Endpoints
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The following was originally posted to Verrill Dana's Academic and Clinical Research Group blog, Endpoints*, at* ***www.clinicalresearchlawblog.com****.*

The Common Rule NPRM Blog Series: Part 1 – Biospecimens

As **we previously announced**, sixteen federal agencies, including the Department of Health and Human Services ("HHS"), recently published a **Notice of Proposed Rulemaking ("NPRM") in the Federal Register** outlining changes to the existing regulations protecting human subjects (the "Common Rule"). The Common Rule NPRM is the latest development since the **Advanced Notice of Proposed Rulemaking ("ANPRM") was published on July 26, 2011**. The Academic and Clinical Research Group ("ACRG") will be publishing a series of topic-specific blogs in the coming weeks to assist institutions in digesting various aspects of the proposed regulations, preparing to submit any comments by the **December 7, 2015** deadline, and grappling with implementation changes once the final rule issues. We have also prepared an **unofficial redline of the proposed changes against the existing regulations** and a **set of decision charts** to assist with navigating the proposed revisions.

In this installment, we discuss the NPRM's proposed changes to biospecimens research. The NPRM did not back down from one of the more controversial aspects of the ANPRM, proposing a fundamental shift in the applicability of the human subjects protection framework to non-identified biospecimens research. However, once the shock of the new definition of "human subject" wears off, the reality is that most of the changes codify how the research community has tried to apply the existing Common Rule to the challenging arena of biobanking, secondary research, and genomic and other "omics" research. That said, many of the carve-outs (i.e., exclusions and exemptions) intended to balance this shift are more restrictive than at first they seem.

ACRG Rapid Rundown: Six Things You Need to Know

1. **Human Biospecimen = Human Subject**. The definition of "human subject" would include a "living individual about whom an investigator . . . (iii) Obtains, uses, studies, or analyzes biospecimens," *regardless of identifiability*. (§__.102(e)(1).) This would bring research using non-identified biospecimens within the Common Rule's protections for the first time, requiring IRB approval and informed consent unless the research is excluded or exempt (or informed consent is waived). While the intended goal is clear (respect autonomy regarding the use of all biospecimens in research, regardless of identifiability), the revised definition is deficient from a drafting perspective (see further discussion **below** proposing an alternative definition to ensure clarity). In good news, this change is *not retrospective* (i.e., it would *not* apply to biospecimens collected prior to the effective date of the Final Rule) and compliance would not be required until three years after the Final Rule is published. The transition provisions nonetheless raise certain questions discussed further **below**.

2. **"Broad" (but Prescribed) Consent to the Storage and Secondary Research Use of Biospecimens is Sufficient (and Almost Always Required)**. Many of the proposed changes focus on secondary research (i.e., research that is distinct from the context in which a

biospecimen or information was collected or generated). Informed consent to storage, maintenance, or secondary research involving non-identified biospecimens would not need to include all of the basic elements now proposed in revised form at §__.116(a). Instead, such consent would be required to include a subset of those elements (and a subset of the additional elements in §__.116(b), if applicable) *plus* a separate set of elements tailored to the biospecimens research context, including in pertinent part: (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 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). The Secretary of HHS will establish broad consent templates for public comment (and IRB review of the broad consent form is not required if the template is used). (§ __.116(c)(1) and (d).)

3. **Waiver of Broad Consent Would be Exceptionally Rare**. Although the NPRM allows for broad consent to secondary research using biospecimens (storage, maintenance and downstream research uses), a trade-off is that the criteria under which an IRB could waive broad consent for biospecimens research would be narrower than other research contexts. *In addition to* the standard criteria required to waive informed consent generally, for an IRB to waive the broad consent proposed in § __.116(c)(1), it would also have to find "(i) [t]here are compelling scientific reasons to conduct the research; and (ii) [t]he research could not be conducted with other biospecimens for which informed consent was obtained or could be obtained." Additionally, to the extent an individual *was asked and refused to give broad consent* to the storage or maintenance for secondary research use of biospecimens, an IRB is precluded from waiving consent for the storage, maintenance or the secondary use itself, regardless of whether the criteria are met. (§ __.116(f)(2) and (3).)

4. **Narrow Exclusion for Non-Identified Biospecimens if No New Information is Learned**. Secondary research involving non-identified biospecimens would be excluded, even though the research involves a "human subject" under the revised definition, so long as the research is confirmatory in nature and will only generate information about the person that is already

known (e.g., studying how rapidly a new diagnostic test can identify a known disease, condition or genetic abnormality). (§ __.101(b)(3)(i).)

