

# THE UNEXPECTED COST OF COMPLIANCE FOR INSTITUTIONS UNDER THE NPRM REVISIONS TO THE COMMON RULE

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## I. Introduction

While the research environment has been rapidly changing over the past twenty years, the laws and regulations governing research have failed to keep pace with these developments. The accelerated growth in technology, as well as the number and diversity of clinical trials performed in a variety of settings, has resulted in an ever-increasing amount of data generated and processed with relative ease. This amount and diversity of data was likely unimaginable decades ago when the National Research Act was signed into law on July 12, 1974. As such, many within the research community have advocated for changes to these laws and regulations in order to facilitate valuable research with less burden, delay and ambiguity, while also ensuring that the rights of human subjects are protected.

The National Research Act established a regulatory system for experimenting on human subjects in the United States, and created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("Commission"). In 1979, this Commission produced the Belmont Report, which outlines the basic ethical principles in research involving human subjects.<sup>1</sup> The Belmont Report served as foundational background when the Department of Health and Human Services ("HHS") and the Food and Drug Administration revised their existing human subjects' regulations in the early 1980s.<sup>2</sup> Over that decade, HHS led a process that resulted in fifteen U.S. departments and agencies codifying the published Common Rule in separate regulations.<sup>3</sup> The initial purpose of the Common Rule was "to promote uniformity, understanding, and compliance with human subject protections as well as to create a uniform body of regulations across Federal departments and agencies."<sup>4</sup>

For the first time in several decades, HHS, through the Office for Human Research and Protection ("OHRP") has proposed several significant changes to the Common Rule. On July 26, 2011, the Office of the Secretary of HHS, in coordination with the Executive Office of the President's Office of Science and Technology Policy ("OTSP"), published an advanced notice of public rulemaking ("ANPRM") to gather comments on how to balance the protection of human subjects with efforts to reduce the burden and delay, and thus facilitate, important research.<sup>5</sup> After taking such comments into consideration, an updated Notice of Proposed Rulemaking ("NPRM") was issued on September 8, 2015, by sixteen federal departments and agencies,<sup>6</sup> soliciting comments on the revised ANPRM proposals that were updated as a result of recommendations from a variety of public, stakeholder, and expert sources.

The goals of the NPRM are to "increase human subjects' ability and opportunity to make informed decisions . . . and facilitate current and evolving types of research that offer promising approaches to treating and preventing medical and societal problems through reduced ambiguity in interpretation of the regulations, increased efficiencies in the performance of the review system, and reduced burdens on researchers that do not appear to provide commensurate protections to human subjects."<sup>7</sup> While the NPRM only directly applies to research conducted at a U.S. institution that receives federal research funding,<sup>8</sup> the proposals will likely impact industry-sponsored research as well.

Although eight major changes to the Common Rule have been proposed in the NPRM, this analysis will focus on the two issues that will likely pose the largest compliance costs to institutions: (i) expanding the definition of "human subject" to include biospecimens, and (ii) mandating that all U.S.-based institutions engaged in cooperative, multi-site research studies use a single, centralized IRB for review.

## **II. Biospecimens**

With goals of "increasing transparency in when and how biospecimens collected in a variety of circumstances will be used for research purposes and increasing opportunities for consent," the NPRM alters the definition of "human subject,"<sup>9</sup> and thus requires that individuals provide consent for use of identified and deidentified biospecimens in secondary and future research.<sup>10</sup> These biospecimens could include specimens that were originally collected from either research or non-research settings (e.g., leftover newborn blood from the newborn blood screen program or leftover tissue from a clinical biopsy).<sup>11</sup> Currently, if the purpose of the patient interaction is to collect the biospecimen for research, this would be considered a primary research activity and, thus, is already covered under the current regulations.<sup>12</sup>

