Regulatory Compliance for Biospecimen Repositories and the Use of Biospecimens in Research[*]

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Because of the intense focus in the research community on obtaining biospecimens for research, many health systems, hospitals, clinical laboratories and other sources of biospecimens are looking to building biospecimen repositories to source both internal and external researchers. This is an area with substantial regulatory change; organizations that collect, store and distribute biospecimens for research are encouraged to keep a close eye on these regulatory developments.

This White Paper discusses legal compliance issues in the collection, storage, and distribution of biospecimens for research, including:

(1) Health Insurance Portability and Accountability Act ("HIPAA") regulations;
(2) "Common Rule" regulations and the Notice of Proposed Rulemaking ("NPRM") to amend the Common Rule;[1]
(3) Food and Drug Administration ("FDA") regulations; and
(4) The National Institutes of Health ("NIH") Genomic Data Sharing Policy.

The White Paper then suggests a way of "putting it all together" and includes a unified check list of items to include in an informed consent document to comply with these federal laws, and what items will need to be added if the NPRM is finalized as proposed.

This White Paper does not discuss state laws that may affect the collection, storage and distribution of biospecimens for research. Organizations are encouraged to look at applicable state laws that might regulate the use of biospecimens or associated clinical data, including state health information confidentiality laws that regulate "sensitive" information, such as HIV status; state laws related to research participant rights; and state laws governing the use or sale of human tissue.

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[1] The Office for Human Research Protections ("OHRP") issued a Notice of Proposed Rulemaking ("NPRM") on September 8, 2015, which proposes sweeping changes to the Common Rule, particularly regarding biospecimen research. Throughout this White Paper, we reference where the NPRM proposes to change existing requirements.

I. HIPAA Compliance

This White Paper discusses the HIPAA Privacy Rule[2] requirements that govern the use or disclosure of PHI for research, including revisions to the HIPAA Privacy Rule made in 2013[3] to implement the Health Information Technology for Economic and Clinical Health Act (the "HITECH Act"). The paper also discusses HIPAA Security Rule[4] requirements.

A. Application of HIPAA

Under HIPAA, "covered entities" (health plans, health care clearinghouses, and most heath care providers)[5] may use or disclose individually identifiable information (called protected health information or "PHI") only as expressly permitted by the HIPAA Privacy Rule.[6]

Where biospecimens are not associated with the HIPAA "identifiers," such as name, medical record number, or dates of service or collection, the biospecimens themselves are not treated as PHI and the use and disclosure of the biospecimens is not regulated by HIPAA.[7] The Office for Civil Rights (the "OCR") has concluded that biospecimens themselves are not protected under HIPAA unless they are correlated with HIPAA identifiers.[8] Of course, for biospecimens to be useful for research, biospecimens often are "annotated" with PHI, such as dates of diagnosis of the patient, dates of service, or dates of biospecimen collection. This White Paper thus discusses compliance with the HIPAA Privacy Rule.

B. Compliance with the HIPAA Privacy Rule

HIPAA often applies to three separate stages in biospecimen research: (1) the collection and processing of biospecimens to include in a biospecimen repository; (2) storage of biospecimens (and often associated clinical data); and (3) release of the biospecimens to researchers. If any HIPAA identifiers (PHI) are utilized for any of these steps, a covered entity must meet at least one of the HIPAA rules for that step.

Under the HIPAA Privacy Rule, covered entities may use or disclose PHI for research only if the requirements of at least one of nine rules below are met:[9]

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[2] 45 C.F.R. Part 160 and Part 164, Subpart E.
[3] 78 Fed. Reg. 5466 (Jan. 25, 2013) (the "Omnibus Rule").
[4] 45 C.F.R. Part 160 and Part 164, Subpart C.
[5] 45 C.F.R. § 160.103.
[6] 45 C.F.R. § 164.502.
[7] *See* Research Repositories, Databases, and the HIPAA Privacy Rule, at 3 (OHPR and NIH, Jan. 12, 2004), at http://privacyruleandresearch.nih.gov/pdf/research_repositories_final.pdf.
[8] *Id.* at 11 ("Under the Privacy Rule, neither blood nor tissue, in and of itself, is considered individually identifiable health information; therefore, research involving only the collecting of blood or tissue would not be subject the Privacy Rule's requirements. Remember, however, blood and tissue are often labeled with information (e.g. admission date or medical record number) that the Privacy Rule considers individually identifiable and thus, PHI. A covered entity's use or disclosure of this information for research is subject to the Privacy Rule. In addition, the results from an analysis of blood and tissue, if containing or associated with individually identifiable information, would be PHI.").
[9] 45 C.F.R. § 164.512(i) (general rules for use and disclosure of patient information for research). Other HIPAA rules are cited as applicable.

1. The research involves only de-identified data; [10]
2. The research uses or discloses a "Limited Data Set" and the covered entity has a "Data Use Agreement" in place with the recipient of the Limited Data Set; [11]
3. The research subject or the subject's authorized representative has signed a written HIPAA authorization (or an informed consent document that integrates all HIPAA authorization requirements);[12]
4. An IRB has waived the requirement for authorization;[13]
5. The activities are just to prepare for research and required representations are obtained from the researchers; [14]
6. The use or disclosure is for patient recruitment purposes, within the limits described below; [15]
7. The research involves only the information of decedents and required representations are obtained from the researchers; [16]
8. The disclosure of the PHI is required by law;[17] or
9. The research is "grandfathered" under the HIPAA rules[18]

The HIPAA rules apply both to internal use of PHI (including employees accessing, collecting, or otherwise using PHI) and to access by or disclosure to third parties outside of the HIPAA covered entity.

1. Only De-identified Data Accompanies the Biospecimens

The HIPAA Privacy Rule protects all information that could identify a covered entity's patients or plan members. HIPAA permits two ways to "de-identify" information before a researcher (or someone on behalf of a researcher) reviews, collects or releases information for research: removal or coding of all HIPAA identifiers or obtaining a statistical certification of de-identification.[19]

The first method is to remove or code all of the HIPAA identifiers in the information, the so-called "safe harbor" method. HIPAA identifiers include all of the following data elements about individuals and their family members, household members, or employers:

- Name;
- Street address, city, county, precinct, or zip code (unless only the first three digits of the zip code are used and the area has more than 20,000 residents);
- The month and day of dates directly related to an individual, such as birth date, admission date, discharge date, dates of service, or date of death;
- Age if over 89 (unless aggregated into a single category of age 90 and older);

[10] 45 C.F.R. § 164.514(a)-(b).
[11] 45 C.F.R. § 164.514(c).
[12] 45 C.F.R. § 164.508.
[13] 45 C.F.R. § 164.512(i).
[14] 45 C.F.R. § 164.512(i).
[15] 45 C.F.R. § 164.506 (treatment or health care operations).
[16] 45 C.F.R. § 164.512(i).
[17] 45 C.F.R. § 164.512(a).
[18] 45 C.F.R. § 164.512(i).
[19] 45 C.F.R. § 164.514(a)-(b).

- Telephone numbers;
- Fax numbers;
- Email addresses;
- Social security numbers;
- Medical record numbers;
- Health plan beneficiary numbers;
- Account numbers;
- Certificate/license numbers;
- Vehicle identifiers, serial numbers, and license plate numbers;
- Device identifiers and serial numbers;
- Web Universal Resource Locators (URLs) and Internet Protocol (IP) addresses;
- Biometric identifiers, such as fingerprints
- Full-face photographs and any comparable images; or
- Any other unique identifying number, characteristic, or code.

If the covered entity has actual knowledge that, even with these identifiers removed or coded, the remaining information could be used alone or in combination with other information to identify the individual, then the information still must be treated as PHI.

If the identifiers are coded before access, review, collection or release for the research, the code may not be derived from any information about the patient or plan member.[20] For example, the code may not be derived from the individual's social security number, medical record number or name (such as initials), and may not be capable of being translated to identify the individual.

The second method of de-identification, the "expert determination method," is to have a qualified statistical expert determine that the risk is very small that the HIPAA identifiers present could be used alone, or in combination with other available information, to identify the patient.[21] The statistical expert must be a person with knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information non-individually identifiable, and must document the methods and results of the analysis that justifies the conclusion of very small risk.[22] The HIPAA covered entity must keep this documentation for six years.[23] The OCR published an extensive guidance document on de-identification of PHI.[24]

A covered entity may have one of its employees or a third party de-identify the PHI before use or disclosure of the de-identified information for research purposes. This process of de-identifying PHI is treated as covered entity "health care operations," which may be done without the individual's authorization.[25] When a non-employed third party (including a non-employed researcher) does the de-identification, the covered entity must have a business

[20] 45 C.F.R. § 164.514(c)(1).
[21] 45 C.F.R. § 164.514(b)(1).
[22] *Id.*
[23] 45 C.F.R. §§ 164.514(b)(1)(ii), 164.530(j)(2).
[24] See Guidance Regarding Methods for De -identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (Nov. 26, 2012), at http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/De-identification/hhs_deid_guidance.pdf.
[25] 45 C.F.R. § 164.501 (defining health care operations); 45 C.F.R. § 164.506 (use or disclosure of PHI for health care operations).

associate agreement in place with that third party.[26] The de-identification process is a "health care operations" function of the covered entity, *whether or not the covered entity participates in the use of the de-identified data*. The HIPAA Privacy Rule specifically says that a covered entity may disclose PHI to a business associate for purposes of de-identification "whether or not the de-identified information is to be used by the covered entity."[27] Moreover, the definition of health care operations does not carry any requirement that the covered entity receive financial or other benefit from the activity.[28] However, after the de-identification process, the business associate may not retain the fully identifiable information for research without following one of the other HIPAA rules for use or disclosure of PHI for research.[29]

As noted above, where biospecimens are not associated with the HIPAA "identifiers," such as name, medical record number, or dates of service or collection, the biospecimens themselves are not treated as PHI and the use and disclosure of the biospecimens is not regulated by HIPAA.[30] The OCR has concluded that biospecimens themselves are not protected under HIPAA unless they are correlated with HIPAA identifiers.[31]

2. The Research Uses or Discloses a "Limited Data Set"

A "Limited Data Set" is partially de-identified patient information. A Limited Data Set excludes all of the HIPAA identifiers listed above, except that a Limited Data Set may include: (1) geographic designations above the street level or PO Box; (2) dates directly related to a patient, such as dates of service, birth date, admission date, discharge date, or date of death; or (3) any other unique identifying number, characteristic, or code that is not expressly listed as an "identifier."[32] The research personnel who access, review, collect, or receive a Limited Data Set must sign a "Data Use Agreement" in which they agree to protect the confidentiality of the information.[33] This requirement applies to internal personnel, as well to outside researchers.

A Data Use Agreement must do the following:

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[26] 45 C.F.R. § 164.502(e); 45 C.F.R. § 164.504(e). *See Clinical Research and the HIPAA Privacy Rule*, p. 15 (NIH 6/22/04), at http://privacyruleandresearch.nih.gov/clin_research.rtf ("The Privacy Rule considers [de-identification] to be a health care operation, as defined at section 164.501, of the covered entity. As such, a covered entity could contract with a business associate, including a researcher, to create de-identified data or a limited data set.").

[27] 45 C.F.R. § 164.502(d)(1). *See also* "Clinical Research and the HIPAA Privacy Rule" (NIH Feb. 2004), available at http://privacyruleandresearch.nih.gov/pdf/clin_research.pdf (concluding that a covered entity may disclose its PHI to a third party researcher, for the researcher to de-identify that information to support the researcher's research (not the covered entity's research)).

[28] *See* 45 C.F.R. § 164.501 (defining "health care operations").

[29] 45 C.F.R. § 164.502(e); 45 C.F.R. § 164.504(e).

[30] *See* Research Repositories, Databases, and the HIPAA Privacy Rule, at 3 (OHPR and NIH, Jan. 12, 2004), at http://privacyruleandresearch.nih.gov/pdf/research_repositories_final.pdf.

