. Even if the Common Rule is not applicable to the institution, incorporating this paper’s proposals into the Common Rule would provide a baseline or standard for the review of research involving biospecimens. Institutions will often apply the Common Rule to research regardless of funding source, even if the box is not checked.

The Common Rule requires review by an Institutional Review Board unless the research qualifies for an exemption. Approval criteria such as evaluation of risks and benefits, the informed consent process, and selection of subjects are specified and must be met in order for the IRB to approve the research. These requirements would also apply to research involving biospecimens, although provisions of the regulation exclude certain uses of biospecimens from IRB review, including informed consent requirements.¹⁴

¹¹ 45 C.F.R. § 46.101(a) (2011).

¹² 45 C.F.R. § 46.103(a) (2011).

¹³ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44528 (advanced notice of proposed rulemaking July 26, 2011).

¹⁴ 45 C.F.R. § 46.101 (2011).

Research involving existing biospecimens can be excluded from applicability of the Common Rule through several provisions.¹⁵ First, the definition of human subject limits who a human subject is to identifiable private information.¹⁶ Currently, a biospecimen is not considered identifiable in and of themselves.¹⁷ Therefore, unless a name or code is associated with the biospecimen, research can be conducted using the biospecimen without falling under the Common Rule.¹⁸ Second, even if the biospecimen is considered a human subject, the research may qualify for an exemption and be exempt from the Common Rule requirements.¹⁹ Third, even if the research comes under the Common Rule and is not exempt, the IRB may grant a waiver of consent if the research meets certain criteria.²⁰ Under each of these scenarios, informed consent from the individual to use their biospecimen in the research would not be required. Each of these provisions will be applied in Part II and III to highlight deficiencies in the regulation.

B. Advanced Notice of Proposed Rulemaking

The changes suggested in the ANPR are the most significant since proposed rules were published in 1979²¹ and broadly encompasses provisions for exemptions, multi-site research, data security, and informed consent.²² Some of the changes proposed attempt to address deficiencies related to research involving existing biospecimens.²³ The ANPR proposes that because of the identifiable nature of biospecimens, all research involving biospecimens, whether

¹⁵ 45 C.F.R. § 46.101 (2011).

¹⁶ 45 C.F.R. § 46.102(f) (2011).

¹⁷ *Id.*

¹⁸ 45 C.F.R. § 46.101 (2011).

¹⁹ 45 C.F.R. § 46.101(b)(4) (2011).

²⁰ 45 C.F.R. § 46.116(d) (2011).

²¹ <http://www.hhs.gov/ohrp/humansubjects/index.html> (OHRP explanation of the ANPR) (May 8, 2012).

²² Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512 (advanced notice of proposed rulemaking July 26, 2011).

²³ *Id.* at 44524.

collected, stored, or analyzed, would be considered identifiable information²⁴ in contrast to the current definition of a human subject which excludes biospecimens cannot be readily linked to a name or code. The ANPR proposes to expand the current exempt category (4) that is limited to existing biospecimens to all secondary research use of identifiable data and biospecimens that have been collected for purposes other than the currently proposed research²⁵ but require consent for exempt research.²⁶ Also, rather than IRB review of the exemption, the researcher would instead file a registration with the IRB but are allowed to proceed without IRB review.²⁷ Each of these proposals will be critiqued and arguments will be made in Part II, III, and IV for additional changes based on a trust model.

C. Trust Model

This paper will argue that the current and proposed requirements should be further modified to address issues related to research involving biospecimens. The model proposed is based on a property trust structure. The model for a trust has been proposed to address biospecimens commercial interests²⁸ and in the context of newborn blood spots.²⁹ A structure modeled on a trust could also be effective in a broader context for research involving biospecimens and should be incorporated into the Common Rule as part of its revisions.

A trust is created when there is an intention to form a relationship where property is passed to a person who then holds title to the property and has a duty to manage that property for

²⁴ *Id.* at 44525.

²⁵ *Id.* at 44519.

²⁶ *Id.*

²⁷ *Id.*

²⁸ *See, e.g., Boyle, supra* note 7. The author discusses the establishment of a federal commission where tissue is placed in trust and compensation is provided.

²⁹ Chrysler, *supra* note 8 (describes establishment of Michigan Biotrust based on a charitable trust model based on qualified ownership of the sample).

the benefit of another.³⁰ A settlor creates the trust by providing the property.³¹ The property held by the trust is the property that the settlor provided.³² The trustee is the person who manages the property and may be more than one person.³³ The beneficiary is the person who receives the benefit of the property held in the trust and there may be more than one person also.³⁴ A person may be a corporate or other entity.³⁵ The terms of the trust define the use of the property and defines the intention of the settlor.³⁶ The terms of the trust may be written or may be implied.³⁷ A trust may be created by the inter vivos transfer of property to a trustee for a beneficiary.³⁸ The terms of the trust is created for the benefit of the beneficiary.³⁹ Any type of property may be placed in a trust.⁴⁰ The beneficiary needs to be identified or a definite class defined; the beneficiary must be capable of being identified by the description of the terms of use.⁴¹ The intention of the settlor defines the beneficiaries' interest in the trust.⁴² The settlor may revoke or modify the trust based on the intention expressed in the terms of the trust.⁴³ The trustee is responsible for carrying out the terms of the trust as defined by the settlor.⁴⁴

Research involving biospecimens typically involves three parties: the human subject, the investigator, and the institution. The human subject is the individual who is actually providing

³⁰ RESTATEMENT (THIRD) OF TRUSTS § 2 (2003).

³¹ *Id.* at § 3.

³² *Id.*

³³ *Id.*

³⁴ *Id.*

³⁵ *Id.*

³⁶ *Id.* at § 4.

³⁷ *Id.*

³⁸ *Id.* at § 10.

³⁹ *Id.* at § 27.

⁴⁰ *Id.* at § 40.

⁴¹ *Id.* at § 44.

⁴² *Id.* at § 49.

⁴³ *Id.* at § 63.

⁴⁴ *Id.* at § 70.

the biospecimen or whose existing biospecimen is being used in the research study. The investigator is the individual who has is actually conducting the research. The institution is the entity that employs the investigator and may include hospitals, universities, etc. A framework modeled on a trust structure would appropriately balance the interests of human subjects, investigators, and institutions. The human subject would be the “settlor,” providing the “property,” i.e. the biospecimen, to the trust. The informed consent document would provide the written agreement regarding the use of the biospecimen and would define the scope of usage. The institution would be the “trustee,” providing oversight regarding the use of the biospecimen. The investigator would be the “beneficiary,” conducting research on the biospecimen. While this paper references the institution as part of the trust model, the responsibilities assigned to the institution may be delegated by the institution to the IRB. The framework for the overall trust structure will be developed through this paper and arguments will be made for why this model is more appropriate than the current and proposed requirements.