The NPRM claims that there is "a growing recognition that many people want to have some degree of control over the circumstances in which an investigator can derive information about them . . . " but also recognizes that "maximizing the societal value of research would mean reducing barriers to the secondary use of biospecimens to the extent possible."<sup>13</sup> Attempting to give patients an increased level of control over the biospecimens could be overly burdensome and could create barriers to using these biospecimens in later research studies. Thus, there is a need to properly balance the autonomy of the patient and the facilitation of valuable research,

taking into consideration that the purpose of scientific research is to advance scientific knowledge for society's gain, not just for individual gain. The NPRM acknowledges that under the new regulations, the idea that if significant weight is not given to the autonomy interest of a patient in allowing his or her biospecimen to be used for secondary research, the result could be diminishing public support for research, which could "ultimately jeopardize our ability to be able to conduct the appropriate amount of future research with biospecimens."<sup>14</sup>

*a. Potential Impacts of Expanding the Definition of "Human Subject"*

The NPRM proposes to "require informed consent for research involving biospecimens in all but a limited number of circumstances," but this potentially creates a number of burdens. Expanding the definition of "human subject" to include biospecimens "regardless of identifiability" is expected to greatly increase costs to institutions. The institutions will now need to implement tracking systems to monitor which biospecimens may be used in secondary research. The Regulatory Impact Analysis ("RIA") estimates that the new tracking requirements will result in 80% of the 8,035 institutions with Federal-wide Assurances to incur additional costs to develop or modify their existing tracking systems to handle thousands of consent documents per year and mark which biospecimens had been consented for use and which have not. Additionally, institutions will also need to train personnel to ensure that they are able to appropriately inform patients of the secondary/future research that might be conducted using their biospecimens.

Currently, an estimated 250,000 studies use biospecimens each year that are not subject to oversight by either the Common Rule or FDA regulations because the biospecimens have been de-identified.<sup>15</sup> Additionally, approximately 30 million individuals' biospecimens are collected each year, with 70 percent being collected for clinical purposes and 30 percent being collected for research purposes. Investigators would now be responsible for seeking consent to secondary use of biospecimens or a waiver of consent for 9 million individuals annually, and an employee of the institution or organization collecting the sample for clinical purposes will now be responsible for seeking consent and tracking information for 21 million individuals annually.<sup>16</sup>

While the RIA estimates that this will take an additional 5-10 minutes of the investigators' or employees' time, that estimate does not appear to contemplate training of the employees in the risks and benefits of the secondary research, storage, maintenance, and security of biospecimens, not to mention the extra time required to answer the individual's questions.<sup>17</sup> While many employees of institutions may receive proper training to be able to obtain a broad form of informed consent, personnel of smaller organizations or volunteers who may be interacting with patients before collecting samples (at a blood drive, etc.) may not. The RIA predicts that it will cost the regulated community \$101 million to determine that certain secondary research studies are exempt in accordance with § 104(c), \$12,245 million to obtain consent to secondary use of biospecimens and identifiable private information, and \$457 million for the privacy safeguards for biospecimens and identifiable private information.<sup>18</sup>

The NPRM proposed several options to reduce some of these burdens in response to comments received in the 2011 ANPRM.<sup>19</sup> The new expanded definition of "human subject" will

only apply prospectively, and compliance with the updated definition will be delayed until three years after publication of a final rule.<sup>20</sup> Additional proposals include allowing investigators and institutions to obtain broad consent for secondary and future use of biospecimens using a template provided by HHS. Once an individual gives broad consent to the future use of his or her biospecimens, that consent may cover any biospecimen collected from that person over a 10-year period, at which point the individual must be re-consented for continued use. Also, IRBs may continue to waive the requirement for consent; however, in continuing to tip the scale in favor of patient autonomy and respect for persons, the NPRM adds additional, more stringent waiver conditions to be applied to biospecimens research<sup>21</sup> and makes clear that "the circumstances in which a waiver could be granted by an IRB should be extremely rare."<sup>22</sup>

Importantly, including biospecimens in the definition of human subjects could lead to a new security risk in storing the incredibly large amount of data from the broad consents. Requirements for tracking and verifying consent for each biospecimen will link the database tracking individual consent to the database tracking biospecimens. This is because there will be a need to verify that valid consent was properly obtained, has not expired at the time of collection, and was broad enough to allow for a specific use of a sample. This may encourage investigators or institutions to link individual and biospecimen identifiers in the same database to avoid potential barriers of secondary or future research.