[31] *Id.* at 11 ("Under the Privacy Rule, neither blood nor tissue, in and of itself, is considered individually identifiable health information; therefore, research involving only the collecting of blood or tissue would not be subject the Privacy Rule's requirements. Remember, however, blood and tissue are often labeled with information (e.g. admission date or medical record number) that the Privacy Rule considers individually identifiable and thus, PHI. A covered entity's use or disclosure of this information for research is subject to the Privacy Rule. In addition, the results from an analysis of blood and tissue, if containing or associated with individually identifiable information, would be PHI.").

[32] 45 C.F.R. § 164.514(c).

[33] *Id.*

(A) Establish the permitted uses and disclosures of such information by the limited data set recipient [the purpose of which must be limited to research, public health activities or health care operations]. The data use agreement may not authorize the limited data set recipient to use or further disclose the information in a manner that would violate the requirements of this subpart, if done by the covered entity;

(B) Establish who is permitted to use or receive the limited data set; and

(C) Provide that the limited data set recipient will:

(1) Not use or further disclose the information other than as permitted by the data use agreement or as otherwise required by law;

(2) Use appropriate safeguards to prevent use or disclosure of the information other than as provided for by the data use agreement;

(3) Report to the covered entity any use or disclosure of the information not provided for by its data use agreement of which it becomes aware;

(4) Ensure that any agents, including a subcontractor, to whom it provides the limited data set agrees to the same restrictions and conditions that apply to the limited data set recipient with respect to such information; and

(5) Not identify the information or contact the individuals represented in the information.[34]

A business associate agreement is not required when the covered entity discloses a Limited Data Set under a Data Use Agreement.[35]

[34] 45 C.F.R. § 164.514(e)(4).

[35] 45 C.F.R. § 164.504(e)(3)(iv) ("A covered entity may comply with this paragraph and § 164.314(a)(1) if the covered entity discloses only a limited data set to a business associate for the business associate to carry out a health care operations function and the covered entity has a data use agreement with the business associate that complies with § 164.514(e)(4) and § 164.314(a)(1), if applicable."). *See also* 678 Fed. Reg. at 5601 ("Response: We have prior guidance that clarifies that if only a limited dataset is released to a business associate for a health care operations purpose, then a data use agreement suffices and a business associate agreement is not necessary. To make this clear in the regulation itself, we are adding to § 164.504(e)(3) a new paragraph (iv) that recognizes that a data use agreement may qualify as a business associate's satisfactory assurance that it will appropriately safeguard the covered entity's protected health information when the protected health information disclosed for a health care operations purpose is a limited data set. A similar provision is not necessary or appropriate for disclosures of limited data sets for research or public health purposes since such disclosures would not otherwise require business associate agreements.").

3. The Participant or the Participant's Authorized Representative Has Signed a Written HIPAA Authorization

a. The Basics

The most common way to meet the HIPAA requirements in a clinical trial is to obtain a HIPAA-compliant authorization form, either separately or as integrated into an informed consent document for the clinical trial. The HIPAA authorization form must include a number of items:[36]

- A specific and meaningful description of the PHI to be used or disclosed in the research (such as the participant's medical records or other more limited portions of the record, such as laboratory results);
- The name or specific identification of the persons or class of persons authorized to make the disclosure (such as the participant's physicians and treating hospitals);
- The name or specific identification of the persons or class of persons who will have access to the PHI (such as the research site, principal investigator, IRB, sponsor, other third parties involved in the research, data safety monitoring board, FDA, and HHS);
- A description of the specific research protocol or study;
- An expiration date or event (such as the end of the study), or a statement that the authorization has no expiration;
- A statement of the participant's right to revoke the authorization in writing and a description of how to do so;
- A statement that the participant may not revoke the authorization as to information already disclosed for the research where the information is necessary to maintain the integrity of the study data, or a description of other exceptions where the participant may not revoke the authorization;
- A statement that the entity disclosing the PHI may not condition treatment, payment, enrollment or eligibility for benefits on the participant signing the authorization. If the individual will not be allowed to participate in the clinical trial without signing the authorization, the authorization must include a statement to that effect;
- A statement that the information disclosed for the research may be participant to redisclosure by the recipient and no longer be protected by the federal privacy rule;[37]
- If the participant will not be given access to medical records during the study, a statement that the participant agrees to the denial of access when consenting to participate in the study, and that the right of access to the records will be reinstated upon completion of the study
- The participant's signature and the date of signature; and
- If the authorization is executed by a personal representative of the participant (the participant's health care decision maker), a description of that person's authority to act for the participant.

A copy of the signed authorization must be given to the participant.

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[36] 45 C.F.R. § 164.508.

[37] A reference that the recipient's use of PHI is governed by the informed consent is permissible.

b. HIPAA Authorization for Future Research

Under the HIPAA rules, an authorization now may seek permission to use or disclose PHI for future research, as long as the authorization adequately describes the future research purposes "such that it would be reasonable for the individual to expect that his or her protected health information could be used or disclosed for such future research."[38] The OCR expressly provided covered entities with substantial flexibility in determining appropriate language to accomplish this.[39] This changes the OCR's previous interpretation that a HIPAA authorization could not seek permission to use or disclose PHI for future unspecified research, which conflicted with the Common Rule.[40]

However, if the HIPAA authorization for future research is combined with a HIPAA authorization to participate in a clinical trial, the HIPAA authorization for future research must be an "opt-in" (either by check-box, separate signature, or separate form). A participant may be required to sign a HIPAA authorization to use and disclose PHI for the particular clinical trial, as a condition of participating in the clinical trial.[41] On the other hand, a clinical trial participant cannot be required to sign an authorization to use PHI for future research as a condition of participating in the clinical trial, so the individual must be given the opportunity to say "no" to the future research.[42] If the HIPAA authorization requirements are integrated into the informed

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[38] *See* 78 Fed. Reg at 5612-13 ("In order to satisfy the requirement that an authorization include a description of each purpose of the requested use or disclosure, an authorization for uses and disclosures of protected health information for future research purposes must adequately describe such purposes such that it would be reasonable for the individual to expect that his or her protected health information could be used or disclosed for such future research. This could include specific statements with respect to sensitive research to the extent such research is contemplated. However, we do not prescribe specific statements in the Rule. We agree that it is difficult to define what is sensitive and that this concept changes over time. We also agree with commenters that this approach best harmonizes with practice under the Common Rule regarding informed consent for future research, and allows covered entities, researchers and Institutional Review Boards to have flexibility in determining what adequately describes a future research purpose depending on the circumstances. We have consulted with Office for Human Research Protections (OHRP) and the FDA on this approach to ensure consistency and harmonization with the HHS and FDA human subjects protections regulations, where appropriate.

With respect to commenters that stated it is impossible for individuals to be truly informed about future research, we note that we are aligning with existing practice under the Common Rule in regard to informed consent and still require that all required elements of authorization be included in an authorization for future research, even if they are to be described in a more general manner than is done for specific studies.

Pursuant to this modified interpretation, covered entities that wish to obtain individual authorization For the use or disclosure of protected health information for future research may do so at any time after the effective date of this final rule. Alternatively, covered entities may continue to use only study-specific authorizations for research if they choose.").

[39] *Id.*

[40] 45 C.F.R. § 164.508. *See also* OHRP, *Research Repositories, Databases, and the HIPAA Privacy Rule (NIH July 2004), available at* http://privacyruleandresearch.nih.gov/pdf/research_repositories_final.pdf . *See* 21 C.F.R. § 50.25; 45 C.F.R. § 46.116. *See also Institutional Review Boards and the HIPAA Privacy Rule* (OHRP and NIH Aug. 15, 2003) at 11-12, at http://privacyruleandresearch.nih.gov/pdf/IRB_Factsheet.pdf.

[41] The Privacy Rule permits a covered entity to require an individual to sign an authorization to use or disclose the individual's PHI as a condition of receiving treatment that is part of a clinical trial. 45 C.F.R. § 164.508(b)(4).

[42] 45 C.F.R. § 164.508(b)(3) ("Compound authorizations. An authorization for use or disclosure of protected health information may not be combined with any other document to create a compound authorization, except as follows: (i) An authorization for the use or disclosure of protected health information for a research study may be combined with any other type of written permission for the same or another research study. This exception includes combining an authorization for the use or disclosure of protected health information for a research study with another authorization for the same research study, with an authorization for the creation or maintenance of a research database or repository, or with a consent to participate in research. Where a covered health care provider has

consent document (rather than being a separate form), the informed consent document would need to provide the "opt-in" for future research.

4. An IRB Waives the Requirement for Authorization

If it is not feasible to get research participants' authorization (such as where there will not be a face-to-face interaction with study participants), researchers may ask an IRB to waive authorization. To have the IRB grant this request, the researcher must demonstrate three things:

1. The use or disclosure of the participants' identifiable information involves no more than minimal risk to their privacy, based on: (a) an adequate plan to protect information identifying the participants from improper use and disclosure; (b) an adequate plan to destroy information identifying the participants at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retention or if retention is required by law); and (c) adequate written assurances that the information identifying the participants will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research permitted by the rules;

2. The research could not practicably be conducted without the waiver or alteration of authorization; and

3. The research could not practicably be conducted without access to and use of information identifying the participants.

If the researchers can get HIPAA authorization from the participants for some purposes but not others, the researchers can ask the IRB for partial waiver or alteration of the authorization. For example, researchers could ask the IRB to waive authorization for the initial review of records to determine which patients may be appropriate participants (but not a waiver for enrolling those patients in the clinical trial). Another example is that researchers could ask the IRB to approve verbal authorization if the contact with the participants will be by phone.

5. The Activities Are to Prepare for Research

If researchers merely want to access PHI to prepare for a research project, researchers may obtain that information if they provide the covered entity with the following representations in writing:

1. The PHI is sought solely to prepare for research;

2. The PHI is necessary to prepare for research; and

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conditioned the provision of research-related treatment on the provision of one of the authorizations, as permitted under paragraph (b)(4)(i) of this section, any compound authorization created under this paragraph must clearly differentiate between the conditioned and unconditioned components and provide the individual with an opportunity to opt in to the research activities described in the unconditioned authorization."). *See also* 78 Fed. Reg. at 5609-5611 (interpreting compound authorization requirements in research).

3. No information identifying individuals will be removed from the premises in the course of the review.

Activities to prepare for research include activities such as preparing a research protocol or developing a research hypothesis, identifying prospective research participants, or screening patient records to identify whether there are a sufficient number of patients at a facility to function as a site for a clinical trial.[43] Contacting patients to solicit participation in a clinical trial is not an activity to prepare for research,[44] and is covered in Section 6 below.