D. Phases of Biospecimen Research

This paper divides research involving biospecimens into three distinct phases of the research process. Part II of the paper encompasses the first phase of research involving biospecimens: the prospective collection of the biospecimen. The prospective collection of the biospecimen means the actual taking of the biospecimen from an individual, which may be in the form of blood, tissue, saliva, hair, etc. This prospective collection involves the entry of the biospecimen (the property) into the research (trust) based on the informed consent (terms of the trust) reviewed by the institution (trustee) and presented to the human subject (settlor) by the researcher (beneficiary). For example, the biospecimen may be obtained in a research project for the express purpose for the research or it may be obtained as part of clinical care (e.g. surgery

removal of tumor) where the individual provides consent that the biospecimen (or an extra biospecimen can be obtained during the research study) can be used in research.

Part III of the paper will evaluate issues related to the second phase of research involving biospecimens: research involving existing biospecimens. Research on existing biospecimens means that the biospecimen has already been obtained, is being stored in a lab or facility, could have been obtained under any of the three prospective methods described, and a researcher wants to use the biospecimen for another research purpose. The researcher (beneficiary) will submit the research to the institution (trustee) who will review the use based on the informed consent (terms of the trust) originally provided by the human subject (settlor).

Part IV of the paper will discuss issues related to the third stage of the research, withdrawal or sharing of the biospecimen once it has already been collected and is being used in prospective research, in research involving existing biospecimens, or both. This section will provide additional considerations for withdrawal procedures that the institution (trustee) will coordinate and communicate to researchers (beneficiaries) based on the informed consent (terms of the trust). This section will also discuss considerations when the biospecimen will be shared by other researchers (additional beneficiaries) to assure that such sharing will meet the informed consent (terms of the trust).

II. PROSPECTIVE BIOSPECIMEN RESEARCH

The next section will discuss the prospective collection of the biospecimen for research purposes as the entry into the trust model. The investigator would prospectively submit an application to the institution's IRB describing the proposed research for review and approval of

the research project prior to initiating the research, as is the current practice.⁴⁵ Part A will discuss the informed consent document presented to the human subject that defines the research scope as the terms of the trust. This section argues that the Common Rule and the ANPR do not adequately address informed consent issues raised in litigation and that additional specific standards to define this informed consent process should be incorporated into the Common Rule. Part B will discuss provisions that are currently not included in the Common Rule or the ANPR and should be to define the responsibilities of the investigator and institution.

A. Informed Consent Document

The informed consent document would be considered the “terms of the trust” and would define the boundaries of how biospecimens could be used in current and future research. The institution, as the trustee, would prospectively review and approve the informed consent document, as is the current practice. The human subject, as the settlor, would agree to the terms of the informed consent presented by the researcher as the beneficiary. As the trustee, the institution would review the content of the informed consent document to assure that future research uses on existing biospecimens is fully disclosed to the human subject.

How the informed consent is written is especially important because a court may find that conducting research outside of the scope of the original use or consent may constitute a cause of action.⁴⁶ In 1963, an anthropology professor from Arizona State University began collaborating with the Havasupai tribe, located in the Supai Village at the bottom of the Grand Canyon.⁴⁷ The anthropology professor was approached by a member of the tribe in 1989 to study diabetes.⁴⁸

⁴⁵ 45 C.F.R. § 46.109 (2011) (applicable to expedited or full board review procedure).

⁴⁶ *Havasupai v. Ariz. State Univ.*, 220 Ariz. 214 (2009).

⁴⁷ *Id.* at 217.

⁴⁸ *Id.* at 217.

The anthropology professor then approached a genetics professor at ASU, to work on a diabetes project.⁴⁹ The genetic professor indicated an interest to also study schizophrenia, but the anthropology professor indicated that the tribe would likely not be interested in a schizophrenia study.⁵⁰ The diabetes research was conducted between 1990 – 1992 with 200 Havasupai tribe members participating in the study and providing informed consent for participation on the diabetes research.⁵¹ In 2002, the anthropology professor learned that the blood draws and genetic information obtained for the diabetes study was used by the genetics professor and others in research projects on schizophrenia, evolutionary genetics, inbreeding, and migration of human populations from Asia to Native America.⁵²

The Havasupai tribe filed suit and while the superior court initially granted summary judgment to ASU, the court of appeals reversed the superior court's decision.⁵³ Part of the determination made by the court was whether there was sufficient detail describing the alleged wrongdoing to contain facts supporting the monetary claim of 50 million.⁵⁴ The court noted that the notice provided details asserting that the blood was obtained for a limited use and the additional tests performed were without informed consent and distributed to parties outside ASU, a fact not disclosed in the consent.⁵⁵ The Havasupai alleged that the additional tests performed without consent violated the privacy of the individual tribe members and the cultural and religious privacy of the Havasupai tribe.⁵⁶ The court cited several cases that had held the

⁴⁹ *Id.* at 217.

⁵⁰ *Id.* at 217-18.

⁵¹ *Id.* at 218.

⁵² *Id.*

⁵³ *Id.* at 232.

⁵⁴ *Id.* at 226.

⁵⁵ *Id.*

⁵⁶ *Id.*

performance of additional unauthorized tests on biospecimens may be sufficient to state a claim for relief upon violation of privacy and is subjective.⁵⁷

The informed consent used in the research involving the Havasupai tribe did not describe the possibility of future research involving schizophrenia and other topics or provide an opportunity to consent.⁵⁸ However, this use likely did not violate the Common Rule. While the Common Rule requires basic elements of informed consent be provided to subjects prior to being involved in a research study⁵⁹ and additional elements when applicable, this provision is not applicable to research exempt from the Common Rule.⁶⁰

The advance notice proposes to require written general consent for exempt research.⁶¹ This means that the individual participating in the research could consent to the current research project and for all future research uses.⁶² For example, if the Havasupai tribe members who participated in the research agreed to participate in the diabetes research but did not permit general research use, the biospecimens could not have been used for the other research studies. Providing permission for general research has been argued for in the past⁶³ and would appear to address the concerns raised by the litigation involving the Havasupai tribe. It would also address the argument that individuals want to provide permission for use of their biospecimen in research, but not necessarily for every use.⁶⁴ The advance notice proposes a brief general consent

⁵⁷ *Id.* at 227.

⁵⁸ *Id.* at 226.

⁵⁹ 45 C.F.R. § 46.116 (2011).

⁶⁰ 45 C.F.R. § 46.101(b) (2011).

⁶¹ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44519 (advanced notice of proposed rulemaking July 26, 2011).