While seeking to engage patients more in the decisions regarding the future uses of their biospecimens, requiring institutions to obtain consent from each patient and to track the storage, maintenance, and future uses of biospecimens may ultimately result in imbalanced research. As a result, smaller facilities in low income or underrepresented minority areas may be unable to (i) provide the infrastructure to obtain informed consent from each patient for secondary and future research uses each time a biospecimen is collected, (ii) store and track the consents and biospecimens, and (iii) provide the security level required for the amount of data now housed by the institutions. These smaller facilities would thus be unable to participate in secondary research with biospecimens, which would limit patient selection and the ability to contribute to future research. This, in turn, is contrary to the ethical principle of justice found in the Belmont Report.<sup>23</sup> Under the Belmont Report, "[a]n injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly."<sup>24</sup> Ultimately, this could mean that biobanks may represent a more homogenous population, as individuals from certain geographic regions, socioeconomic status, or underserved populations are excluded from the pool of biospecimens used for research. Research findings may thus not be applicable across a broader population and may not be appropriate to use to assess and improve health disparities and inequities.

To potentially address some of these concerns, two alternative proposals for limiting the expansion of the definition of "human subject" were offered in the NPRM.<sup>25</sup> Each alternative limits the expansion of the definition: Alternative Proposal A would expand the definition of "Human Subject" to include whole genome sequencing, and Alternative Proposal B would expand the definition to include certain biospecimens used in technologies that generate information unique to an individual.<sup>26</sup> Although each alternative proposal would limit the instances that require informed consent, this lightened burden of obtaining consent may be

replaced with increased burdens in other areas. For instance, the alternative definitions may lead to (i) confusion regarding which biospecimens and technologies are covered under the definition; (ii) downstream requirements that would necessitate substantial resources and information technology infrastructure that is not yet widely available; and (iii) continual monitoring and evaluation of new technologies and the nature and amount of information produced by such technologies by HHS or another organization, which could add additional uncertainty to the definition and could delay research progress.

#### *b. Broad Consent*

The NPRM references several studies dealing with patient privacy preferences.<sup>27</sup> All of these studies support the idea that patients are concerned about the protection of privacy in research studies, but offer differing insights as to how to best address this concern. These studies also indicated that when patients receive assurances that their privacy will be protected in the best possible manner, the participant's acceptance of consent for broad research uses of their biospecimens and data increases. Based upon its findings, one study recommends that potential research participants should be provided with "transparent, forthright explanations of the privacy risks that they may face," and details about what data will be collected and may be shared.<sup>28</sup> Ultimately, the study posits, this may satisfy the desire of research participants to know what risks, and may establish trust, based on an honest assessment of risks and protections, between researchers and those research participants who choose to continue."<sup>29</sup>

The expanded definition of "human subject" to include biospecimens aims to address the issues raised in the studies cited in the NPRM, as investigators and institutions will now be required to obtain consent from patients and other individuals to use their biospecimens for secondary and future research. As mentioned above, one concession offered under the NPRM to ease the burden caused by the expanded definition is allowing the use of broad consent for secondary and future use of biospecimens. Such broad consent would need to provide sufficient information to the patient to provide informed consent for a variety of secondary and future research, including a general description of the types of research that may be conducted, the types of biospecimens that might be used, and the types of institutions that might conduct research with the biospecimens. A broad consent form could be completed any time biospecimens are collected and could cover storage or maintenance of the biospecimens and future unspecified uses.

Currently, HHS is working on a template that may be used as a form for individuals to provide broad consent. An added benefit of using this template is that if the investigator does not anticipate returning individual research results to subjects, the research study could be considered to satisfy the requirements of one of the new exemption categories proposed under the NPRM (\_\_\_\_.104(f)(2)).<sup>30</sup> If the secondary research study does not meet the requirements of this exemption category, the investigator would need to seek IRB review of the study and obtain study-specific consent or a waiver of informed consent.<sup>31</sup> It should also be noted that the broad consent may be combined with a study-specific consent, as long as the patient is able to make the two decisions separately.