If researchers will need to remove the information from the covered entity's premises to review it, the researchers must ask the IRB to waive authorization under Section 4 instead, or another HIPAA option must be satisfied. In its guidance document, entitled "Health Services Research and the HIPAA Privacy Rule," OCR emphasized that PHI cannot be removed from the covered entity premises, but permitted remote access to a server containing PHI under certain circumstances. OCR explained:

> Remote access connectivity (i.e., out-of-office computer access achieved through secure connections with access permission and authentication) involves a transmission of electronic PHI, which is not necessarily a removal of PHI under the Privacy Rule. However, although the access to PHI through a remote access connection is not itself a removal of PHI, the printing, copying, saving, or electronically faxing of such PHI would be considered to be a removal of PHI from a covered entity.
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> The Privacy Rule permits a covered entity to rely on representations from persons requesting PHI if such reliance is reasonable under the circumstances. In the case of a request by a researcher to access PHI remotely, this means that, among other things, the risk of removal, as described above, should be assessed in order to determine whether it is reasonable to rely on the researcher's representation that the PHI will not be removed from the covered entity. The covered entity should determine whether its reliance is reasonable based on the circumstances of the particular case.
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> For example, a covered entity may conclude that it can reasonably rely on representations from researchers who are its employees or contractors because their activity is manageable through the covered entity's employment and related policies establishing sanctions for the misuse of PHI. On the other hand, where the researcher has no connection to the covered entity, the covered entity may conclude that it cannot reasonably rely on the researcher's representations that PHI will not be removed from the covered entity, unless the researcher's activity is managed in some other way.
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> Covered entities that permit their workforce or other researchers to access PHI via a remote access connection must also comply with … the Security Rule's requirements for appropriate safeguards to protect the organization's electronic

[43] *See* Clinical Research and the HIPAA Privacy Rule (NIH), at p, 11, available at http://privacyruleandresearch.nih.gov/pdf/clin_research.pdf.
[44] *Id.*

PHI. Specifically, the standards for access control (45 CFR § 164.312(a)), integrity (45 CFR § 164.312(c)(1)), and transmission security (45 CFR § 164.312(e)(1)) require covered entities to implement policies and procedures to protect the integrity of, and guard against the unauthorized access to, electronic PHI. The standard for transmission security (§ 164.312(e)) also includes addressable specifications for integrity controls and encryption. This means that the covered entity must assess its use of open networks, identify the available and appropriate means to protect electronic PHI as it is transmitted, select a solution, and document the decision.[45]

6. The Use or Disclosure of PHI Is for Patient Recruitment Purposes

HIPAA permits the use or disclosure of PHI for patient recruitment.[46] First, a health care provider may contact the provider's own patients to determine if the patients are interested in participating in a clinical trial. If the provider or the provider's employees contact the providers' own patients, that use of PHI is for either "treatment" (if the clinical trial involves treatment) or "health care operations" purposes, both of which are permitted without patient authorization under HIPAA.[47] The health care provider also may use a non-employed third party (including the researcher) to contact patients for recruitment purposes, but the provider first would have to obtain a business associate agreement with the third party.[48] Finally, the researcher can request an IRB to partially waive authorization under Section 4; under that option, authorization would not be required for the initial contact, but would be required to use PHI for the study. Contacting patients for recruitment is not a "preparatory to research" activity under Section 5 above.[49]

7. The Research Involves Only the Information of Decedents

Where the research involves only the information of deceased individuals, researchers may access this information if they provide the covered entity with the following representations in writing:

1. The use or disclosure of information is sought solely for the research on the information of decedents;

2. The information is necessary for the research; and

3. The researcher will provide documentation of the death of the research participants upon request.

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[45] http://privacyruleandresearch.nih.gov/pdf/HealthServicesResearchHIPAAPrivacyRule.pdf.
[46] HHS, *Clinical Research and the HIPAA Privacy Rule*, p. 4 (NIH 6/22/04), at 11, available at http://privacyruleandresearch.nih.gov/clin_research.rtf.
[47] 45 C.F.R. § 164.501 and § 164.506.
[48] 45 C.F.R. § 164.502(e) and § 164.504(e).
[49] *See* OHRP, *Clinical Research and the HIPAA Privacy Rule*, p. 4 (NIH 6/22/04), at http://privacyruleandresearch.nih.gov/clin_research.rtf ("Under the "preparatory to research" provision, covered entities may use or disclose PHI to researchers to aid in study recruitment. The covered entity may allow a researcher, either within or outside the covered entity, to identify, but not contact, potential study participants under the "preparatory to research" provision.").

8. The Disclosure of the PHI Is Required by Law

HIPAA permits the disclosure of PHI if that disclosure is required by another law.[50] HIPAA covered entities thus may disclose PHI to the Food and Drug Administration ("FDA") as required by the FDA regulations, the OHRP as required by the Common Rule HHS regulations, and other government agencies if required by federal or state statute or regulations.

9. The Research Is "Grandfathered" under the HIPAA Privacy Rule

Research is "grandfathered" under HIPAA if the participant signed an informed consent before April 14, 2003 (and the informed consent has not been modified since that date) or if the IRB waived informed consent before April 14, 2003.[51] This does not apply to any participants enrolled in a study after April 14, 2003 or to participants who signed a new informed consent document after this date, and so is unlikely to apply today. If research is grandfathered under HIPAA, researchers may continue to use the participant information they have and also may continue to collect information from the participant.

C. Business Associate Agreements in Research

In the rules published in 2013, the OCR has clarified that a business associate[52] agreement is required in research where the covered entity provides PHI to a third party to de-identify the PHI or to create a Limited Data Set on behalf of the covered entity, because de-identification and creation of a Limited Data Set are health care operations of the covered entity.[53] A business associate agreement also would be required for a non-employed individual to assist in recruiting patients to participate in clinical trials, if that recruitment is a health care operations function (see discussion of Section 6, above). The business associate must return the PHI after the de-identification or creation of the Limited Data Set. This is consistent with previous guidance issued by the OCR.[54]

A business associate agreement is not required if a disclosure of PHI follows one of the other HIPAA research rules, such as IRB waiver of HIPAA authorization.

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[50] 45 C.F.R. § 164.512(a).
[51] 45 C.F.R. § 164.532(c).
[52] 45 C.F.R. § 164.103 (defining business associate).
[53] See 78 Fed. Reg. at 5575 ("A person or entity is a business associate only in cases where the person or entity is conducting a function or activity regulated by the HIPAA Rules on behalf of a covered entity, such as payment or health care operations, or providing one of the services listed in the definition of ''business associate,'' and in the performance of such duties the person or entity has access to protected health information. Thus, an external researcher is not a business associate of a covered entity by virtue of its research activities, even if the covered entity has hired the researcher to perform the research. See http://www.hhs.gov/ocr/privacy/hipaa/faq/business_associates/239.html. Similarly, an external or independent Institutional Review Board is not a business associate of a covered entity by virtue of its performing research review, approval, and continuing oversight functions.However, a researcher may be a business associate if the researcher performs a function, activity, or service for a covered entity that does fall within the definition of business associate, such as the health care operations function of creating a de-identified or limited data set for the covered entity. See paragraph (6)(v) of the definition of ''health care operations.'' Where the researcher is also the intended recipient of the de-identified data or limited data set, the researcher must return or destroy the identifiers at the time the business associate relationship to create the data set terminates and the researcher now wishes to use the deidentified data or limited data set (subject to a data use agreement) for a research purpose.").
[54] *See* http://privacyruleandresearch.nih.gov/pdf/HIPAA_Booklet_4-14-2003.pdf at page 7.

D. Sale of PHI

The HIPAA Privacy Rule used to permit a covered entity to receive payment for a disclosure of PHI where that disclosure was otherwise permitted by the regulations (such as for research with IRB waiver of authorization). The new rules prohibit indirect and direct remuneration from or on behalf of the recipient of PHI in exchange for the PHI, without the individual's authorization,[55] with some exceptions. The authorization document must explain whether PHI can be further exchanged for remuneration by the downstream entity receiving the PHI.[56]

The first issue to examine is whether the covered entity is receiving "remuneration" under the regulations. The OCR clarified that this includes both payment and non-financial benefit. The OCR comments in the Preamble to the regulations are instructive:

> In response to questions by commenters, we also clarify the scope of the term "remuneration." The statute uses the term "remuneration," and not "payment," as it does in the marketing provisions at section 13406(a). Because the statute uses different terms, we do not believe that remuneration as applied to the sale provisions is limited to financial payment in the same way it is so limited in the marketing provisions. Thus, the prohibition on sale of protected health information applies to the receipt of nonfinancial as well as financial benefits. … Thus, a covered entity or business associate may not disclose protected health information in exchange for in kind benefits, unless the disclosure falls within one of the exceptions discussed below. Consider, for example, a covered entity that is offered computers in exchange for disclosing protected health information. The provision of protected health information in exchange for the computers would not be considered a sale of protected health information if the computers were solely used for the purpose of preparing and transmitting protected health information to the person collecting it and were returned when such disclosure was completed. However, if the covered entity is permitted to use the computers for other purposes or to keep the computers even after the disclosures have been made, then the covered entity has received in kind remuneration in exchange for the protected health information above what is needed to make the actual disclosures.[57]

A careful analysis also will be required in many circumstances to determine whether a covered entity or business associate is receiving remuneration "in exchange for" PHI. The OCR provided some commentary on this issue, which demonstrates that payment for services rendered—even if those services involve the provision of PHI—will not be treated as the "sale" of PHI, such as funding received to conduct a clinical trial. Rather, the prohibition applies where the covered entity or business associate *primarily* is being compensated to supply PHI. The OCR explained that:

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[55] 45 C.F.R. § 164.502(a)(5)(ii), implementing Section 13405(d) of the HITECH Act, codified at 42 U.S.C. § 17935(d).
[56] 45 C.F.R. § 164.508.
[57] *See* 78 Fed. Reg. 5607 (Jan. 25, 2013).

> [W]e do not consider sale of protected health information in this provision to encompass payments a covered entity may receive in the form of grants, or contracts or other arrangements to perform programs or activities, such as a research study, because any provision of protected health information to the payer is a byproduct of the service being provided. Thus, the payment by a research sponsor to a covered entity to conduct a research study is not considered a sale of protected health information even if research results that may include protected health information are disclosed to the sponsor in the course of the study. Further, the receipt of a grant or funding from a government agency to conduct a program is not a sale of protected health information, even if, as a condition of receiving the funding, the covered entity is required to report protected health information to the agency for program oversight or other purposes. (Certain of these disclosures would also be exempt from the sale requirements, depending on whether the requirement to report data was included in regulation or other law.)
>
> … In contrast, a sale of protected health information occurs when the covered entity primarily is being compensated to supply data it maintains in its role as a covered entity (or business associate). … For example, a disclosure of protected health information by a covered entity to a third party researcher that is conducting the research in exchange for remuneration would fall within these provisions, unless the only remuneration received is a reasonable, cost-based fee to cover the cost to prepare and transmit the data for such purposes (see below).[58]

The prohibition on the sale applies to Limited Data Sets.[59] Because Limited Data Sets may include indirect identifiers, such as dates related to patients and geographic designations, Limited Data Sets are technically PHI (unless a qualified statistician certifies that the Limited Data Set is actually de-identified information). As PHI, Limited Data Sets are subject to the rule.[60]

However, the regulations contain several exceptions where a covered entity is permitted to receive remuneration for disclosures:

- For public health activities,
- <u>For research, where the price charged reflects the costs of preparation and transmittal of the data</u>,
- For treatment,
- For the sale, merger or transfer of the covered entity (which is a health care operation),
- To or by a business associate to perform functions for the covered entity, where the only remuneration to the business associate is for those activities,
- To an individual who wants copies of his or her PHI,
- As required by law, and

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[58] *See* 78 Fed. Reg. 5606 (Jan. 25, 2013).

[59] *See* 45 C.F.R. § 164.514 (defining Limited Data Set).

[60] *See* 78 Fed. Reg. 5609 (Jan. 25, 2013) ("Disclosures of health information that has been de-identified in accordance with the Privacy Rule at § 164.514(b)-(d) are not subject to the remuneration prohibition as such information is not protected health information under the Rule.... [However, we] decline to completely exempt limited data sets from these provisions as, unlike de-identified data, they are still protected health information.").

- "For any other purpose permitted by and in accordance with the applicable requirements of this subpart, where the only remuneration received by the covered entity or business associate is a reasonable, cost-based fee to cover the cost to prepare and transmit the protected health information for such purpose or a fee otherwise expressly permitted by other law."[61]

The regulations do not contain any details on the price cap for research disclosures, so we await guidance from the OCR to determine how it will interpret what is included in the "costs of preparation and transmittal of data."

The rule grandfathers research conducted pursuant to the rules in place before January 25, 2013 (the date the new rules were published).[62] So, if a covered entity is receiving payment for PHI for research approved under an IRB waiver of authorization obtained before that date, it may continue to receive payment for that PHI without obtaining individual authorization. Moreover, the disclosure of a Limited Data Set pursuant to a Data Use Agreement in compliance with the previous rule may continue, regardless of whether the covered entity or business associate receives remuneration in exchange for disclosure of the Limited Data Set.[63]

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[61] 45 C.F.R. § 164.502(a)(5)(ii).