⁶² *Id.* at 44519.

⁶³ *E.g.*, Henry T. Greely, *Breaking the Stalemate: A Prospective Regulatory Framework for Unforeseen Research Uses of Human Tissue Samples and Health Information*, 34 WAKE FOREST L. REV. 737 (1999).

⁶⁴ *See, e.g.*, Leslie Wolf, *Advancing Research on Stored Biological Materials: Reconciling Law, Ethics, and Practice*, 11 MINN. J.L. SCI. & TECH. 99, 150-51 (2012), Greely, *supra* note 63.

that could be allowed for a set of encounters with an institution and provide subjects to say no to all future research.⁶⁵ Certain categories of research could also be included to restrict certain research use.⁶⁶ Subjects would be allowed to participate, even if they said no to future research.⁶⁷ The proposal also suggests that a template could be used.⁶⁸ Because this is an advanced notice, specific criteria have not yet been published. I would argue that the following criteria should be included in the proposed rule if the investigator is would like to obtain permission for future use. These requirements would be in addition to the current basic and additional elements of consent.⁶⁹ The requirements could be added as an additional element of consent or added as a new section that encompasses consent elements for future research.

1. Explanation of Future Research

Currently an individual is provided specific information about a particular research study and agrees to participate in that study.⁷⁰ General consent for all future research is not permitted under the Common Rule.⁷¹ The advance notice proposes to change this requirement and allow consent for future research.⁷² While there may be debate on whether a subject can truly provide informed consent to general research⁷³, presenting them with the option and allowing them to decide balances the subject's interest in deciding to participate and the investigator's interest in conducting additional research in the future. If an investigator was required obtain consent from

⁶⁵ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44519 (advanced notice of proposed rulemaking July 26, 2011)

⁶⁶ *Id.* at 44519-20.

⁶⁷ *Id.* at 44520.

⁶⁸ *Id.* at 44523.

⁶⁹ 45 C.F.R. § 46.116 (2011).

⁷⁰ *Id.*

⁷¹ *Id.* (specific to the research study)

⁷² Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44519 (advanced notice of proposed rulemaking July 26, 2011)

⁷³ *See, e.g.,* Wolf, *supra* note 64.

the subject for each study, it may be very difficult to locate the subject especially if names and identifiers were removed from the biospecimen.⁷⁴ If the subject provides general consent, this difficulty is solved while still obtaining informed consent from the subject for the future research. However, the informed consent should fully explain what “future research” means and explain that this could include any type of research study (if there are no limitations). Individuals may not completely understand what future research truly means and to obtain full informed consent, complete disclosure should be provided.

If the researcher has an intent to conduct another type of research project, even if the research proposal is not fully developed, such a project should be described in the future research section as an example of the future research. From the Havasupai court opinion, it appears that planning for the schizophrenia research commenced at the same time the diabetes research was begun, based on the preparation of a grant application.⁷⁵ It is that type of scenario that should be fully disclosed to the subject. If there is likelihood that a certain type of research may be performed, that should also be disclosed to the subject in the future research explanation.

2. Sharing of Biospecimen

The informed consent should also disclose that as part of the future research, the biospecimen may be shared. Individuals may not realize that biospecimen may be shared with collaborators at other institutions, such as universities, hospitals, research institutes, etc. Subjects may not realize that future research could mean future research by individuals other than the investigator or the institution where the investigator is employed. Because of this, an explanation should also be provided that the biospecimen may be stored in multiple locations. It has been proposed that if

⁷⁴ See, e.g., Greely, *supra* note 63.

⁷⁵ Havasupai v. Ariz. State Univ., 220 Ariz. 214, 217-18 (2009).

such sharing is contemplated at the time of the research, it should be disclosed to the subject and if information about sharing is not provided, the biospecimen could not be shared.⁷⁶ I would argue that information about sharing must be included even if such use is not contemplated; it should not be an optional statement that could or could not be included in the consent document. However, such sharing should be limited to the terms of the scope of the informed consent⁷⁷ and should be specifically addressed in a Material Transfer Agreement which is discussed in further depth in Part IV.

3. Confidentiality

While confidentiality is included in the current basic elements of consent⁷⁸, because of the unique characteristics of biospecimens, the informed consent should also explain the type of confidentiality that can be promised and limits on that confidentiality based on those characteristics. For example, if the biospecimen was shared, even if there is no name or code associated with it, the biospecimen would still be considered identifiable based on the DNA the specimen contains.⁷⁹ In addition to describing limits of confidentiality based on the genetic information in the biospecimen, the informed consent should also explain whether names and codes will be maintained with the biospecimens.⁸⁰

4. Retention

The informed consent should also explain how long the specimen will be kept⁸¹, explaining whether the specimen may be kept for many years or whether the specimen will be used up in the

⁷⁶ Greely, *supra* note 63at 755.

⁷⁷ *Id.*

⁷⁸ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44525 (advanced notice of proposed rulemaking July 26, 2011).

⁷⁹ See, Wolf, *supra* note 64at 147-48(for general discussion of DNA identification).

⁸⁰ Greely, *supra* note 63at 755.

⁸¹ *Id.*

research. Some have argued that storage should be limited in time or that indefinite storage must be approved by the IRB.⁸² However, if the subject has provided informed consent for the usage and it has been explained that the biospecimen may be stored for many years or indefinitely, there is no need for a limited retention period. Practically, tracking a limited retention period would be difficult, especially if the biospecimen is shared. If the subject provided consent for the storage period, there should not be a need for additional review and approval by the IRB.

5. Categories

The ANPR proposes providing categories of research that subjects could opt out of (e.g. categories that may be controversial).⁸³ Subjects may want to participate in certain studies but not others.⁸⁴ These categories could be pre-defined or written in by the subject.⁸⁵ Very careful consideration and drafting should be given to what, if any categories of research, should be included in the Common Rule for opt out purposes. Specific definition of the categories should be provided (e.g. what is considered gene research). Difficulties may be presented if subjects were to write in categories. Practically, the tracking of such potentially diverse categories may be very difficult. In addition, guidance may need to be given to subjects who may not be aware of the types of potentially controversial studies that could be written in. While the underlying purpose of this criteria is understandable from a respect for persons perspective (i.e. biospecimens should not be included in research that would be objectionable), the operationalization of this requirement may prove problematic.

⁸² *Id.*

⁸³ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44519-20 (advanced notice of proposed rulemaking July 26, 2011)

⁸⁴ See generally Julie A. Burger, *What is Owed Participants in Biotechnology Research?* 84 CHI. KENT L. REV. 55, 70-73 (2009).

⁸⁵ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44520 (advanced notice of proposed rulemaking July 26, 2011)

6. Commercialization

Several cases indicate the need to directly address commercialization through an informed consent process.