5. **Exemptions May Apply (with Strings Attached)**. Certain biospecimens research would be *exempt* from aspects of the regulatory requirements. The NRPM proposes two exemptions aimed at secondary biospecimens research, one related to the *storage* or *maintenance* of biospecimens collected for purposes other than the anticipated secondary research on such specimens, and the second for the secondary research *use* of such stored specimens. However, in order to be exempt the research would need to meet several regulatory requirements: (i) apply the heightened protections for biospecimens in proposed § __.105; (ii) obtain broad informed consent in accordance with proposed § __.116(c); and (iii) obtain limited IRB review and approval (reviewing the broad consent process and any changes that would impact the required privacy protections) performed in accordance with proposed § __.111(a)(9). Additionally, the exemption must be recorded according to proposed § __.104(c). Therefore, unlike the current framework, an exemption determination for biospecimens research is not a free pass; several protections remain. (§ __.104(f).) Like with the other proposed exemptions, if the exemption decision tool (to be developed by federal departments and agencies) is used, the institution is not required to evaluate the merits of the exemption determination.

6. **Heightened Protections for Biospecimens Research Required**. The NPRM proposes a new section outlining explicit privacy and security protections that must be applied to research involving the collection, storage, or use of biospecimens. These protections would apply to non-exempt biospecimens research and are also part of the conditions to meet the exemptions in proposed § __.104(f). To meet these requirements, institutions would have the choice of complying with a list of safeguards to be promulgated by the Secretary of HHS or complying with certain provisions of the HIPAA Security Rule; additionally, institutions are limited in how they can use, release or disclose the stored biospecimens, similar to the downstream restrictions HIPAA imposes in the Data Use Agreement context. (§ __.105.)

Compare and Contrast: Biospecimens Research Under the Common Rule vs. NPRM

Topic	Common Rule	NPRM
Scope of "**human subject**"	Research on non-identified biospecimens ≠ "human subjects research".	The definition of "human subject" is modified to bring research on non-identified biospecimens within the definition of "human subjects research" (research on non-identified *information* is still outside the definition, even if the information is derived from a biospecimen). **Excluded** from the regulations is secondary research involving non-identified biospecimens if the research will not generate any new information about the individual.
Prospective collection of biospecimens for research purposes	Prospective collection is "human subjects research"; IRB oversight and informed consent is required.	Requirements remain essentially unchanged (IRB oversight and standard informed consent is required for prospective research collections).
Storage and maintenance of biospecimens for secondary research	Qualifies as "research," but only "human subjects research" if the biospecimens are identifiable; IRB oversight and informed consent is required (unless consent is waived).	Storage and maintenance of non-identified biospecimens = "human subjects research"; **exempt** from the full requirements *if* (i) broad consent using the HHS template occurred; (ii) additional protections in § __.46.105 are applied; and (iii) limited IRB review occurs.
Secondary research use of stored biospecimens	Qualifies as "research," but only "human subjects research" if the biospecimens are identifiable; IRB oversight and informed consent generally required (may be waived, or IRB may determine that the original consent at the time of collection is sufficient to cover the secondary use). If stored biospecimens are identifiable, the research may still be exempt (no IRB oversight and no informed consent) if any data are recorded in non-identified manner [exemption category 4].	Secondary research use of non-identified stored biospecimens is also human subjects research; **exempt** from full requirements *if* (i) broad consent using the HHS template occurred prior to storage; (ii) additional protections in § __.46.105 are applied; (iii) limited IRB review occurs; and (iv) there is no intention to return results to participants.

A Few Comments on Comments

As with the ANPRM, the NRPM's proposed changes to biospecimens research will likely elicit a high volume of comments given some of the core shifts contemplated by the proposed changes. Institutions preparing comments in advance of the **December 7** deadline may wish to prioritize the following high-impact areas:

Definition of Human Subject

The proposed revisions to the definition of "human subject" could be more precise; as written, the clause that applies to biospecimens is grammatically awkward ("*Human subject* means a living individual about whom an investigator . . . Obtains, uses, studies, or analyzes biospecimens". § __.102(e)(1)(iii).) Investigators don't really "obtain" biospecimens "about" a human subject. The "about whom" concept is nonetheless an important one that OHRP has clarified carves out from the definition certain biospecimens research where the focus of the research is not intended to generate information about the biospecimens per se (i.e., where a biospecimen is merely the medium within which other research with aims unrelated to the biospecimen occurs). An alternative revised definition[1] of "human subject" that would tighten the language might look like this: "(e)(1) *Human subject* means a living individual: (i) about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual; (ii) about whom identifiable private information is obtained, used, studied, analyzed or generated by an investigator (whether professional or student); or (iii) from whom an investigator (whether professional or student) conducting research obtains biospecimens, or uses, studies or analyzes biospecimens in a manner such that information is generated about the individual through the biospecimen, whether or not the information is individually identifiable."