[62] 45 C.F.R. § 164.532(c) "Implementation specification: Effect of prior permission for research. Notwithstanding any provisions in §§ 164.508 and 164.512(i), a covered entity may, to the extent allowed by one of the following permissions, use or disclose, for research, protected health information that it created or received either before or after the applicable compliance date of this subpart, provided that there is no agreed-to restriction in accordance with § 164.522(a), and the covered entity has obtained, prior to the applicable compliance date, either: (1) An authorization or other express legal permission from an individual to use or disclose protected health information for the research; (2) The informed consent of the individual to participate in the research; (3) A waiver, by an IRB, of informed consent for the research, in accordance with 7 CFR 1c.116(d), 10 CFR 745.116(d), 14 CFR 1230.116(d), 15 CFR 27.116(d), 16 CFR 1028.116(d), 21 CFR 50.24, 22 CFR 225.116(d), 24 CFR 60.116(d), 28 CFR 46.116(d), 32 CFR 219.116(d), 34 CFR 97.116(d), 38 CFR 16.116(d), 40 CFR 26.116(d), 45 CFR 46.116(d), 45 CFR 690.116(d), or 49 CFR 11.116(d), provided that a covered entity must obtain authorization in accordance with § 164.508 if, after the compliance date, informed consent is sought from an individual participating in the research; or (4) A waiver of authorization in accordance with § 164.512(i)(1)(i)."). *See also* 78 Fed. Reg. at 5608 ("We agree that ongoing research studies that are based on a prior permission under the Privacy Rule for the research use or disclosure of protected health information should be grandfathered so as not to disrupt these ongoing studies. We have added a reference to the authorization requirements that apply to the sale of protected health information at § 164.508(a)(4) to make clear that the transition provisions in § 164.532 apply to permissions existing prior to the applicable compliance date of the Rule. Thus, a covered entity may continue to rely on an authorization obtained from an individual prior to the compliance date even if remuneration is involved but the authorization does not indicate that the disclosure is in exchange for remuneration. This would apply to authorizations for any permissible purpose under the Rule and not just for research purposes. Further, in the research context, where a covered entity obtained documentation of a waiver of authorization from an Institutional Review Board or Privacy Board prior to the compliance date for this final rule, the covered entity may continue to rely on that documentation to release protected health information to a researcher, even if the covered entity receives remuneration in the form of more than a reasonable, cost based fee to prepare and transmit the data. Finally, we also provide at new § 164.532(f) that a covered entity may continue to use or disclose a limited data set in accordance with an existing data use agreement that meets the requirements of § 164.514(e), including for research purposes, until the data use agreement is renewed or modified or until one year from the compliance date of this final rule, whichever is earlier.").

[63] *Id.*

E. HIPAA Security Rule Compliance in Research

HIPAA covered entities must comply with the HIPAA Security Rule.[64] In addition, the HITECH Act imposed a bulk of the Security Rule directly to business associates of a covered entity. So, the HIPAA Security Rule requirement applies to a covered entity's or a business associates' storage or transmission of PHI for research.

The Security Rule requires certain efforts to protect PHI against outside hackers or access by unauthorized individuals, to protect the hardware on which PHI is stored, to protect the facilities that house that hardware, and to preserve the availability of PHI in the event of natural disasters or other threats to a Covered Entity's physical facility or medical records systems. The HIPAA Security Rule addresses these issues, requiring covered entities (and now business associates) to protect the "confidentiality, integrity, and availability" of PHI. To achieve these goals, the Security Standards establish administrative, technical, and physical security measures covered entities and business associates must take when they store or transmit health information in electronic form.

Unlike the Privacy Rule, which applies to PHI in all forms (written, oral and electronic), the Security Rule applies only to PHI that is transmitted or maintained in electronic form ("EPHI"). The Security Rule therefore applies to PHI stored in any electronic media, whether in the form of computer hardware (hard drives or server storage) or any transportable media (such as disks, CDs, "flash" memory cards, etc.). This of course would include any EPHI stored in biospecimen repositories.

This paper does not cover these requirements in detail, as HIPAA covered entities should apply their general HIPAA Security Rule compliance activities to any EPHI stored or transmitted in research. Each organization's Security Rule policies are detailed and are written specifically for that organization's information security environment.

II. Common Rule Compliance

A. Application of the Common Rule

1. Federally-Funded Research

An organization must comply with the federal Common Rule[65] if research is federally funded, or if it has voluntarily agreed to extend its Federalwide Assurance ("FWA") to all of its research regardless of the funding source.[66]

NPRM Proposed Changes: The Office for Human Research Protections ("OHRP") issued a Notice of Proposed Rulemaking (the "NPRM") on September 8, 2015, which proposes sweeping changes to the Common Rule.[67] One fundamental change proposed by the OHRP is to expand its jurisdiction to all non-exempt, non-excluded research (regardless of funding source

[64] 45 C.F.R Part 160 and Part 164, Subpart C.
[65] *See* 45 C.F.R. Part 46.
[66] 45 C.F.R. §46.101.
[67] 80 Federal Register ("Fed. Reg.") 53933 (Sept. 8, 2015), at http://www.gpo.gov/fdsys/pkg/FR-2015-09-08/pdf/2015-21756.pdf.

for the particular research) conducted by an institution that receives federal funding for any research, unless that research is regulated by the FDA.[68] The proposed rule thus would prevent overlapping jurisdiction by the FDA and the OHRP.

If finalized, the rule will apply only prospectively, not to "[o]ngoing human subjects research in which human subjects [] were involved prior to the compliance dates for the cited provisions…"[69] As related to biospecimens, research involving prior collections of biospecimens will not have to comply with the new regulations if: (1) the biospecimens were collected before the compliance date; and (2) any individually identifiable information associated with the biospecimens is removed.[70]

2. "Human Subjects" Research

Research is defined as the "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[71] Human subjects include "living individual(s) about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable personal information."[72] On the other hand, if all patients for whom samples are provided are deceased, then it is not human subject research that is regulated by the Common Rule.[73] (Of course, the HIPAA Privacy Rule applies to the information of deceased individuals for up to 50 years after death,[74] but the HIPAA requirements for research involving deceased patient information are quite easy to meet.)

If the organization's personnel or outside third parties access individually identifiable patient information (of living patients) to evaluate whether a patient's biospecimen should be included in a research repository or to collect that identifiable information for the repository, that curation or processing activity is itself "human subject research." Even if the Privacy Rule does not require patient authorization or IRB waiver of authorization for "preparatory to research" activities, the Common Rule requires IRB waiver of informed consent for a researcher to review patient information to review the records of living patients and to identify potential research participants.[75] Researchers should comply with these stricter requirements if the Common Rule applies.

When releasing biospecimens for research, the question of whether the activity is "human subject research" gets more complex. The OHRP has provided guidance that, if the biospecimens are not collected for currently proposed research and the investigator cannot readily ascertain the identity of the subjects, the release of those biospecimens to the

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[68] Proposed 45 C.F.R. § 46.101(a).
[69] Proposed 45 C.F.R. § 46.101(k).
[70] *Id.*
[71] 45 C.F.R. § 46.102(d).
[72] 45 C.F.R. § 46.102(f)(1).
[73] The Common Rule does not apply to the use of decedents' information for research, because the Rule regulates only research involving living human participants. 45 C.F.R. § 46.101.
[74] 45 C.F.R. § 160.103 (definition of "protected health information").
[75] *See* 45 C.F.R. § 46.102(d), (f) (defining "research" on "human participants" as including examination of private information); 45 C.F.R. § 46.109(a) (requiring IRB approval of research on human participants); 45 C.F.R. § 46.116(c) (IRB approval of consent procedure to waive informed consent).

investigator is not human subject research.[76] Conversely, if information included with the biospecimens could lead an investigator to readily ascertain the identity of the subjects or if the biospecimens are collected for a particular research protocol, the organization must comply with the Common Rule in releasing those biospecimens to the researcher. Three concepts are important to explore in more detail.

(1) When were the biospecimens collected for the currently proposed research project through an interaction or intervention with living individuals? Biospecimens that are collected as part of a clinical trial clearly are collected for a currently proposed research project. At the other extreme, "leftover" pathology and other tissue specimens that were collected in the past for diagnostic or therapeutic purposes were not collected for research. The tougher question is posed when the biospecimen is collected for diagnostic or therapeutic purposes, but where the collector knows in advance that the patient's biospecimen will be used for research. Interestingly, OHRP has concluded that, where biospecimens are collected for inclusion in a repository, the biospecimens are not collected "for currently proposed research" if there is no intent at the time of collection to use the tissues for a particular research protocol.[77]

(2) When can investigators "readily ascertain" the identity of the individuals? In general, the OHRP considers private information or biospecimens to be individually identifiable, as defined at 45 C.F.R. § 46.102(f), when they contain direct identifiers (such as names, addresses or social security numbers) or where they can be linked to specific individuals by the investigators, either directly or indirectly through coding systems. Conversely, OHRP considers private information or biospecimens not to be individually identifiable when the investigators cannot link the specimens to specific individuals. (The concept of whether data is non-identifiable under the Common Rule thus is more limited than whether data is de-identified under HIPAA.)

The OHRP does not consider research involving only coded private information or biospecimens to involve human subjects if one of the following conditions is met:

(1) The key to decipher the code is destroyed before the research begins;

(2) The investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the participants are deceased. The Common Rule does not require the IRB to review and approve this agreement;

(3) There are IRB-approved written policies and operating procedures for a repository that prohibit the release of the key to the investigators under any circumstances, until the participants are deceased; or

(4) There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.[78]

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[76] 45 C.F.R. § 46.102. See also OHRP, Guidance on Research Involving Coded Private Information or Biological Specimens (Aug. 2004) at http://hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf.

[77] *Id.*

[78] *See OHRP Guidance on Research Involving Coded Private Information or Biological Specimens* 2-3 (Oct. 2008), *available at* http://www.hhs.gov/ohrp/policy/cdebiol.pdf.

On the other hand, the release of coded specimens is human subject research if the holder of the key to the code and the investigators are collaborators in the particular study or in the research repository activities. The OHRP explained that, while the "act of solely providing coded private information or specimens" is not research, "if the individuals who provide coded information or specimens collaborate on other activities related to the conduct of this research with the investigators who receive such information or specimens, then OHRP would consider such additional activities to constitute involvement in the conduct of the research. Examples of such additional activities include, but are not limited to: (1) the study, interpretation, or analysis of the data resulting from the coded information or specimens; and (2) authorship of presentations or manuscripts related to the research."[79] Thus, even if the directly identifying information is coded, OHRP will treat this as human subject research if organization personnel will be assisting the investigators in the interpretation or analysis of data or will be a co-author in publications or presentations.

OHRP noted in its guidance document that research institutions should have policies in place that designate an individual or entity to determine whether research involving coded private information or specimens is human subjects research. The investigator should not make this determination.[80]

NPRM Proposed Changes: One of the most substantial changes proposed in the NPRM is to treat research with non-identifiable biospecimens as "human subjects" research, with a limited exception. The OHRP proposes to require individual consent to store or use biospecimens for future research, with very little opportunity to obtain waiver of informed consent.

The NPRM proposes the drastic change of requiring consent for the use of non-identifiable biospecimens for research, citing a "growing body of literature [that] shows that in general people prefer to have the opportunity to consent (or refuse to consent) to research involving their own biological materials."[81] While the OHRP currently "does not consider whole genome analysis to produce identifiable private information unless additional information is available to the investigator that would enable the investigator to 'readily ascertain' the identity of the individual, it is acknowledged that a time when investigators will be able readily to ascertain the identity of individuals from their genetic information may not be far away."[82] Thus, despite the fact that the majority of commenters to the Advanced Notice of Proposed Rulemaking (the "ANPRM") opposed requiring consent to use non-identifiable biospecimens for research,[83] the OHRP believed that not seeking consent could undermine the public's support for research.[84]

As an alternative to requiring consent to research for all biospecimens, the OHRP also proposes two potential alternatives on which it seeks public comment. The first alternative is to

[79] *Id.* at 3.
[80] *Id.* at 4.
[81] 80 Fed. Reg. at 53942 (citations omitted).
[82] 80 Fed. Reg. at 53943.
[83] 80 Fed. Reg. at 53943.
[84] 80 Fed. Reg. at 53942.

expand the definition of human subjects only to include whole genome sequencing[85] data, regardless of identifiability. Under this "Alternative Proposal A," use of identifiable biospecimens would continue to fall within human subjects research, but secondary research using non-identifiable biospecimens would fall outside of the scope of the Common Rule, unless whole genome sequencing will be performed with those biospecimens.