In 1976, John Moore was diagnosed with leukemia and went to UCLA where biospecimens were obtained by his physician.⁸⁶ Additional biospecimens were obtained on subsequent visits and used to develop a cell line which was patented and highly valuable.⁸⁷ John Moore was unaware that the biospecimens being obtained were being used in research and he filed suit.⁸⁸ The court held that the physician breached his fiduciary duty and held a lack of informed consent because the physician failed to disclose the extent of the research and economic actions.⁸⁹ The physician failed to disclose facts material to the patient consent.⁹⁰ Because of the physician-patient relationship, the physician had a duty to disclose personal interests unrelated to the patient's health, including research or economic interests, which may affect the patients' health, including research or economic interests.⁹¹

In another lawsuit, plaintiffs approached Dr. Matalon to study Canavan disease in 1987.⁹² The plaintiffs approached other families of children that had Canavan disease to participate in the research and provide biospecimens.⁹³ Dr. Matalon isolated the gene and unknown to the plaintiffs, a patent application was submitted for the genetic sequence.⁹⁴ Because the subjects were not told about the patent and because of the consequences of the patent, such as restricting

⁸⁶ Moore v. Regents Univ. Cal., 51 Cal.3d 120, 125-26 (1990).

⁸⁷ *Id.* at 126 (1990).

⁸⁸ *Id.* at 126-27 (1990).

⁸⁹ *Id.* at 129 (1990).

⁹⁰ *Id.*

⁹¹ *Id.*

⁹² Greenberg v. Miami Children's Hosp. Research Inst. 264 F. Supp. 2d 1064, 1066-67 (2003).

⁹³ *Id.*

⁹⁴ *Id.* at 1064.

activity related to Canavan disease like prenatal testing and development of other treatments, the plaintiffs filed suit.⁹⁵ The court determined that the medical consent law did not apply to medical researchers⁹⁶, as distinguished from Moore⁹⁷. The court declined to extend the duty of informed consent disclosure in research to include a researcher's economic interest.⁹⁸

If the Common Rule was applied to both Moore and Greenberg, prospective review by the IRB⁹⁹ and informed consent to use the biospecimens in the research¹⁰⁰ would be required; however, the Common Rule would not necessarily require disclosure of the commercialization interest¹⁰¹. In the broader context of research involving biospecimens, the current elements of consent do not explicitly require disclosure of commercial interests and would not be addressed in any case if the research did not meet the definition of human subject or met exemption category 4.¹⁰²

While an existing conflict of interest may not exist at the time the research is proposed (e.g. the researcher may not be aware of a commercial opportunity or discovery), there may be likelihood for commercialization and a statement that explains that commercialization may occur should be required.¹⁰³ The subject should be informed that they will not directly profit from providing the biospecimen.¹⁰⁴ There has been debate about reimbursing subjects through various

⁹⁵ *Id.* at 1067.

⁹⁶ *Id.* at 1069.

⁹⁷ Moore v. Regents Univ. Cal., 51 Cal.3d 120, 129 (1990).

⁹⁸ Greenberg v. Miami Children's Hosp. Research Inst. 264 F. Supp. 2d 1064, 1070 (2003).

⁹⁹ 45 C.F.R. § 46.101 (2011) (requirement to undergo review under either expedited or full board review).

¹⁰⁰ 45 C.F.R. § 46.116 (2011).

¹⁰¹ *Id.* (basic and additional elements of consent may not require this disclosure).

¹⁰² 45 C.F.R. § 46.101(b)(4) (2011).

¹⁰³ Greely, *supra* note 63 at 755-56.

¹⁰⁴ 2009 NIH Guidelines for Stem Cell Research, <http://stemcells.nih.gov/policy/2009guidelines.htm> (May 8, 2012) (similar type of statement required to be included in informed consent).

models when a research project is commercially successful.¹⁰⁵ Whether subjects should be reimbursed for commercialization is beyond the scope of this paper, but the issue of commercialization should be addressed in the informed consent document. However, there will need to be a balance between explaining commercialization and assuring that such a statement is not exculpatory, which is not allowed under the current Common Rule.^{106, 107} In addition, while the Moore and Greenberg court distinguished whether a disclosure was required based on fiduciary duty^{108, 109}, disclosure of commercialization information which is material to the decision making process should be included in the informed consent document even if a fiduciary relationship may not exist.

7. Disclosure of Research Findings

Some have argued that subjects should have the option to be informed of findings of the study.¹¹⁰ While findings should be provided if appropriate and if subjects wish to be re-contacted, such determination must be made on a case by case basis. This provision is the in current additional elements of consent.¹¹¹ Practically, there are limits on the ability to contact subjects if the research involves general consent. For example, the biospecimen may be used in a future research study and de-identified with no name or code. In such case, findings of that study could not be provided to the subject based on the lack of name identification. Such limits should be explained to the subject.

¹⁰⁵ See, e.g., Charlotte Harrison, *Neither Moore nor the Market: Alternative Models for Compensating Contributors of Human Tissue*, 28 AM. J.L. & MED. 77, 93 (2002) (very valuable tissue, after original consent, when commercial value established), Greely, *supra* note 63 at 758 (dedicating share to organizations represent subjects).

¹⁰⁶ 45 C.F.R. § 46.116 (2011).

¹⁰⁷ http://stemcells.nih.gov/research/newcell_qa.htm#do (May 8, 2012) (U.S. N.I.H. provides a frequently asked question on use of exculpatory language for research involving embryonic stem cells).

¹⁰⁸ Moore v. Regents Univ. Cal., 51 Cal.3d 120, 129 (1990).

¹⁰⁹ Greenberg v. Miami Children's Hosp. Research Inst. 264 F. Supp. 2d 1064, 1070 (2003).

¹¹⁰ Greely, *supra* note 63 at 754.

¹¹¹ 45 C.F.R. § 46.116 (2011).

8. Right to Withdraw

The right to withdrawal is a current basic element of informed consent.¹¹² However, as discussed in Part IV, there are complications related to withdrawal when research involves a biospecimen. While some argue that subjects should be able to withdraw from general or specific types of research,¹¹³ there may be practical limitations to this right which should be fully explained to the potential research subjects. Similar to the concern raised in the Research Findings section, if a name or code is no longer associated with the biospecimen, there may not be a way to withdraw that specimen from the study. This should be fully explained to the subject. If the researcher prospectively collecting the biospecimen plans to remove names and codes, eliminating the possibility for identification, this should be explained to the subject and information about when a subject would no longer be able to withdraw because of this should be fully explained in the consent document.

Explaining what the right to withdraw does not mean should also be included within the consent document, such as the ability to have the biospecimen returned or directed to another party as discussed in Part IV.