The NPRM does not contain a definition of "broad," and, at this point, HHS has not issued the template for broad consent to clarify what is intended of this proposed consent process; however, the NPRM did outline elements of this broad consent. In addition to the eight elements outlined in the current rule,<sup>32</sup> three new elements are proposed, including:

- (i) requiring that prospective participants be informed that their biospecimens may be used for commercial profit and whether the participant will share in the profits;
- (ii) requiring that prospective participants be informed of whether clinically relevant research results, including individual results, will be disclosed; and
- (iii) requiring that participants (or their legally authorized representatives) consent to being contacted for additional information or biospecimens.<sup>33</sup>

Concerns abound in the comments to the NPRM that this form of broad consent may not actually be "meaningful." However, a 2011 study determined that broad consent can be informed consent based on the idea that the participant is consenting not to each specific future use of his or her sample, but rather giving permission for someone else to decide how to use that sample.<sup>34</sup> This result has been further supported by additional studies. A 2010 study of consent preferences of a random sample of blood donors found that 85.9% of the donors accepted surrogate decision-making by a regional research ethics committee.<sup>35</sup> Further, a 2009 empirical study of public trust in research done by academic biobanks demonstrated that members of the general public found academic biobank researchers and their institutions to be highly trustworthy and do not see the need for recurrent, project-specific consent.<sup>36</sup> This is consistent with the findings of other studies, showing that the majority of tissue donors were "happy to give open-ended consent to future research (or, at least, to give open-ended consent for a specified period of time) or for a broad area of research, such as cancer research."<sup>37</sup>

Although broad consent may not be considered by some to be as beneficial as study-specific informed consent, it may still serve an important purpose. Under the Belmont Report, the idea of "beneficence" requires that "[p]ersons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being."<sup>38</sup> Further, one general rule of beneficence is to "maximize possible benefits and minimize possible harms," both in individual research investigations and in longer term research goals where the research community and "members of the larger society are obliged to recognize the longer-term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures."<sup>39</sup> Broad consent may serve to strike a balance between these ideas: respecting the decisions of individuals, while recognizing the larger, longer-term benefits of important research. Overall, the conversation necessary to make this broad delegation of decision-making in an informed manner will likely require different elements and considerations than a study-specific consent, and although the information may be of a different variety, the decision may be informed and autonomous.

Additionally, the information presented in these studies may be useful in developing an informed and meaningful broad consent form. One study suggested that potential research participants should be told about: "the different levels of deidentification of data that are possible, the fact that studies including DNA may not be completely deidentifiable, explicit details of the protections offered by the study protocol, and the privacy risks that remain. In addition to providing research participants with transparent, forthright explanations of the privacy risks that they may face, consent documents should detail what data could be gathered through study protocols, with whom the data could be shared, how the data might be analyzed, and what formats the data are likely to be published in."<sup>40</sup> Additional studies have suggested that an informed opt-out format was slightly preferred among research participants already seeking clinical treatment for an illness,<sup>41</sup> but that a random selection of healthy individuals from one geographical region supported the idea of an opt-in consent approach and preferred broad consent over either categorical or study-specific consent.

However, broadly informing people of the risks that could potentially happen in a possible future study may not provide enough specific information to allow people to make an informed decision and may actually result in people not providing consent for research, thus, creating a barrier to quality research. But when 264 cancer patients were asked their preferences about consent procedures, 99% of patients consented to research with their residual tissue, with a majority of those patients expressing appreciation at being informed about research with their remaining tissue.<sup>42</sup> This study, which compared patient preferences of various consent procedures, indicated that patients preferred a method of consent whereby they were provided with several pages of information in a leaflet and could then choose to opt-out of having their residual tissue involved in future research.<sup>43</sup> Fewer demands were placed on administrative resources under this method, as responses were more readily provided for the opt-out procedure than for opting-in. Additionally, the practitioners were able to address the information needs of patients using both procedures – by providing a leaflet with information along with a brief conversation with their practitioner.<sup>44</sup> Overall, the study found that the patients felt respected and valued by being informed (actually giving consent was of secondary importance), and no negative effect of the interventions (such as patients withholding consent) was observed.<sup>45</sup>