The OHRP also proposes an "Alternative Proposal B," which would expand the definition of "human subjects" to include "the research use of information that was produced using a technology applied to a biospecimen that generates information unique to an individual such that it is foreseeable that, when used in combination with publicly available information, the individual could be identified."[86] The proposed rule refers to this as "bio-unique information."[87] This proposal would require consent for any research that might generate information unique to an individual, that when combined with publicly available information could be used to identify the individual, such as genomic sequencing of small portions of the genome. This would be implemented through a list published by the OHRP of the technologies that produce bio-unique information.

Whatever proposal is eventually adopted, the NPRM proposes that biospecimen holders may obtain "broad" consent for future unspecified research with biospecimens, which will not have to describe the particular research to be conducted with the biospecimens. See discussion of broad consent in Section 6, below.

The NPRM also proposes an "exclusion" from the Common Rule for "research designed to only generate information about the person that is already known." [88] This would include the use of biospecimens to validate tests and assays, develop diagnostic testing, and conduct quality assurance, where the research results would be compared against information already known about particular subjects. A further discussion of excluded activities is in Section 4 below.

This amended definition of "human subjects" will apply prospectively, and thus will not apply to biospecimens obtained prior to adoption of a final rule.[89] Compliance with this provision will be delayed until three years after publication of the final rule,[90] which will allow substantial time to come into compliance if the rules are finalized as proposed.

3. Exempt Research

Even if the curation of biospecimens or the provision of biospecimens for a protocol or to biorepository is "human subject research," it is possible that this research will be exempt from Common Rule compliance. The current OHRP regulations exempt a number of different categories of research from IRB review, including research involving collection or study of existing data, documents, or pathological or diagnostic specimens, if the information is

[85] Defined as "the sequencing of a human germline or somatic biospecimen with intent to generate the genome or exome sequence of that biospecimen."
[86] 80 Fed. Reg. at 53945-46.
[87] *Id.*
[88] Proposed 45 C.F.R. § 46.101(b)(3).
[89] 80 Fed. Reg. at 53944.
[90] 80 Fed. Reg. at 53944.

recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers.[91]

Leftover biospecimens that were collected for treatment purposes clearly are "existing" under the regulations, as they existed before the research was proposed. The OHRP IRB Guidebook gives an example exactly on point: "If [an] Investigator … proposes to use specimens that had been collected prior to the initiation of her research and are, for some reason, 'on the shelf,' the protocol will qualify as exempt under 46.101(b)(4), assuming the other requirements of 46.101(b)(4) are met (i.e., the sources are either publicly available or the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects).[92] However, if during curation of the tissue specimens, personnel record information in a manner that the patient may be identified through links (which may be necessary if the repository seeks annotated clinical information in addition to the samples), the curation activities would not be exempt from IRB review.

NPRM Proposed Changes: OHRP proposes a different approach to determining whether research is exempt. OHRP will produce a decision tool, which if completed accurately (including by the investigator), will meet the exemption requirements and will not require further review by the institution or the IRB.[93] The institution or IRB must maintain documentation of the exemption determination (such as maintaining the completed decision tool).

The OHRP also proposes to expand the categories of exempt research. As relevant to this White Paper, OHRP proposes to exempt secondary use of identifiable private information (but not biospecimens) obtained for non-research purposes if prior notice has been given to individuals that their information may be used in research, and the "identifiable private information is used only for purposes of the specific research for which the investigator or recipient entity requested access to the information."[94] For example, this would allow a hospital that includes a description of research activities in its HIPAA Notice of Privacy Practices, to provide to an investigator PHI from the electronic health record, pursuant to a particular research protocol. It would not permit the hospital to provide identifiable information to a third party's data repository to use for future research. Note that the proposed rule would also require prior notice to the particular individual whose information would be used for the research, so the institution may be required to confirm before using an individual's identifiable information that the individual had actually received the Notice of Privacy Practices. IRB review would be required for these category of exempt research but only for the following requirements:

> "(i) The procedures for obtaining broad consent for storage, maintenance, and secondary research use of biospecimens or identifiable private information will be conducted in accordance with the requirements of the first paragraph in §____.116.
> (ii) If there will be a change for research purposes in the way the biospecimens or information are stored or maintained, that the privacy and information protection

[91] 45 C.F.R. § 46.101(b)(4).
[92] OHRP, IRB Guidebook, p. 33, at http://www.hhs.gov/ohrp/irb/irb_guidebook.htm.
[93] Proposed 45 C.F.R. § 46.104(c).
[94] Proposed 45 C.F.R. § 46.104(e)(2).

standards at § ____.105 are satisfied for the creation of any related storage database or repository."[95]

This IRB review to determine whether the exemption requirements are met may be done by expedited review.[96]

OHRP also proposes to exempt research that involves storing biospecimens or identifiable private information if the research utilizes biospecimens or information not collected for the particular research, and the individual has provided written broad consent for the storage and use of biospecimens using the template that will be published by the OHRP (with oral consent permitted for identifiable information in limited circumstances).[97] In addition, OHRP proposes to exempt research using stored biospecimens or identifiable private information if broad consent is obtained using the HHS template, and the investigator does not intend to return individual research results to the participant.[98]

Both of these new exemption categories are subject to the requirements to document exempt status, and are subject to the standards for information and biospecimen protection, discussion in Section E below.[99]

4. Excluded Activities: NPRM Proposed Changes

The NPRM proposes a new category of activity that will be "excluded," and not subject to any of the procedural, recordkeeping or other requirements of the Common Rule.[100] The proposed rule first clarifies that some activities would be excluded because they are not "research" activities at all, such as "data collection and analysis, including the use of biospecimens, for an institution's own internal operational monitoring and program improvement purposes, if the data collection and analysis is limited to the use of data or biospecimens originally collected for any purposes other than the currently proposed activity, or is obtained

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[95] Proposed 45 C.F.R. § 46.111(9).

[96] Proposed 45 C.F.R. § 46.110(b)(iii).

[97] Proposed 45 C.F.R. § 46.104(f)(1) "(i) Storage or maintenance for secondary research use of biospecimens or identifiable private information that have been or will be acquired for research studies other than for the proposed research study, or for nonresearch purposes, if the following criteria are met:
(A) Written consent for the storage, maintenance, and secondary research use of the information or biospecimens is obtained in accordance with §____.116(c) and (d)(2), and the template published by the Secretary of HHS in accordance with §____.116(d)(1) must be used. Oral consent, if obtained during the original data collection and in accordance with §___.116(c) and
(d)(3), would be satisfactory for the research use of identifiable private information initially acquired in accordance with activities excluded from this policy under §____.101(b)(2)(i) or exempt from this policy in accordance with §___.104(d)(3) or (4), or §___.104(e)(1);
(B) The reviewing IRB makes the determinations required by §___.111(a)(9).
(ii) [Reserved.]"

[98] Proposed 45 C.F.R. § 46.104(f)(2) "(i) Research involving the use of biospecimens or identifiable private information that have been stored or maintained for secondary research use, if consent for the storage, maintenance, and secondary research use of the information and biospecimens was obtained as detailed in paragraph (f)(1)(i)(A) of this section.
(ii) If the investigator anticipates that individual research results will be provided to a research subject, the research may not be exempted under this provision and must be reviewed by the IRB and informed consent for the research must be obtained to the extent required by §ll.116(a) and (b)."

[99] Proposed 45 C.F.R. § 46.104(e), (f).

[100] Proposed 45 C.F.R. § 46.101(b).

through oral or written communications with individuals (e.g., surveys or interviews)."[101] So, for example, the internal use of blood samples for an infection control program would not be governed by the Common Rule.

Second, OHRP proposes to exclude low-risk human subjects research when the research governed by alternative regulation, such as HIPAA.[102] However, these exclusions do not apply when the research involves the collection or analysis of biospecimens.[103]

Third, OHRP proposes to exclude low-risk human subjects research when it "does not meaningfully diminish subject autonomy.[104] Specifically, this would exclude:

> "The secondary research use of a non-identified biospecimen that is designed only to generate information about an individual that already is known, including but not limited to the development and validation of certain tests and assays (such as research to develop a diagnostic test for a condition using specimens from

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[101] Proposed 45 C.F.R. § 46.101(b)(1)(i). *See* 80 Fed. Reg. at 53947. Other activities related to biospecimens that will not be treated as "research" and thus will be excluded include:

"(iii) Collection and analysis of data, biospecimens, or records by or for a criminal justice agency for activities
authorized by law or court order solely for criminal justice or criminal investigative purposes.

(iv) Quality assurance or improvement activities involving the implementation of an accepted practice to improve the delivery or quality of care or services (including, but not limited to, education, training, and changing procedures related to care or services) if the purposes are limited to altering the utilization of the accepted practice and collecting data or biospecimens to evaluate the effects on the utilization of the practice. This exclusion does not over the evaluation of an accepted practice itself.

(v) Public health surveillance activities, including the collection and testing of biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority and limited to those necessary to allow the public health authority to identify, monitor, assess, or investigate potential public health signals or the onset of a disease outbreak, including trends, or signals, and patterns in diseases, or a sudden increase in injuries from using a consumer product, or conditions of public health importance, from data, and including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health, including natural or man-made disasters.

(vi) Surveys, interviews, surveillance activities and related analyses, or the collection and use of biospecimens conducted by a defense, national security, or homeland security authority solely for authorized intelligence, homeland security, defense, or other national security purposes."

[102] Proposed 45 C.F.R. § 46.101(b)(2). As relevant to biomedical (non-educational research), the exclusions for low risk research would include:

"(ii) Research involving the collection or study of information that has been or will be acquired solely for non-research activities or were acquired for research studies other than the proposed research study, when either of the following two criteria is met: (A) These sources are publicly available, or (B) The information is recorded by the investigator in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects or otherwise conduct an analysis that could lead to creating identifiable private information.

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(iv) Research as defined by this policy that involves only data collection and analysis involving the recipient's use of identifiable health information when such use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of ''health care operations'' or ''research'' as those terms are defined at 45 CFR 164.501 or for the purpose of ''public health activities'' as described under 45 CFR 164.512(b)." This last exclusion would not apply if a covered entity discloses PHI to an investigator that is not covered by HIPAA. 80 Fed. Reg. at 53954.

[103] Id.

[104] Proposed 45 C.F.R. § 46.101(b)(3).

individuals known to have the condition and those known not to have the condition), quality assurance and control activities, and proficiency testing."[105]

As OHRP explains: "If the research is designed not to generate any new information about the person, but only confirm something about them that is already known, then the interest in respective the person's autonomy would appear to be relatively weak."[106] For example, if a person has already been diagnosed with a genetic disease, using that person's biospecimens to develop a biomarker test for that genetic disease would be activity excluded from the Common Rule.[107]

B. Informed Consent Requirements

The Common Rule requires an informed consent document to include the following elements:[108]

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of participation;
- A description of any reasonably foreseeable risks;
- A description of any benefits to the subject or to others, which may reasonably be expected;
- Disclosure of appropriate alternative procedures or courses of treatment that may be advantageous to the subject;
- A statement describing confidentiality protections;
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available;
- An explanation of whom to contact for answers to pertinent questions, and
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue

[105] Id.
[106] 80 Fed. Reg at 53944-45.
[107] Id.
[108] 45 C.F.R. § 46.116(a).

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

In addition, the Common Rule provides a host of informed consent elements to be included "when appropriate," including:[109]

- A statement that the particular treatment or procedure may involve risks to the subject;
- Circumstances under which the subject's participation may be terminated without the subject's consent;
- Additional costs to the subject that may result from participation;
- The consequences of a subject's decision to withdraw from the research;
- A statement that significant new findings which may relate to the subject's willingness to continue participation will be provided to the subject; and
- The approximate number of subjects involved in the study.