9. Applicable State Laws

A requirement should be included that states that any relevant state laws or requirements must be included as applicable. For example, while Michigan's law on informed consent for genetic tests excludes biomedical research conducted in compliance with the Common Rule¹¹⁴, other states may not have similar exclusions. Michigan also has additional informed consent

¹¹² 45 C.F.R. § 46.116(a)(8) (2011).

¹¹³ Greely, *supra* note 63 at 754-55.

¹¹⁴ MI COMPILED LAWS 333.17020 (2000).

requirements if the research involves embryos.¹¹⁵ Because biospecimens may have additional state requirements in regards to informed consent, the provision should be included to remind both investigators and institutions that requirements in addition to the Common Rule may also govern the informed consent process.

10. If a Subject Declines Future Research

The ANPR proposes that the subject's decision for general research should have no bearing on the participation in the current research.¹¹⁶ Such a statement should be included in the consent document to fully explain to the subject that future research participation is optional and not required to participate in the prospectively proposed research study. If a subject declines to participate in future research that the biospecimen cannot be used in the future research without permission. If additional projects are proposed, the subject should be approached to obtain informed consent for the particular project. At the time the new project is proposed, the subject could again be presented with the option for general research and he or she may choose to now allow the biospecimen to be used for general research. However, the subjects' wishes must govern and the informed consent process would need to conform to the prospective requirement to obtain informed consent for general research.

B. Duties

In addition to informed consent provisions, there are additional approval criteria for research involving biospecimens that should be incorporated into the Common Rule to reflect the trust model. The current regulation has specific approval criteria that must be satisfied to approve the

¹¹⁵ MICHIGAN CONSTITUTION OF 1963, § 27 Human Embryo and Embryonic Stem Cell Research (2008).

¹¹⁶ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44520 (advanced notice of proposed rulemaking July 26, 2011)

research.¹¹⁷ An additional provision should be added that defines the duties of the researcher and the institution when reviewing biospecimens. A trust requires that beneficiaries and trustees have duties as part of the trust and a trust may fail for lack of duties.¹¹⁸ The following provisions should be incorporated into the Common Rule.

1. Duties of the Researcher

Investigator responsibilities for research involving biospecimens should be included in the Common Rule. This provision relates to his or her responsibility in the trust model as the “beneficiary” of the biospecimen.

a. Storage and Recordkeeping

While recordkeeping is required within the Common Rule, the investigator should be separately responsible for having in place a process to store and track biospecimens collected prospectively and to distinguish biospecimens for which subjects have provided consent for future research from biospecimens for which subjects have declined consent for future research. A description of the process should be provided to the institution for evaluation as part of the prospective review process. Because institutions may not have central biorepositories, the biospecimens may be stored and kept by the investigator. Additional information should be provided to assure proper storage and cataloging of which biospecimens could be eligible for future research and which would not. Best practices could be developed or required by the institution. Such best practices could be modeled on existing biorepository standards and could be promulgated as guidance by OHRP. Because the investigator will be in possession of the

¹¹⁷ 45 C.F.R. § 46.111 (2011).

¹¹⁸ RESTATEMENT (THIRD) OF TRUSTS § 13 (2003).

biospecimen, they have a responsibility as the beneficiary to assure that the biospecimen is stored and used as agreed upon in the informed consent document.

b. Submission for Future Research

Each future research use must be submitted to the institution so that the scope of the informed consent can be compared to the actual proposed use. The investigator should understand that the research is limited to what has been approved by the IRB and that future research needs to be submitted to the IRB for review prior to use.

2. Duties of the Institution

Institution responsibilities for research involving biospecimens should be included in the Common Rule. This provision relates to his or her responsibility in the trust model as the “trustee” of the biospecimen.

a. Approval and Monitoring

Corresponding to the investigator’s responsibility for storage and tracking, the institution should be responsible for evaluating and approving the plan as part of the prospective review process. Modeled on a trustee, the institution has responsibility for assuring that the biospecimen is being used according to the informed consent document. This review should include not only the prospective review, but may also include monitoring of the approved research project. The monitoring would assure that the investigator is following the approved protocol for storage and tracking.

b. Group Harms

Concerns related to use of the biospecimens obtained from Havasupai tribe members included not only individual concerns about the research use, but cultural and group harms as

well.¹¹⁹ The Common Rule does not directly address cultural or group harms.¹²⁰ The proposed changes would address the individual consent issues, but would not address cultural or group harms.¹²¹ It has been proposed that possible risks to the group should be disclosed through the informed consent process.¹²² This is a difficult area to address because defining the group and applicable standards may vary in context and may not be capable of simple definition. Native American groups could develop research codes that would require certain permissions before individual tribe members could participate in the research.¹²³ The IRB could consider whether to require the researcher to obtain consent from the group,¹²⁴ whether the researcher should consult with the tribe in the development of the research,¹²⁵ or consider cultural and spiritual harms as part of the review process when research involves Native Americans.¹²⁶ This is also difficult to address because the principle of respect for person centers on an individual's autonomy to decide whether to participate in the research.¹²⁷ However, for certain types of research, particularly involving Native tribes, a focus of the research is related specifically to the group.¹²⁸ To better

¹¹⁹ *Havasupai v. Ariz. State Univ.*, 220 Ariz. 214, 226 (2009).

¹²⁰ See 45 C.F.R. § 46.111 (2011) (does not include group harms).

¹²¹ See Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512 (advanced notice of proposed rulemaking July 26, 2011) (does not specifically address cultural or group)

¹²² *E.g.*, Greely, *supra* note 63 at 755, Richard Sharp, *An Analysis of Research Guidelines on the Collection and Use of Human Biological Materials From American Indian and Alaskan Native Communities*, 42 JURIMETRICS J. 165 (2002).

¹²³ *E.g.*, Debra Harry, *Indigenous Peoples and Gene Disputes*, 84 CHI. KENT L. REV. 147 (2009), Ron J. Whitener, *Research in Native American Communities in the Genetics Age: Can the Federal Data Sharing Statute of General Applicability and Tribal Control of Research be Reconciled?* 15 J. TECH. L. & POL'Y 217 (2010) (Native American tribal codes should specifically address research and permission requirements).

¹²⁴ Greely, *supra* note 63 at 756-57.

¹²⁵ *E.g.*, Harry, *supra* note 123 at 193-97, Sharp, *supra* note 122.

¹²⁶ Katherine Drabiak-Syed, *Lessons from Havasupai Tribe v. Arizona State University Board of Regents: Recognizing Group, Cultural, and Dignitary Harms as Legitimate Risks Warranting Integration into Research Practice*, 6 J. HEALTH & BIOMEDICAL L. 175, 215-16 (2010) (factor cultural and spiritual harms when reviewing research that involves Native American biospecimens).