To achieve one of the overall goals of the revised regulations (i.e., promoting patient autonomy and increasing respect for persons), in addition to requiring broad consent, HHS or another organization could consider doing a broad education campaign about the benefits of participating in research and the use of biospecimens for secondary and future research. A campaign of this sort could help people understand biospecimens, deidentification, biobanks, and general uses of secondary and future research, and aid people in becoming more comfortable with their biospecimens being used in this way. This could ultimately decrease the burden on the investigators and institutions to provide an extensive amount of information to their patients, and perhaps could further encourage the adoption of the less administratively burdensome opt-out approach.

### III. Proposed Single-IRB Mandate for Cooperative Research

In an effort to promote efficiency in IRB operations, the NPRM also proposes a new requirement that all U.S.-based institutions engaging in cooperative, multi-site research studies use a single, centralized IRB for reviewing the study.<sup>46</sup> This is not a novel idea, as over the past decade the Food and Drug Administration ("FDA"), the Office of Human Research Protections ("OHRP"), and the National Institutes of Health ("NIH") have all issued guidance,<sup>47</sup> notices of proposed rule making,<sup>48</sup> and draft policies<sup>49</sup> proposing the use of a single IRB for multi-site clinical trials. Additionally, institutions may currently choose to have cooperative research studies reviewed by an external, unaffiliated IRB at the institution's discretion.<sup>50</sup> Most institutions, however, have been hesitant to replace the review by their local IRBs with review by an external IRB, since OHRP enforces compliance with the Common Rule through the institution that holds the Federal-wide Assurance, even where the violation of the Common Rule is caused by the actions of the external IRB.<sup>51</sup> Recognizing that these liability concerns would create an obstacle to having institutions rely on external IRBs, the NPRM proposes to include a new provision that would give Federal departments and agencies the authority to enforce compliance with the Common Rule directly against the IRB conducting the review.<sup>52</sup> However, such enforcement would be limited to institutional compliance with the IRB review requirements of the Common Rule, and would not relieve institutions of compliance with other regulatory requirements.<sup>53</sup>

While the NPRM's proposed revisions to the Common Rule would mandate review of cooperative research studies by a single IRB, the NPRM would not prevent an institution from choosing to still conduct its own local review of a cooperative research study.<sup>54</sup> Such review would be at the institution's sole expense, and would not be binding on the local institution or enforced by OHRP unless it was adopted by the single IRB.<sup>55</sup> Yet this permissive approach to concurrent local IRB review belies HHS's assertion that "multiple IRB reviews for cooperative studies adds bureaucratic complexity to the review process [...] without evidence that multiple reviews provide additional protections to subjects."<sup>56</sup> In fact, HHS concedes that "external IRB review of cooperative research may be problematic given the current lack of direct regulatory accountability and the large volume of cooperative reviews."<sup>57</sup> Although the NPRM now addresses the first issue by permitting enforcement directly against the IRB conducting the review, it has not addressed how the responsibilities should be shared between the local institution and the external IRB in order to ensure overall compliance with the Common Rule. Instead, the NPRM has left it up to the institution and the reviewing IRB to establish and follow written procedures that outline the specific roles and responsibilities of each party.<sup>58</sup> For institutions that have not previously chosen to use an external IRB for cooperative research, this new mandate may result in additional administrative time and expense as institutions revise existing policies and procedures in order to ensure compliance with this requirement.

#### a. *Documentation & Establishing Procedures*

All institutions engaging in research covered under the Common Rule must certify that the research has been reviewed and approved by an IRB provided for in the assurance.<sup>59</sup> While most institutions will have their local IRB designated under their Federal-wide Assurance,



institutions participating in cooperative research that engage an external IRB for the first time will need to ensure that the external IRB is designated as the reviewing IRB under the institution's Federal-wide Assurance.<sup>60</sup> As such, institutions should consider implementing a central intake form for all new studies, which indicates whether the institution's local IRB will be the reviewing IRB for the study, or if it will be ceding review of the study to an external IRB. If review will be ceded to an external IRB, the intake form should clearly identify the external IRB that will be responsible for reviewing the study. Use of an intake form will help ensure that studies are handled properly from the beginning, and will help avoid confusion or lack of accountability.