The Office for Human Research Protections ("OHRP") has addressed how an informed consent document to contribute biospecimens to a repository should address these regulatory requirements. Specifically, the OHRP expects to see the following elements:

- A clear description of the operation of the repository, including whether identifiable information will be maintained in the repository and whether research results will be linked to the biospecimens;
- The conditions under which data and specimens will be released to recipient investigators;
- Procedures for protecting the privacy of human subjects and confidentiality of data;
- Specific descriptions of the nature and purpose of the research; and
- Where genetic research is anticipated, information about the consequences of DNA typing.[110]

Confidentiality: The Common Rule requires an informed consent document to discuss how the participant's identifiers will be treated confidentially in the study, but does not have specific requirements.[111] An informed consent document "should state whether identifiable or coded information will be maintained in the biospecimen resource and if research results will be linked to other data about the human subject, such as clinical data... If longitudinal data will be collected, the informed consent document should state that the subject's medical records will be accessed for this purpose. Informed consent documents also should describe whether the biospecimens and/or the data associated with or derived from the biospecimens will be shared with other investigators and, if so, the oversight mechanisms for such sharing."[112]

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[109] 45 C.F.R. § 46.116(b).

[110] See OHRP Guidance on Research Involving Coded Private Information or Biological Specimens (Oct. 16, 2008), at http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf; see also OPRR Guidance: Issues to Consider in the Research Use of Stored Data or Tissues (Nov. 7, 1997), at http://www.hhs.gov/ohrp/humanparticipants/guidance/reposit.htm.

[111] 45 C.F.R. § 46.116 (requiring a "statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained").

[112] *See* National Cancer Institute's, Best Practices for Biospecimen Resources (June 2007), http://biospecimens.cancer.gov/global/pdfs/NCI_Best_Practices_060507.pdf at 18.

A study must minimize risk to participants, and "when appropriate, [make] adequate provisions to protect the privacy of participants and to maintain the confidentiality of data."[113] IRB practices on this point vary widely, but an IRB should at least require an explanation in writing on how information directly identifying participants is coded or otherwise protected against disclosure.

Risks to Participants and Genetic Research: The Common Rule requires an informed consent document to discuss any reasonably foreseeable risks to participating in research.[114] If the biospecimens contributed to a research repository could be used for genetic research (which is likely), the informed consent document should expressly address the risks of accidental release of genetic information.

The passage of the Genetic Information Nondiscrimination Act of 2008 ("GINA")[115] has decreased the risks of genetic testing in research. GINA prohibits discrimination based on genetic information in health insurance and employment, but does not protect against discrimination in life insurance, disability insurance, or long-term care insurance. In addition, GINA does not apply to employers with fewer than 15 employees.[116] GINA protects "genetic information," which includes the information derived from an individual's genetic testing, but also protects information about an individual's family history ("the manifestation of a disease or disorder in family members"), genetic testing of an individual's family members, an individual's or his family members' request for or receipt of genetic services (testing, counseling or education) or participation in clinical research involving genetic services.[117] For additional details regarding the provisions of GINA see the NIH, National Human Genome Research Institute Web site,[118] OHRP guidance on GINA,[119] and the National Cancer Institute ("NCI") guidance on GINA. [120]

The NCI published a template informed consent document for research,[121] in which NCI suggests addressing privacy risks as follows: "The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small." However, the NCI language does not provide information about the potential

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[113] 45 C.F.R. §46.111(a)(1), (a)(7).
[114] 45 C.F.R. § 46.116(a)(2).
[115] Public Law 110-233 (110th Cong. 2008), 122 Stat. 881, c*odified at* 42 U.S.C. § 2000ff note; *see also* 45 C.F.R. § 160.103. For additional details regarding the provisions of GINA see http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf.
[116] *See* http://www.hhs.gov/ohrp/humanparticipants/guidance/gina.html#fn.
[117] 42 U.S.C. § 2000ff, *et al* DOL, FAQs of the Genetic Information Nondiscrimination Act, http://www.dol.gov/ebsa/faqs/faq-GINA.html.
[118] *See* The Genetic Information Nondiscrimination Act of 2008, Information for Researchers and Health Care Professionals (April 6, 2009), at http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf.
[119] *See* OHRP Guidance on the Genetic Information Nondiscrimination Act: Implications for Investigators and Institutional Review Boards (Mar. 24, 2009) at http://www.hhs.gov/ohrp/humansubjects/guidance/gina.pdf.
[120] *See* National Cancer Institute's, Best Practices for Biospecimen Resources (June 2007), http://biospecimens.cancer.gov/global/pdfs/NCI_Best_Practices_060507.pdf at 18.
[121] The NCI Cancer Diagnosis Program's model tissue consent form can be found at http://www.cancerdiagnosis.nci.nih.gov/specimens/model.pdf.

effect of the release of information, and thus does not do a good job in communicating the risk to individuals.

Moreover, in the OHRP guidance document entitled, "Guidance on the Genetic Information Nondiscrimination Act: Implications for Investigators and Institutional Review Boards,"[122] the OHRP noted the limitations of GINA, and urged Investigators and IRBs not to overstate the protections provided. OHRP suggested the following language for consideration by IRBs:

> A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
>
> - Health insurance companies and group health plans may not request your genetic information that we get from this research.
> - Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
> - Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.
>
> All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.
>
> Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

In addition, OHRP noted that, "for research that involves determining whether participants have an already manifest genetic disease or disorder, investigators and IRBs may wish to consider including additional language in the informed consent document indicating that GINA does not prohibit discrimination on the basis of an already manifest genetic disease or disorder."[123]

This language is quite detailed, and many organizations have chosen to include more limited information about GINA. Alternative language to consider:

> "The [entity] has extensive precautions in place to prevent any unauthorized disclosure of personally identifiable information. However, if there is an inadvertent or accidental disclosure of clinical data or data obtained from the study about you, this could have adverse effects on your insurability, employment or social standing. [If the study involves genetic information] It could also involve DNA typing, which may support paternity determinations and affect your

[122] http://www.hhs.gov/ohrp/humanparticipants/guidance/gina.html.
[123] *Id*.

family relationships. There may be unforeseeable risks that are not known at this time. However, you will be informed of any new risk as they become known."

Exculpatory Language: An informed consent forms may not include exculpatory language, which waives or appears to waive any of the subject's legal rights, or releases or appears to release the investigator, sponsor, institution or agents from liability for negligence.[124]

NPRM Proposed Changes: The OHRP proposes to streamline informed consents to require only the basic elements of informed consent to be in the main consent form; any additional information must be included in appendices.[125] The purpose of this proposed change is to emphasize in the main consent document essential information that a reasonable person would want to know to make an informed decision about participating in research. This would include HIPAA authorization requirements if there is not a separate HIPAA authorization form. Any "non-essential" information would be in an appendix. This is an effort to lead to substantially shorter consent forms highlighting the most important information in the body of the form. The proposal further emphasizes the need to use language understandable to the subject.[126]

One substantial change proposed is to require an informed consent document to tell a participant if identifiable private information collected about the participant will be de-identified, and then subsequently used for research.[127] The informed consent form must include a statement either that: (1) identifiers might be removed from the data and used for future research studies without additional informed consent, or (2) the participant's data will not be used for future research studies, even in non-identifiable form.[128] In addition, if the research involves biospecimens, the informed consent must include a statement that the biospecimens "may be used for commercial profit and whether the subject will or will not share in this commercial profit."[129] The new informed consent elements also would require, "as appropriate," telling a participant whether clinically relevant research results will be disclosed to the participants and under what circumstances, and to provide an option to be re-contacted for future research studies or to provide additional information or biospecimens.[130]

The proposed regulations also have a substantial new requirement to obtain "broad" consent for the storage, maintenance, and secondary research use of biospecimens or identifiable private information. This broad consent would not have to be specific to a particular research project, but would be required to include a host of elements: [131]

[124] 45 C.F.R. § 46.116.
[125] Proposed 45 C.F.R. § 46.116. See 80 Fed. Reg at 53970-71.
[126] *Id*.
[127] Id.
[128] Proposed 45 C.F.R. § 46.116(a)(9).
[129] Proposed 45 C.F.R. § 46.116(b)(7).
[130] Proposed 45 C.F.R. § 46.116(b)(8), (9).
[131] Proposed 45 C.F.R. § 46.116(c).

- A description of any reasonably foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject or to others that reasonably may be expected from the research;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
- A general description of the types of research that may be conducted with information and biospecimens and the information that is expected to be generated from the research, the types of information or biospecimens that might be used in research, and the types of institutions that might conduct research with the biospecimens or information;
- A description of the scope of the informed consent must be provided, including:
    - (A) a clear description of the types of biospecimens or information that were or will be collected and the period of time during which biospecimen or information collection will occur. This may include all biospecimens and information from the subject's medical record or other records existing at the institution at the time informed consent is sought; and
    - (B) for purposes of paragraph [(A) immediately above], the period of time during which biospecimen or information collection will occur cannot exceed 10 years from the date of consent. For research involving children as subjects, that time period cannot exceed 10 years after parental permission is obtained or until the child reaches the legal age for consent to the treatments or procedures involved in the research, whichever time period is shorter. The time limitations described do not apply to biospecimens or information that initially will be collected for research purposes.
- A description of the period of time during which an investigator can continue to conduct research using the subject's biospecimens and information described in paragraph [(A) above] (e.g., a certain number of years, or indefinitely);
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may withdraw consent, if feasible, for research use or distribution of the subject's information or biospecimens at any time without penalty or loss of benefits to which the subject is otherwise entitled, and information about whom to contact in order for the subject to withdraw consent. The statement must make clear that information or biospecimens that already have been distributed for research use may not be retrieved;
- If applicable, a statement notifying the subject or the representative that the subject or the representative will not be informed of the details of any specific research studies that might

be conducted, including the purposes of the research, that will use the subject's information and biospecimens;

- If applicable, a statement notifying the subject or the representative of the expectation that the subject's information and biospecimens are likely to be used by multiple investigators and institutions and shared broadly for many types of research studies in the future, and this information and the biospecimens might be identifiable when shared;
- The names of the institution or set of institutions at which the subject's biospecimens or information were or will be collected, to the extent possible (in recognition that institutions might change names or cease to exist);
- If relevant, an option for an adult subject or the representative to consent, or refuse to consent, to the inclusion of the subject's data, with removal of the identifiers listed in 45 CFR 164.514(b)(2)(i)(A) through (Q), in a database that is publicly and openly accessible to anyone. This option must be prominently noted, and must include a description of risks of public access to the data.
- If applicable, a statement that the subject's biospecimens may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- If applicable, a statement regarding whether clinical relevant research results, including individual research results, will be disclosed to subject, and if so, under what conditions; and
- If applicable, an option for the subject or the representative to consent, or refuse to consent, to investigator's re-contacting the subject to seek additional information or biospecimens or to discuss participation in another research study.

IRB review of a broad consent will be required unless the organization uses the OHRP template broad informed consent (which has not yet been published).[132]

The proposed regulations would require an informed consent form to be posted on the federal Web site within 60 days after the trial is closed to recruitment.[133]

C. Waiver of Informed Consent

The HIPAA Privacy Rule and Common Rule requirements are strikingly similar in this respect. In order for an IRB to waive informed consent under the Common Rule, the IRB must find that: (1) the research involves no more than minimal risk to the participants; (2) the waiver or alteration of consent will not adversely affect the rights and welfare of the participants; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the participants will be provided with additional pertinent information after participation. [134]

NPRM Proposed Changes: The NPRM proposes to permit IRBs to waive informed consent for secondary research involving biospecimens only in "rare circumstances." [135]

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[132] Proposed 45 C.F.R. § 46.116(d).
[133] Proposed 45 C.F.R. § 46.116(h)(2).
[134] 45 C.F.R. § 46.117(c)-(d); 45 C.F.R. §46.101(i) and 61 Federal Register 51531 (Oct. 2, 1996) (waiver of informed consent in emergency research).
[135] 80 Fed. Reg. at 53945.