¹²⁷ *E.g.*, 45 C.F.R. § 46 (2011) (principles embodied in regulations).

¹²⁸ *E.g.* *Havasupai v. Ariz. State Univ.*, 220 Ariz. 214 (2009).

define this area, OHRP should obtain comments on how such criteria could be used and develop guidance that could then be published and used by institutions reviewing such research.

III. RESEARCH INVOLVING EXISTING BIOSPECIMENS

This part highlights the deficiencies in the Common Rule as applied to research involving existing biospecimens, compares the ANPR, and argues that additional changes as part of a trust model are needed to better protect subjects, investigators, and institutions. Part A discusses provisions related to when review by the institution should be required for existing biospecimens in research. Part B discusses considerations that the institution should take into account as part of the trust model for review of the proposed research involving an existing biospecimen.

A. Common Rule Applicability

This part discusses when the Common Rule is applicable under the current requirements and the advance notice proposal, highlighting the deficiencies and proposing a trust model.

1. Definition of a Human Subject

A human subject is defined under the Common Rule as a living individual about whom an investigator . . . conducting research obtains data through intervention or interaction with the individual, or [i]dentifiable private information.¹²⁹ Identifiable means the identity of the subject is or may be readily ascertained by the investigator or associated with the information.¹³⁰ In the case of the blood obtained from the Havasupai tribe members, if the ASU investigator de-identified the biospecimen, i.e. removed names or other identifiers and did not maintain or have access to codes linking an identifier to the subject,¹³¹ the blood sample obtained from the

¹²⁹ 45 C.F.R. § 46.102(f) (2011).

¹³⁰ 45 C.F.R. § 46.102(f) (2011).

¹³¹ OHRP Guidance on Research Involving Coded Private Information or Biological Specimens, <http://www.hhs.gov/ohrp/policy/cdebiol.html> (May 8, 2012).

Havasupai tribe members may not have been considered a “human subject” under the Common Rule and would not have required IRB review, approval, or informed consent for the use of the blood sample by ASU in the research. The current definition of human subject as it relates to biospecimens excludes a significant amount of secondary research involving biospecimens and highlights a flaw in the current regulation. A biospecimen holds an individual’s genetic make-up and can potentially identify a subject and it has been argued that biological materials should be considered identifiable based on the DNA.¹³² However, DNA alone is not considered “identifiable” under the Common Rule.¹³³

To address this concern, the ANPR proposes that because DNA could be extracted from a biospecimen and used to link to other data to identify an individual, regardless of how the biospecimen is coded or de-identified, it is identifiable in and of itself.¹³⁴ Because of this characteristic, biospecimens would be considered identifiable under the proposed changes.¹³⁵

While use of biospecimens in research, regardless of whether a name or code is maintained, should be reviewed by the institution as part of the trust model, distinctions should be maintained in terms of identification. While all research use involving biospecimens should be reviewed under the Common Rule because of the unique characteristics of biospecimens, there should be a tiered approach when evaluating the usage of the biospecimen. The first tier of identification would be those specimens that are identifiable or readily identifiable to an individual person. This tier would include biospecimens that are associated with a name or code. The second tier of identification would be those specimens who cannot be tied directly to an

¹³² *E.g.*, Wolf, *supra* note 64 at 147-48, Burger, *supra* note 84 at 76-80 (2009).

¹³³ 45 C.F.R. § 46.102(f) (2011). (interpretation has not included DNA)

¹³⁴ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44525 (advanced notice of proposed rulemaking July 26, 2011)

¹³⁵ *Id.*

individual, i.e. no name or code. The rationale for this distinction is linked to the ability to withdraw from a research study. The ability to withdraw is discussed in Part IV and will highlight the need for this distinction.

A potential issue that may arise if considering all biospecimens identifiable under the Common Rule is whether the individual is living which is a criterion to be considered a human subject.¹³⁶ It is possible that biospecimens may be stored for many years and it may be difficult to determine if an individual is still living. Therefore, for research involving biospecimens, several options could be adopted. First, the year of birth could be obtained and maintained with the biospecimen and there could be a presumption that based on the age the individual is no longer living (e.g. 100) unless actual information is obtained to determine the individual is deceased. A second option, if researchers did not want to obtain year of birth, would be that the year of collection would be maintained and years would be added to that date for a determination if the individual is living (e.g. 100 years). This could be much longer than the first option, but could be used in cases where researchers did not want to collect year of birth.

The Common Rule is applicable to private identifiable information.¹³⁷ Another consideration related to the definition of human subject is what is considered private. Any collection of the biospecimen (either through research or clinical care) should be considered private. However, obtaining a commercial cell line would not be considered private as it is commercially available. However, consideration should be given to how commercial cell lines are developed to assure that concerns related to use of biospecimens in research are addressed.

¹³⁶ 45 C.F.R. § 46.102(f) (2011).

¹³⁷ 45 C.F.R. § 46.102(f) (2011).

2. Exemption 4

Even if the blood samples from the Havasupai tribe members originally fell under the Common Rule, the ASU investigators could have qualified for an exemption if the sample was de-identified.¹³⁸ The Common Rule provides six exemptions, including Category 4 that specifically exempts research involving collection or study of existing materials, including biospecimens, so long as the subjects cannot be identified.¹³⁹ This category could apply to biospecimens collected for research or it could apply to biospecimens collected for clinical purposes, so long as the biospecimens were existing at the time the research is proposed.¹⁴⁰ Because the research use is exempt from the Common Rule, informed consent is not required and it may have never been obtained for this particular research use (e.g. while Havasupai tribe members consented to diabetes research, they did not consent to research involving schizophrenia¹⁴¹). Typically, the institution's IRB reviews the research to determine if the proposed research meets the exempt category.¹⁴²

The ANPR proposed to expand the exemption category 4 to all secondary research use of identifiable data and biospecimens collected for purposes other than the currently proposed research, no matter when it is collected but requires written general consent for use of the biospecimen in research.¹⁴³ While this initially sounds like it would address the concerns raised

¹³⁸ 45 C.F.R. § 46.101(b)(4) (2011).

¹³⁹ 45 C.F.R. § 46.102(b)(4) (2011) (research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subject).

¹⁴⁰ 45 C.F.R. § 46.101(b)(4) (2011).

¹⁴¹ *Havasupai v. Ariz. State Univ.*, 220 Ariz. 214, 226 (2009).

¹⁴² *E.g.*, Michigan State University Human Research Protection Program Manual Section 8-1, <http://www.humanresearch.msu.edu/hrpmanual.html> (May 8, 2012) (sample institutional policy on exempt review).