In addition, institutions must include in their written assurance the written procedures that the IRB will follow for conducting review of the research, as well as the procedures for ensuring prompt reporting of any unanticipated problems involving risks to study subjects (or others) or suspension or termination of IRB approval.<sup>61</sup> While OHRP has put forth a sample IRB Authorization Agreement on its website for use by an institution that is relying on the IRB of another institution, many institutions may not find this form to be sufficient to address their needs.<sup>62</sup> This sample IRB Authorization Agreement is only one page long, and merely provides the following:<sup>63</sup>

- The institution or organization providing IRB review ("designated IRB") will meet the human subject protection requirements of the OHRP-approved Federal-wide Assurance of the institution relying on the designated IRB.
- The designated IRB will follow written procedures for reporting its findings and actions to appropriate officials at the institution.
- The relevant minutes of IRB meetings will be made available to the institution upon request.
- The institution remains responsible for ensuring compliance with the IRB's determinations and with the terms of the institution's OHRP-approved Federal-wide Assurance.

As such, the sample IRB Authorization Agreement does not specifically define the roles and responsibilities of each party, but instead proposes a more general acknowledgment of each party's responsibility under the authorization.

Given the complexity of multi-site, cooperative research studies, institutions should use the three-year compliance window from the publication of the Final Rule to work with legal counsel to develop their own standard template Authorization Agreements for when the institution's IRB will be ceding review to an external IRB, as well as when the institution's IRB will be the designated IRB for the cooperative study. Such standard Authorization Agreements should consider the institution's current policies and procedures, as well as any requirements that may be specific to the institution. For example, Catholic healthcare institutions that are required to comply with the Ethical and Religious Directives for Catholic Health Care Services<sup>64</sup> should include specific language in their template agreements which acknowledges the institution's obligation to comply with such Directives and requires the designated IRB to promptly notify the

institution if any aspect of the study or implementation thereof may cause the institution to violate the Directives. In addition, the institution should consider including an indemnification provision requiring the designated IRB to indemnify the institution where the institution's violation of Common Rule requirements is a direct result of the designated IRB's noncompliance with the IRB review requirements of the Common Rule. Alternatively, if the institution's local IRB is the designated IRB, the institution may want to include an indemnification provision requiring that the institution ceding review to the designated IRB will indemnify the designated IRB where the designated IRB's noncompliance with the IRB review requirements of the Common Rule is directly caused by the institution's failure to provide accurate information to the designated IRB, or to timely report issues to the designated IRB.

*b. Education of Investigators on External IRB Policies and Procedures*

Investigators (as well as institutions) will encounter additional obstacles under the new proposed mandate for cooperative research studies. Whereas most investigators are likely familiar with their local IRB's policies and procedures, requiring review of cooperative research by an external IRB will mean that investigators have to learn the policies, procedures, forms, and reporting mechanisms of the external IRB. Since the designated external IRB may vary from study to study, the investigators will need to expend considerable time and effort each time a study with a new external IRB is contemplated. In order to reduce the burden on investigators, and to ensure compliance with the institution's Federal-wide Assurance and Authorization Agreement with the designated IRB, the institution should appoint a liaison either within its institution or its local IRB to assist investigators with questions that may arise when his or her study is being reviewed by an external IRB. Alternatively, the institution could require in its template Authorization Agreement that the designated IRB provide the contact information of an individual that investigators can easily reach if they have questions regarding the policies or procedures of the external IRB.