Specifically, an IRB would be permitted to waive informed consent for the use of biospecimens if the IRB finds and documents the following items:

- The research involves no more than minimal risk to the subjects;
- The research could not practicably be carried out without the requested waiver or alteration;
- If the research involves accessing or using identifiable biospecimens or identifiable information, the research could not practicably be carried out without accessing or using identifiers;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation;
- There are compelling reasons for the research use of biospecimens; and
- The research could not be conducted with other biospecimens for which informed consent was or could be obtained. [136]

If an individual was asked to consent to the storage of biospecimens or identifiable private information and refused, an IRB would not subsequently be permitted to waive consent.[137]

D. Minor Assent and Need for Consent at Majority

Under HHS (and FDA definitions), a "legally authorized representative" ("LAR") who may consent to participate in research on behalf of an individual without capacity, is a person or judicial or other body authorized under applicable law to consent on behalf of the prospective participant to the *procedures* involved in the research.[138] If there are not state statutes or regulations expressly governing who may consent to research on behalf of an individual without capacity, organizations should look to their health care surrogacy or legal representative statutes or regulations to determine the appropriate LAR.

The Common Rule requires parental or guardian consent for minors to participate in research.[139] In instances where research involves no greater than minimal risk, or the research involves greater than minimal risk but presents a direct benefit to the child, consent of only one parent is required.[140] Other research requires consent of both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.[141] In instances where consent is not required (e.g. following an IRB waiver), parental or guardian consent is not necessary.[142]

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[136] Proposed 45 C.F.R. §46.116(f)(1)-(2)
[137] Proposed 45 C.F.R. §46.116(f)(3).
[138] 21 C.F.R. § 50.3(l); 45 C.F.R. §46.102(c) (defining legally authorized representative). *See also* 21 C.F.R. § 50.20; 45 C.F.R. §46.116 ("Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative."). Federal law defers to state law to determine who is a legally authorized representative.
[139] 45 C.F.R. § 46.408.
[140] *Id*.
[141] *Id*.
[142] HHS, Research with Children Frequently Asked Questions, http://www.hhs.gov/ohrp/policy/childrenfaqsmar2011.pdf.

The Common Rule requires that "adequate provisions are made" to solicit a minor child's "assent" to participate in research.[143] "Assent" means a child's affirmative agreement to participate in research; mere failure to object should not, absent affirmative agreement, be construed as assent.[144] The Common Rule allows IRB discretion in determining when assent is appropriate, and instructs IRBs to take into account ages, maturity, and psychological state of the children involved.[145]

The HHS Secretary's Advisory Committee on Human Research Protections ("SACHRP") addressed consent for minors in the use of biospecimens in its July 20, 2011 guidance entitled "*FAQs, Terms and Recommendations on Informed Consent and Research Use of Biospecimens*" (available at http://www.hhs.gov/ohrp/sachrp/commsec/attachmentdfaq%27stermsandrecommendations.pdf). In its FAQ #22, SACHRP addressed the following question:

> A 13-year-old child is enrolled by his/her parents in a tissue banking protocol that involves storage of specimens for future research. Is the child's assent required at the time of the original enrollment in the repository, in addition to parental permission?
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> Response–
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> HHS Common Rule Issues. Yes, if the IRB determines that the children are capable of providing assent, taking into account the ages, maturity and psychological state of the subjects [45 CFR 46.408(a) and 46.116]. Given that most projects that store tissues for future unspecified research are not likely to hold out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, it is anticipated that affirmative agreement on the part of the child would generally be required.
>
> HIPAA Issues. The HIPAA Privacy Rule does not require assent.
>
> FDA Issues. Tissue banking in and of itself does not constitute an FDA regulated clinical investigation, and the FDA regulations would not apply.

Federal regulators also have addressed the need to obtain consent from an individual at the age of majority. They concluded that the continued storage of identifiable specimens or data does not require consent at age of majority, but that use of the specimens or data is human subjects research that requires consent at the age of majority unless an IRB waives the requirement to obtain consent. OHRP addressed this issue in its FAQs related to research with children, at http://www.hhs.gov/ohrp/policy/faq/children-research/child-reaches-consent-during-study.html). When a child who is enrolled in a research study with parental permission reaches the legal age of consent, that research subject is no longer considered a child for purposes of 45 C.F.R. Part 46, Subpart D.[146] If the activity meets the regulatory definition of human subjects research by utilizing identifiable information,[147] the now-adult must consent to the ongoing research. In its guidance on biobanking, SACHRP explained:

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[143] 45 C.F.R. § 46.404.
[144] 45 C.F.R. § 46.402.
[145] 45 C.F.R. § 46.408.
[146] *See* 45 C.F.R. § 46.402(a) ("Children means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.").
[147] 45 C.F.R. 46.102(f).

A child is enrolled by his/her parents in a tissue banking protocol that involves storage of specimens for future research. Should there be a process in place for the child to give consent for continued storage and use of specimens when he/she reaches the age of majority?

Response–

HHS Common Rule Issues. In and of itself, the retention of specimens in a biobank is not considered to be research involving human subjects. However, ongoing use of such specimens (e.g., continued analysis of specimens or data for which the subject's identity is readily identifiable to the investigator(s)), or ongoing collection of identifiable information, is human subjects research. In these cases, it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects.

The IRB may consider, if appropriate, a waiver under 45 CFR 46.116(d) of the requirements for obtaining informed consent in order for the subjects to continue their participation in the research. Such a waiver may be considered at the time of initial review or during a subsequent amendment. Factors that may make it impracticable to conduct the research, and therefore would support a waiver, include the number of subjects, length of time since first enrolled, and ability to locate subjects (see also FAQ #5).

HIPAA Issues. A valid HIPAA authorization signed by a parent, as the personal representative of a minor child at the time the authorization is signed, remains valid until it expires or is revoked, even if such time extends beyond the child's age of majority. However, if the authorization expires on the date the minor reaches the age of majority, a new authorization would be required at that time for continued use or disclosure of protected health information. Absent obtaining a new authorization, a covered entity may only continue to use and disclose for research purposes if 1) an IRB or privacy board has waived the requirement for an authorization, or 2) if the use or disclosure is of a limited data set after the signing of a data use agreement that complies with the requirements in 45 CFR 164.514(e)(4), or if 3) information has been de-identified in a manner that complies with 45 CFR 164.514(b) so that the HIPAA Privacy Rule would not govern.

FDA Issues. Tissue banking in and of itself does not constitute an FDA regulated clinical investigation, and the FDA regulations would not apply.

On the other hand, the National Cancer Institute in its *Best Practices for Biospecimen Resources* from 2011 (available at http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf) recommends that an entity storing identifiable biospecimens or identifiable data from children for future research should consider the need for obtaining informed consent for that storage when the child reaches the age of majority. Its recommended operational best practices include:

- Consulting with the IRB during the planning and development of the biorepository to determine whether future research uses of stored biospecimens are likely to constitute no more than minimal risk. If future uses of identifiable stored biospecimens are likely to constitute greater than minimal risk, developing procedures for re-contacting the child participants to obtain consent when they reach the age of majority. This includes

ensuring that accurate contact information is maintained so that re-contact can be made. Where practicable, the now-adult participants should be re-contacted for consent by an individual or institution with which they have an ongoing relationship.

- Drafting permission and/or assent documents to state whether re-contact and consent will be attempted once the child reaches the age of majority.
- Considering community engagement when planning a biorepository, if appropriate. Community engagement may range from public forums to inclusion of patient advocates of community representatives on access or governance committees. As part of biobanking planning activities, input from the affected community may be sought in regard to the perceived risk-benefit ratio of the proposed research and whether a waiver of consent or consent at age of majority would be preferable. Community engagement may be unnecessary or inappropriate in some cases, such as for the use of archived biospecimens or for minimal-risk research.[148]

The NIH Best Practices is not binding. As another best practices resource for research repositories, organizations may want to examine the Children's Hospital of Philadelphia ("CHOP") policy on "*Creating a Registry-Repository*" (available at https://irb.research.chop.edu/sites/default/files/documents/creating_a_registry-repository.pdf). When a CHOP registry participant turn 18 years of age, CHOP will consent the patient or destroy the link between individually identifiable data and the research database.

In summary, mere retention of the data and biospecimens in the "research repository" does not require consent by patients who turn 18 years old. However, subsequent use of *identifiable* data or biospecimens after the patient turns 18 years old will require consent from the patient (or waiver of consent by the IRB), if the use of the data or biospecimens is subject to the Common Rule (or subject to the FDA regulations). A new HIPAA authorization is not required at age of majority. Use of de-identified or coded information or specimens is not human subjects research, and will not require consent of the patients who turned 18 years old.

E. New Safeguards for the Protection of Biospecimens and Identifiable Information: NPRM Proposed Changes

The OHRP proposes to adopt safeguards for the protection of the security and integrity of identifiable information and biospecimens, and to prevent the intentional or unintentional use, release or disclosure of identifiable information or biospecimens in violation of the rules.[149] These rules would apply both to exempt and non-exempt research (but will not apply to excluded research). The OHRP proposes to establish a list of specific measures that would function as a safe harbor.[150] Institutions or investigators will have the option of applying the safe harbor measures, or can choose to meet the requirements of the HIPAA Security Rule.

Further, the proposed rule would prevent the use or disclosure of biospecimens or identifiable information only for public health purposes, for any lawful purpose with the consent for the subject, for research regulated by the Common Rule, or for other research purposes if the

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[148] NCI Best Practices, Section C.2.5 Considerations for Use of Pediatric Biospecimens at pages 40-41.

[149] Proposed 45 C.F.R. § 46.105(a).
[150] Proposed 45 C.F.R. § 46.105(b).

adequate assurance are obtained from the recipient that: (1) recipient will adopt the safe harbor safeguards, (2) that IRB approval has been obtained (unless the research is exempt or excluded), and (3) the recipient will not further release the biospecimens or identifiable information (unless otherwise permitted by this rule).[151]

III. FDA Compliance

A. Application of the FDA Regulations

Under the FDA regulations, biospecimen research used to support an application to market a drug or device requires informed consent, whether or not the biospecimen is identifiable, because the FDA definition of "human subject" includes "human specimens."[152]

B. Informed Consent and Waiver of Informed Consent

The FDA regulations do not permit an IRB to waive informed consent unless the clinical trial involves emergency or military research.[153] So, unlike the OHRP regulations discussed above, FDA regulations do not contain exceptions to informed consent when the specimens used are not identifiable or where they are "leftovers" from clinical care.

In April 2006, however, the FDA issued guidance that permits the use of non-identifiable human specimens for in vitro diagnostic (IVD) studies in certain circumstances.[154] Specifically, the FDA will exercise enforcement discretion (i.e., the FDA will not enforce its informed consent regulations) when all of the following elements are met:

(1) The investigation meets the investigational device exemption criteria at 21 C.F.R. § 812.2(c)(3);

(2) The study uses leftover specimens collected for routine clinical care or analysis that would have been discarded, or the study uses specimens from repositories;

(3) The specimens are not individually identifiable to the investigator or any other individuals associated with the investigation, including the sponsor. If the specimen is coded, it will not be considered individually identifiable if no one associated with the investigation can link the specimen to the individual. The specimens may be accompanied by clinical information as long as it does not make the specimen identifiable to the individuals associated with the investigation;

(4) The individuals caring for the patients are different from and do not share information about the patient with individuals associated with the investigation. The test results cannot be reported to the participant or the participant's health care providers;

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[151] Proposed 45 C.F.R. § 46.105(c).
[152] 21 C.F.R. § 812.3(p).
[153] 21 C.F.R. § 50.23 and § 50.24.
[154] See 71 Fed. Reg. at 23924 (April 25, 2006).
[20] 45 C.F.R. § 46.101(b).

(5) The supplier of the specimens has established policies and procedures to prevent the release of personal information about the patients; and

(6) The study has been reviewed by an IRB in accordance with FDA guidelines.