¹⁴³ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44519 (advanced notice of proposed rulemaking July 26, 2011)

by the Havasupai tribe members¹⁴⁴, there are potential flaws to this proposed change. Rather than review by the institution or the IRB office, researchers would file a registration with the IRB and would then be allowed to proceed without IRB review with IRB review not being required or recommended.¹⁴⁵ Instead, auditing by the institution of the ongoing studies would be relied upon to assure that the exempt criteria had been met.¹⁴⁶

A trust model would better protect the interests of the subject, institution, and investigator with prospective submission by the investigator to the institution for review prior to research use of the existing biospecimen. For example, a researcher may mistakenly believe that the research qualifies for the exemption or does not realize the scope of the informed consent does not encompass the proposed research. This could be especially problematic if the use of categories to exclude certain types of research from the future use is permitted.¹⁴⁷ Requiring the institution, through the IRB, to review the proposed use to assure that the informed consent originally provided encompasses the proposed research provides a check and balance and operates within the trust model. The institution, as the trustee, has a responsibility to assure that the biospecimen is being used within the scope of informed consent.

B. Responsibilities

In the trust model proposed, the investigator would be required to submit a request for the secondary research to the institution for review. The investigator should be required to comply with the investigator responsibilities outlined in Part II. For example, investigators should describe where the biospecimen will be stored. The institution should also be required to comply

¹⁴⁴ *Havasupai v. Ariz. State Univ.*, 220 Ariz. 214, 226 (2009).

¹⁴⁵ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44519 (advanced notice of proposed rulemaking July 26, 2011)

¹⁴⁶ *Id.*

¹⁴⁷ *Id.* at 44519-20.

with the institution responsibilities in Part II. For example, it has been argued that subsequent research that involves potentially sensitive topics, such as stigmas, should be taken into consideration when reviewing the secondary research request by the IRB.¹⁴⁸ The discussion related to cultural or group harms would also be applicable to secondary research use.

In addition to the responsibilities discussed in Part II, the institution should also be responsible for reviewing the scope of the original informed consent against the proposed research project involving existing biospecimens. This is the main consideration of whether the research can proceed using the existing biospecimens; the proposed research must meet the scope of original consent document. Because the original informed consent document would be considered the terms of the trust, the document provides the boundaries of the types of research the human subject agreed to when signing the original document. This evaluation by the institution will be particularly important if the controversial categories of research that subjects can opt out of participating in are included in the informed consent document.¹⁴⁹ The IRB would review the proposed research project with the consent forms presented to the subject. If multiple consent forms were reviewed and approved by the IRB (e.g. revisions to the document), each consent document would be reviewed by the IRB. The IRB should assure that the research proposed is consistent to what the human subject agreed to within the informed consent.

IV. WITHDRAWAL AND SHARING

This section will evaluate withdrawal and sharing of the biospecimen after the research is approved and argue that the trust model provides a better structure to address these areas. Part A describes withdrawal procedures if a subject who provided informed consent requests

¹⁴⁸ Greely, *supra* note 63 at 752-54.

¹⁴⁹ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44519-20 (advanced notice of proposed rulemaking July 26, 2011)

withdrawal and this paper argues that the right to withdraw would be facilitated by using a trust based model. Part B describes the sharing of the biospecimen and argues that if the biospecimen is going to be shared outside the institution, such use should also be reviewed by the institution to assure the use conforms to the subjects' wishes.

A. Withdrawal

The right of an individual participating in research to withdraw at any time for any reason is an essential component of the human research protection regulations.¹⁵⁰ However, if the research did not include a human subject or was exempt, the option to withdraw was not presented to the individual, who may not even know what research projects the biospecimen is being used in.¹⁵¹ The right to withdraw typically was presented to subjects during the informed consent process to obtain the biospecimen,¹⁵² but after the biospecimen became de-identified, that ability to withdraw was lost.

With the ANPR, the general consent option addresses the issue of obtaining consent for all research involving the biospecimen.¹⁵³ However, the ANPR did not indicate how the right to stop participating would be incorporated into the Common Rule.¹⁵⁴ Because all specimens are considered identifiable under the ANPR, it would logically follow that individuals could withdraw their permission and allow the specimen to stop being used at any time. However, this practically would not be possible unless a name or code was associated with the biospecimen. If the biospecimen has become de-identified with no name or code associated with the specimen,

¹⁵⁰ 45 C.F.R. § 46.116(a)(8) (2011).

¹⁵¹ 45 C.F.R. § 46.101 (2011) (applicability of Common Rule)

¹⁵² 45 C.F.R. § 46.116(a)(8) (2011).

¹⁵³ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44519 (advanced notice of proposed rulemaking July 26, 2011)

¹⁵⁴ See Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512 (advanced notice of proposed rulemaking July 26, 2011) (does not include withdrawal procedures for biospecimens)

there is no way for a researcher to be able to remove that biospecimen from all the biospecimens being analyzed.¹⁵⁵ It has been argued that names should be unlinked from the biospecimen or strongly coded.¹⁵⁶ For example, the study may be on a very sensitive topic that an individual may not want their name associated with, such as perhaps a study involving use of illegal drugs, sexually transmitted diseases, etc. Strong confidentiality protections are necessary, but requiring unlinking may eliminate the ability to withdraw.

If biospecimens are considered identifiable in two tiers as discussed in Part II, withdrawal in the first tier of identification where there is a name or code link to a name could be accomplished since there would be a way to link the request to a biospecimen. In the second tier where there is no code, there are several options. One option is to fully explain in the consent process what this type identification means and at what point subjects would no longer be able to withdraw. Another option would be to code the specimens in such a way where a number is provided to the subject and linked to the specimen, but no record is kept on who has what number. This could maintain the ability to remove name or other explicit identifiers but still allow the subjects to withdraw their biospecimens from research.

Because the right of withdrawal might impact multiple studies, a prerequisite to research use of existing biospecimens is the understanding that if a subject requests withdrawal, this withdrawal would extend to all ongoing research use. The trust model can facilitate the right to withdraw because at the institutional level, the original research project could be linked to all research projects involving existing biospecimens. The institution could then contact each individual researcher and provide information about the subject request for withdrawal. A

¹⁵⁵ Wolf, *supra* note 64 at 155-56 (2012).

¹⁵⁶ Greely, *supra* note 63 at 756.

prerequisite to participating in research involving existing biospecimens would be the understanding that request for subject withdrawal would need to be reported to the institution so that it may be shared for all research projects using the biospecimen.