#### **IV. Conclusion**

The proposed changes under the NPRM, while streamlining and removing inefficiencies from research, will also pose several new administrative burdens and compliance costs on U.S.-based institutions that should not be overlooked. First, institutions will need to implement tracking systems to monitor biospecimens in order to determine which biospecimens may be used in secondary research. Second, institutions will need to train its personnel on the new consent requirements for biospecimens, as well as the risks and benefits of secondary research and the storage, maintenance, and security of biospecimens, so that employees may be able to answer individual's questions regarding the secondary or future uses of his or her biospecimens. In the case of cooperative research studies, institutions will also need to train study personnel on the policies, procedures, forms, and reporting mechanisms of the external IRB. Finally, institutions will need to spend considerable time and effort revising its own internal policies and procedures in order to accommodate these new requirements.

Once the Final Rule is published, U.S.-based institutions should use the three-year window for compliance with the Final Rule to provide training to all research personnel to

ensure that these individuals have a sufficient understanding of these additional requirements. In addition, Institutions should work closely with their legal counsel to develop updated templates, policies, and procedures that will help institutions remain compliant with these changes, while also reducing overall costs for institutions.

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<sup>1</sup> Dep't of Health, Education, & Welfare, Belmont Report (1979), available at

<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

<sup>2</sup> See 45 CFR 46 (Part A) (2009), available at <http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html#>

<sup>3</sup> *Id*

<sup>4</sup> 80 Fed Reg 53934, 53935 (Sept 9, 2015), available at <https://www.federalregister.gov/articles/2015/09/08/2015-21756/federal-policy-for-the-protection-of-human-subjects#h-223>

<sup>5</sup> 76 Fed Reg 44512 (July 26, 2011).

<sup>6</sup> Dep't of Health & Human Services, Dep't of Homeland Security, Dep't of Agriculture, Dep't of Energy, National Aeronautics & Space Admin, Dep't of Commerce, Social Security Admin, Agency for Int'l Development, Dep't of Justice, Dep't of Labor, Dep't of Defense, Dep't of Education, Dep't of Veterans Affairs, Environmental Protection Agency, National Science Foundation, and Dep't of Transportation.

<sup>7</sup> 80 Fed Reg at 53935

<sup>8</sup> *Id*

<sup>9</sup> The current definition of "human subject" is "a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information." 45 CFR §46.102(f) (2009).

<sup>10</sup> 80 Fed Reg at 53942

<sup>11</sup> *Id*

<sup>12</sup> *Id*

<sup>13</sup> *Id*

<sup>14</sup> *Id*

<sup>15</sup> *Id*

<sup>16</sup> *Id*

<sup>17</sup> *Id*

<sup>18</sup> *Id*

<sup>19</sup> *Id*

<sup>20</sup> *Id* at 53944.

<sup>21</sup> See *id* at 53976. These conditions include that (1) there are compelling scientific reasons for the research use of the biospecimens; and (2) the research could not be conducted with other biospecimens for which informed consent was or could be obtained.

<sup>22</sup> 80 Fed Reg at 53976

<sup>23</sup> See Belmont Report, *supra* n. 1, available at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

<sup>24</sup> *Id*

<sup>25</sup> 80 Fed Reg at 53945

<sup>26</sup> *Id*

<sup>27</sup> *Id*

<sup>28</sup> Kaufman, DJ et al, *Public Opinion about the Importance of Privacy in Biobank Research*, Am J of Human Genetics, 85(5) 643-654 (Nov 2009).

<sup>29</sup> *Id*

<sup>30</sup> 80 Fed Reg at 53945.

<sup>31</sup> *Id*

<sup>32</sup> See 45 CFR 46.116 (2009) The eight elements include: (i) a general description of the types of research that may be conducted using the biospecimens, the expected information to be generated from the research, the types of biospecimens anticipated to be used in the research, and the types of institutions that might conduct secondary research using the biospecimens; (ii) the intended scope of the informed consent, including the time-period for *collection* (which is limited for specimens collected outside the research context to 10 years for adults, and for minors, 10 years after parental permission or until the minor reaches the age of majority, whichever is shorter); (iii) the time-period within which the investigator can use the biospecimens for research (which is not subject to the 10

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year limit on collections and can even be indefinite); (iv) a statement indicating that participation is voluntary, the participant will not be penalized or otherwise lose entitled benefits as a result, and the participant may withdraw, if feasible, at any time, however biospecimens (and information) already distributed may not be able to be retrieved; (v) if applicable, a statement notifying the participant that she will not be informed of the details of any specific study that may be conducted using the biospecimens; (vi) if applicable, notification to the participant that the biospecimens will likely be used by multiple investigators and institutions, and shared broadly, including in identifiable format; (vii) the name(s) of the institution(s) where the biospecimens were or will be collected; and (viii) if relevant, the option for adult participants to consent, or refuse to consent, to the inclusion of de-identified data in a publicly available database (with a description of the associated risks).