C. FDA Electronic Informed Consent Draft Guidance

In March 2015, the FDA released industry guidance on the use of electronic informed consent in clinical investigations.[155] Although this guidance is not legally enforceable, it reflects the FDA's current thinking on the topic in anticipation of the publication of enforceable rules following public comment.

Electronic informed consent refers to using electronic systems and processes that employ electronic media (such as podcasts, interactive Web sites, biological recognition devices, and card readers) to convey information related to the study and to obtain and document informed consent.[156] The FDA provides a host of recommendations regarding the presentation of an electronic informed consent form. An electronic informed consent should be presented in language understandable to the subject, and should be easy to navigate (while taking account of individuals with poor eye sight or others who may have difficulty navigating through the program).

The consent process may take place remotely or at the study site. If the consent takes place on site, study personnel may personally verify the subject's identity, answer questions, and witness the signing of the electronic informed consent. If any or all processes take place off site, all responses, witness, or other involved parties should be documented electronically to ensure that responses cannot be altered. Additionally, if study personnel do not personally witness the subject signing the document, the system should include a method to ensure that the person signing the electronic informed consent is in fact the subject. In any event, the subject should have an opportunity to ask questions and receive answers prior to signing the electronic informed consent (either in person or through media including electronic messaging, telephone class, videoconferencing, or live chat).

When written informed consent is required, the use of FDA-compliant digital signatures is permitted. Although the FDA does not mandate a specific method of electronic signature, it suggests that IRBs should consider how to determine the legitimacy of the signature, and if the consent document can be produced in hard copy upon the subject's request.

FDA regulations require that the person signing the electronic informed consent receive a copy of the consent form. Although FDA does not require the subject's copy to include a signature, it recommends that a copy of the signed consent form include the signature and the date on which the form was signed. A copy of the informed consent document could be in paper form, or an e-copy that can be transmitted via electronic media. The copy should include a transcript of any audiovisual presentations of the electronic informed consent. Subjects should be informed of the risks of storing an e-copy of the informed consent document on a personal electronic device.

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[155] FDA, Use of Electronic Informed Consent in Clinical Investigations, March 2015, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf.
[156] *Id*.

The computerized system that supports the electronic informed consent should be secure, and contain safeguards protecting subject's identity, study participation, and personal information. HIPAA requirements may apply to HIPAA covered entities and business associates. The FDA also recommends that the system have a method for archiving documents, and that the system has audit trail capability to obtain revisions to the electronic informed consent, the identity of the person making the changes, the reasons for the change, and the date of their occurrence.

IV. National Institutes of Health Genomic Data Sharing Policy

The National Institutes of Health Genomic Data Sharing Policy (the "GDS Policy") requires informed consent for use of de-identified biospecimens for certain genetic research. The policy applies to all "NIH-funded research that generates large-scale human or non-human genomic data as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies, single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, metagenomic, epigenomic, and gene expression data."[157]

The GDS Policy applies to: (1) competing grant applications that are submitted to NIH on or after January 25, 2015; (2) proposals for contracts that are submitted to NIH on or after January 25, 2015; and (3) NIH intramural research projects generating genomic data on or after January 25, 2015. Although the GDS Policy does not apply to research submitted prior to the Policy's effective date, NIH strongly encourages investigators to comply with the expectations outlined in the Policy. Investigators should provide an updated genomic data-sharing plan to the funding NIH Institute or Centers ("IC") in the submission of the research performance progress report.

For studies involving human participants that were initiated before the Policy's effective date and which used consents that do not meet the expectations of the GDS Policy, investigators are expected to plan to transition to a consent for future research uses and broad sharing, if possible, particularly for new or additional collections of specimens. There will be reasonable accommodation, determined on a case-by-case basis by the funding IC, for long-term projects ongoing at the time of the Policy's effective date to come into alignment with NIH's expectations for consent and data sharing. The goal is to bring these projects into alignment, to the extent possible, in a reasonable timeframe.[158]

[157] *See* http://gds.nih.gov/PDF/NIH_GDS_Policy.pdf, published Aug. 28, 2014.
[158] http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-111.html

V. Putting It All Together: A Checklist for Biorepository Consents

The federal laws discussed above all have different requirements for consent to collect, store and use biospecimens for research. Rather than tracking what federal (or state) laws apply to what research, many organizations choose to incorporate required elements into an informed consent document that comply with all of these laws. The following checklist may be a helpful tool for organizations taking this approach. Biorepository consents should include:

- ✓ A statement that the study involves research, an explanation of the purposes of the research and the expected duration of participation:
    - Most biorepository consent forms will describe why biospecimens and associated clinical data are important for research. Present federal law does not require the specific types of research to be listed, although some organizations take the approach of listing various type of research that may be conducted, along with "catch all" language to ensure that the list does not preclude other research in the future.
    - Many biospecimen repositories intend to maintain biospecimens and associated clinical data into the future without a defined time limit, and some will continue to collect clinical data into the future to ensure richly annotated biospecimens. There is nothing in present federal law that requires a time limit for collection or retention. (Note regarding the NPRM: OHRP proposes to limit biospecimen or information collection to 10 years from the date of consent (or until the age of majority for children) The NPRM does not have a proposed time limit for retention of specimens collected during this 10-year period.)

- ✓ A description of any reasonably foreseeable risks: An informed consent document should discuss potential risks to participants if identifiable information is inadvertently released. In addition, because almost all research will utilize biospecimens for some type of genetic research, best practices include a description of potential risks related to inadvertent release of genetic information. See GINA discussion above.
    - For research involving more than minimal risk, the Common Rule requires an explanation of compensation and medical treatments available. If the consent is limited to the biorepository, this element would not be applicable.

- ✓ A statement describing confidentiality protections: The Common Rule requires an informed consent document to discuss how the participant's identifiers will be treated confidentially in the study, but does not have specific requirements. The HIPAA Privacy Rule has a host of specific requirements:
    - A specific and meaningful description of the PHI to be used or disclosed in the research (such as the participant's medical records or other more limited portions of the record, such as laboratory results);
    - The name or specific identification of the persons or class of persons authorized to make the disclosure (such as the participant's physicians and treating hospitals);
    - The name or specific identification of the persons or class of persons who will have access to the PHI (such as the research site, principal investigator, IRB, sponsor,

other third parties involved in the research, data safety monitoring board, FDA, and HHS);
    - Many informed consent documents will contain detail related to whether directly identifiable information or PHI will be available to the biorepository personnel, and if so, how that directly identifiable information will be protected against disclosure. For example, the consent should explain the mechanism for coding or linking the participants' biospecimens to their identifiable medical records or other clinical data.
  - A description of the specific research protocol or study (which for a biorepository is the protocol for how the biospecimens are collected, maintained and distributed);
  - An expiration date or event (such as the end of the study), or a statement that the authorization has no expiration;
  - A statement of the participant's right to revoke the authorization in writing and a description of how to do so;
  - A statement that the participant may not revoke the authorization as to information already disclosed for the research where the information is necessary to maintain the integrity of the study data, or a description of other exceptions where the participant may not revoke the authorization;
  - A statement that the entity disclosing the PHI may not condition treatment, payment, enrollment or eligibility for benefits on the participant signing the authorization.
    - If the individual will not be allowed to participate in the clinical trial without signing the authorization, the authorization must include a statement to that effect;
  - A statement that the information disclosed for the research may be participant to redisclosure by the recipient and no longer be protected by the federal privacy rule (if that is accurate);
  - If the participant will not be given access to medical records during the study, a statement that the participant agrees to the denial of access when consenting to participate in the study, and that the right of access to the records will be reinstated upon completion of the study (although that generally will not be applicable in a biorepository protocol).

- ✓ A description of any benefits to the subject or to others, which may reasonably be expected: Generally, participation in a biorepository is not expected to generate benefit for the individual contributing the biospecimen.

- ✓ Disclosure of appropriate alternative procedures or courses of treatment that may be advantageous to the subject: This element is not applicable to a biorepository consent.

- ✓ Additional costs to the subject that may result from participation (if applicable).

- ✓ Circumstances under which the subject's participation may be terminated without the subject's consent (if applicable): This generally is not applicable to consent to participate in a biorepository.

- ✓ A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
    - Generally, a biorepository consent will inform an individual that a participant can instruct the biorepository to remove the individual's biospecimens and any associated data from the repository, but that the repository cannot retrieve biospecimens or clinical data already distributed to researchers.

- ✓ An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

- ✓ A statement that significant new findings which may relate to the subject's willingness to continue participation will be provided to the subject.

- ✓ The approximate number of subjects involved in the study.

- ✓ An informed consent forms may not include exculpatory language, which waives or appears to waive any of the subject's legal rights, or releases or appears to release the investigator, sponsor, institution or agents from liability for negligence.

- ✓ The participant's signature and the date of signature.

- ✓ If the authorization is executed by a personal representative of the participant (the participant's health care decision maker), a description of that person's authority to act for the participant.

If the NPRM is finalized as proposed, a biorepository consent would require slightly different elements:

- ✓ A description of any reasonably foreseeable risks or discomforts to the subject;

- ✓ A description of any benefits to the subject or to others that reasonably may be expected from the research;

- ✓ A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

- ✓ An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;

- ✓ A general description of the types of research that may be conducted with information and biospecimens and the information that is expected to be generated from the research, the types of information or biospecimens that might be used in research, and the types of institutions that might conduct research with the biospecimens or information;

- ✓ A description of the scope of the informed consent must be provided, including:
    - (A) a clear description of the types of biospecimens or information that were or will be collected and the period of time during which biospecimen or information collection will occur. This may include all biospecimens and information from the subject's medical record or other records existing at the institution at the time informed consent is sought; and
    - (B) for purposes of paragraph [(A) immediately above], the period of time during which biospecimen or information collection will occur cannot exceed 10 years from the date of consent. For research involving children as subjects, that time period cannot exceed 10 years after parental permission is obtained or until the child reaches the legal age for consent to the treatments or procedures involved in the research, whichever time period is shorter. The time limitations described do not apply to biospecimens or information that initially will be collected for research purposes;
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- ✓ A description of the period of time during which an investigator can continue to conduct research using the subject's biospecimens and information described in paragraph [(A) above] (e.g., a certain number of years, or indefinitely);

- ✓ A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may withdraw consent, if feasible, for research use or distribution of the subject's information or biospecimens at any time without penalty or loss of benefits to which the subject is otherwise entitled, and information about whom to contact in order for the subject to withdraw consent. The statement must make clear that information or biospecimens that already have been distributed for research use may not be retrieved;

- ✓ If applicable, a statement notifying the subject or the representative that the subject or the representative will not be informed of the details of any specific research studies that might be conducted, including the purposes of the research, that will use the subject's information and biospecimens;

- ✓ If applicable, a statement notifying the subject or the representative of the expectation that the subject's information and biospecimens are likely to be used by multiple investigators and institutions and shared broadly for many types of research studies in the future, and this information and the biospecimens might be identifiable when shared;

- ✓ The names of the institution or set of institutions at which the subject's biospecimens or information were or will be collected, to the extent possible (in recognition that institutions might change names or cease to exist);

- ✓ If relevant, an option for an adult subject or the representative to consent, or refuse to consent, to the inclusion of the subject's data, with removal of the identifiers listed in 45

CFR 164.514(b)(2)(i)(A) through (Q), in a database that is publicly and openly accessible to anyone. This option must be prominently noted, and must include a description of risks of public access to the data.

- ✓ If applicable, a statement that the subject's biospecimens may be used for commercial profit and whether the subject will or will not share in this commercial profit;

- ✓ If applicable, a statement regarding whether clinical relevant research results, including individual research results, will be disclosed to subject, and if so, under what conditions; and

- ✓ If applicable, an option for the subject or the representative to consent, or refuse to consent, to investigator's re-contacting the subject to seek additional information or biospecimens or to discuss participation in another research study.

In a separate document, we will provide a template ICF incorporates the elements of the current federal regulatory requirements, and notes where the content would need to be modified to comply with the NPRM if finalized as proposed.

Of course, we must include the caveat that this document is not intended to be legal advice or take the place of legal advice. Please consult your legal counsel for questions concerning your particular circumstances.

KBR