B. Sharing

In the case of *Washington v. Catalona*, biospecimens were collected by a researcher for many years and stored at a biorepository at Washington University.¹⁵⁷ The researcher accepted a position at Northwestern and sought to have the samples transferred.¹⁵⁸ To do this, the researcher contacted the subjects to obtain their permission to transfer the samples.¹⁵⁹ However, Washington University filed for a declaratory judgment to establish ownership of the biospecimens.¹⁶⁰ The court determined that under the facts of this case, individuals who make an informed decision to contribute their biological material voluntarily to a research institute for the purpose of medical research do not retain an ownership interest allowing the individuals to direct or authorize the transfer of such materials to a third party.¹⁶¹ The analysis of the court focused on the informed consent documents and Material Transfer Agreements.¹⁶² Material Transfer Agreements are executed when materials are being exchanged with another institution to protect intellectual property rights.¹⁶³ The court's analysis focused on ownership of the particular specimen under gift law¹⁶⁴, which has been a heavily debated topic¹⁶⁵ which is beyond the scope

¹⁵⁷ *Wash. Univ. v. Catalona*, 490 F.3d 667, 670 (2007).

¹⁵⁸ *Id.* at 672.

¹⁵⁹ *Id.*

¹⁶⁰ *Id.*

¹⁶¹ *Id.* at 673.

¹⁶² *Id.* at 674-76.

¹⁶³ <http://ttc.nci.nih.gov/forms/> (May 8, 2012) (U.S. National Cancer Institute forms page that include the Uniform Biological Material Transfer Agreement).

¹⁶⁴ *Wash. Univ. v. Catalona*, 490 F.3d 667, 676 (2007).

¹⁶⁵ See e.g., William Hanes, *Rejection of the Need for Informed Consent in Prostate Tissue Sample Research*, 14 CARDOZO J.L. & GENDER 401, (donation may be a bailment, not a gift), Donna Gitter, *Ownership of Human Tissue: A Proposal for Federal*

of this paper. However, the examination of the language of the informed consent document and Material Transfer Agreements is relevant because it is used to determine what the institution, subject, and investigator understood about the research arrangement.

As part of the trust, the institution should have the office that executes Material Transfer Agreements obtain approval or sign off by the institution through the IRB before an MTA was executed. The approval or sign off would be required to assure that the scope of the informed consent allows the specimen to be transferred to the other party for the purposes of the research being requested. The MTA, in addition to intellectual property provisions, should also incorporate limiting provisions in terms of how the biospecimen can be used, transferred, and withdrawal provisions. These terms should be congruent with the scope of the original informed consent. If such terms were not included and the specimen was released, it would essentially negate the trust model and allow the collaborating institution to use the specimen in such a way that would not have been permitted by the institution's own employees.

The court in *Catalona* also determined that the subjects did retain the right to revoke and physically possess the materials and did not retain the right to direct or authorize the use, transfer, or destination of the biological materials after donation based on biohazard laws.¹⁶⁶ The court in *Moore* came to a similar conclusion applying California biohazard laws.¹⁶⁷ While there is a delicate balance regarding exculpatory language, subjects should know prior to taking part in the research that the biospecimen won't be able to be returned. In addition, use of the term

Recognition of Human Research Participants' Property Rights in Their Biological Materials, 61 WASH. & LEE L. REV. 257 (2004) (create federal law that establishes individual property rights in tissue and would have a cause of action for conversion under certain circumstances), Kimberly Self, *Self-Interested: Protecting the Cultural and Religious Privacy of Native Americans Through The Promotion of Property Rights in Biological Materials*, 35 AM. INDIAN L. REV. 729 (2010), Russell Korobkin, *No Compensation or Pro Compensatio: Moore v. Regents and Default Rules for Human Tissue Donations*, 40 J. HEALTH L 1 (2007)..

¹⁶⁶ Wash. Univ. v. *Catalona*, 490 F.3d 667, 675 (2007).

¹⁶⁷ *Moore v. Regents Univ. Cal.*, 51 Cal.3d 120, 155-56 (1990).

“donation” has been seen as exculpatory.¹⁶⁸ Realizing some of the use of terminology is related to ownership issues which are beyond the scope of this paper, it may be appropriate to solicit comments to develop and provide guidance on this particular topic to assure that language used by institutions is not exculpatory, recognizing some of this will be dependent upon state laws.

CONCLUSION

Research involving biospecimens will likely continue to grow as advances are made in medicine and technology. For example, the U.S National Institute of Health is focusing on repurposing existing molecular compounds¹⁶⁹ and is working on developing 3-D tissue chips that can be used to test the molecular compounds for toxicity and binding on the targets as part of new drug development.¹⁷⁰ These chips would contain human tissue and be microsystems used to eliminate ineffective molecules.¹⁷¹ As research involving existing biospecimens continues to grow, the Common Rule must adapt to balance both the researchers’ need for access to biospecimens for research and the expectations of the individuals who provide their biological materials that are then used in research. The process must be designed to both respect the human subject who participates in the research while also permitting research to occur without unduly burdensome requirements.

At this point in the rulemaking process, the ANPR suggested potential changes and presented questions for input.¹⁷² While the comment period for the ANPR has closed¹⁷³, the next step in the rulemaking process will be a proposed rule that under the Fall 2011 Unified Agenda

¹⁶⁸ Burger, *supra* note 84 at 69.

¹⁶⁹ <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html> (May 9, 2012)

¹⁷⁰ <http://www.ncats.nih.gov/research/reengineering/tissue-chip/tissue-chip.html> (May 8, 2012)

¹⁷¹ *Id.*

¹⁷² Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512 (advanced notice of proposed rulemaking July 26, 2011)

¹⁷³ *Id.*

had been anticipated, but not yet published, for March 2012.¹⁷⁴ Opportunity for providing comments will still be possible.

While the ANPR partially addresses deficiencies in the Common Rule raised by litigation,¹⁷⁵ additional modifications to the Common Rule are needed to protect the interests of the human subject participating in the research, investigators conducting the research, and the institution supporting the research. As this paper has argued, a model based on a trust structure appropriately balances each of the competing interests of the parties. Subjects can decide to provide informed consent for future general research involving their biospecimen. Investigators are able to conduct the future research without having to re-consent each subject for each individual project. The institution provides a check on this process by requiring review of the research on the existing biospecimen to assure that the scope of the consent covers the proposed research use. The model balances each interest while not making the process so overly burdensome that the research could not practicably be carried out.

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¹⁷⁴ OFFICE OF INFORMATION AND REGULATORY AFFAIRS, OFFICE OF MGMT. & BUDGET, EXECUTIVE OFFICE OF THE PRESIDENT, UNIFIED AGENDA, 0937-AA02 (Fall 2011).

¹⁷⁵ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44512, 44524 (advanced notice of proposed rulemaking July 26, 2011)