<sup>33</sup> 80 Fed Reg at 53971.

<sup>34</sup> Sheehan, M, *Can Broad Consent be Informed Consent?* Public Health Ethics, 4(3): 226-235 (Nov 2011).

<sup>35</sup> Hoeyer, K, et al, *The Ethics of Research Using Biobanks*, Arch Intern Med 165(1): 97-100 (2005).

<sup>36</sup> Lipworth, W, et al, *An empirical reappraisal of public trust in biobanking research: Rethinking restrictive consent requirements*, 17 JLM 119 (2009).

<sup>37</sup> *Id*

<sup>38</sup> See Belmont Report, *supra* n. 1, available at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

<sup>39</sup> *Id*

<sup>40</sup> See Kaufman, *supra* n. 28.

<sup>41</sup> Vermeulen, E, et al, *A Trial of Consent Procedures for Future Research With Clinically Derived Biological Samples*, British J of Cancer: 101(9): 1505-1512 (Nov 2009).

<sup>42</sup> *Id*

<sup>43</sup> *Id*

<sup>44</sup> *Id*

<sup>45</sup> *Id*

<sup>46</sup> 80 Fed Reg at 53981. The NPRM also provides limited exceptions to this requirement for (i) cooperative research for which more than single IRB review is required by law (e.g. for FDA-regulated devices); or (ii) research for which the Federal department or agency supporting or conducting the research determines and documents that use of a single IRB is not appropriate for the particular study. *Id* at 53983.

<sup>47</sup> See Food & Drug Admn, *Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials* (2006), available online at <http://www.fda.gov/downloads/RegulatoryInformation/Guidance/UCM127013.pdf>

<sup>48</sup> 74 Fed Reg 9568 (March 5, 2009); 76 Fed Reg 44512 (July 26, 2011).

<sup>49</sup> National Institutes of Health, *Draft NIH Policy on the Use of a Single Institutional Review Board for Multisite Research* (2014), available online at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html>

<sup>50</sup> 21 CFR 56.114 (2015).

<sup>51</sup> 80 Fed Reg at 53981.

<sup>52</sup> *Id* at 53983

<sup>53</sup> *Id* at 53982

<sup>54</sup> *Id* at 53984

<sup>55</sup> *Id*

<sup>56</sup> *Id* at 53982

<sup>57</sup> *Id*

<sup>58</sup> *Id* at 53984

<sup>59</sup> See 45 CFR 46.103(b) (2009).

<sup>60</sup> See 45 CFR 46.103(b)(2); *see also* additional OHRP guidance, "Does a FWA have to be updated if an institution later relies on an IRB not included in the original FWA submission?" available online at <http://www.hhs.gov/ohrp/policy/faq/irb-registration/does-fwa-have-to-be-updated.html>

<sup>61</sup> See 45 CFR 46.103(b)(4) & (5) (2009).

<sup>62</sup> Dep't of Health & Human Services, *Institutional Review Board (IRB) Authorization Agreement*, available online at <http://www.hhs.gov/ohrp/assurances/forms/irbauthorizpdf.pdf>

<sup>63</sup> *Id*

<sup>64</sup> Ethical and Religious Directives for Catholic Health Care Services, Fifth Edition, United States Conference of Catholic Bishops (issued Nov. 17, 2009), available online at: <http://www.usccb.org/issues-and-action/human-life-and-dignity/health-care/upload/Ethical-Religious-Directives-Catholic-Health-Care-Services-fifth-edition-2009.pdf>