Alternative Proposals 1, 2 and 3

The change to the definition of "human subject" is fundamental, notwithstanding the accompanying changes to the consent, exclusion and exemption categories that purport to lessen the practical impact. It would give non-identified human tissue unprecedented protected status in the research context. The NPRM includes two "alternative proposals" that would each expand the reach of the Common Rule to certain types of biospecimens research, but in a manner more narrow than the NPRM's primary proposal. The NPRM specifically asks for public comment on the three alternative proposals for the definition of "human subject" and how far-reaching the Common Rule's requirements should be in the context of biospecimens research. Evaluating these three proposals and submitting comments on which is ethically, analytically, and operationally preferable should be a priority.

[1] The alternative definition proposed here also suggests revisions that are not directly relevant to biospecimens research, for example deleting the proposed addition of "and uses, studies, or analyzes the data" from (e)(1)(i). This suggested change will be discussed in more detail in a future blog post related to research involving data; however, in brief, the proposed addition of this language arguably conflates the definition of "research" with the definition of "human subject" and suggests that if an investigator obtains data from a subject through an intervention but then fails to use, study or analyze it, the activity would not constitute human subjects research.

"Broad" Consent, Albeit Specifically Prescribed

Although the NRPM purports to permit "broad" consent to the storage, maintenance and secondary research use of biospecimens – and, as such, mediate the impact of the expanded definition of "human subject" – it is important to recognize that "broad" does not necessarily equate to flexibility and discretion in the content of such consent. The proposed regulations would require a subset of the existing consent elements, plus additional elements that are specific to biospecimens research. Furthermore, the exemptions for secondary biospecimens research depend on the use of the broad consent template to be published by HHS. What the broad consent actually accomplishes is a more tailored set of elements that are geared to the biospecimens research and secondary research context. These requirements would codify what many institutions and IRBs have historically done through interpretation and application of the existing requirements of informed consent to the unique context of biobanking research. One arguable benefit is that because the HHS broad consent template is required (and IRB review is limited to the process for consent, not the content of the form itself), an IRB would not be required to review the substance of the consent; it would be deemed sufficient and would thus hopefully streamline the review necessary to conduct secondary research using the stored specimens. However, it bears noting that under the existing rules, broad consent to future unspecified research at the time of collection would always be sufficient (more than sufficient, in fact) to the extent the specimens are non-identified at the time they are used for research. Although the NPRM, in implementing a shift in how non-identified specimens are categorized and fundamentally understood, purports to offset the increased requirements for biospecimens research with the ability to seek broad consent to future unspecified use, this is really just the application of the existing rule (and the codification of the way most institutions currently approach front door consent to the collection of biospecimens for research purposes) with more specific requirements for non-identifiable biospecimens.

Transition Provisions

Although, as noted above, the regulations propose to apply the new requirements for biospecimens prospectively, certain ambiguities around the transition provisions would benefit from further clarification. Specifically, although it appears that the intent is to carve the use of prior collections of biospecimens out of the proposed changes to biospecimen research, as drafted, the NPRM is ambiguous on what standards would apply to research on stored *identifiable* specimens. The regulations indicate that grandfathered biospecimens research "need not comply with the requirements of these regulations" if the biospecimens were collected before the compliance date *and* research use only occurs using the biospecimens in non-identified format. (§ __.101(k)(2).) If an institution wishes to use previously collected biospecimens in identifiable format, then such biospecimens research would need to comply with the regulations. However, it is not expressly clear whether such compliance would need to be with the NPRM's proposed changes, or with the Common Rule as it existed at the time of the collection, which occurred prior to the effective date of the new requirements. If the former, the use of such biospecimens in identifiable format may be precluded, as the informed consent presumably would not have met the new requirements and any waiver at the time of the secondary research use, if required to be in accordance with the proposed waiver criteria, may be unobtainable. Institutions commenting on this provision may wish to highlight that unless the intent is to preclude the use of identifiable biospecimens research with appropriate oversight and informed consent to the extent such biospecimens were previously collected, the final

rule should clarify that the standards to which such regulated human subjects research must comply are those in effect at the time the biospecimen was collected.

Stringent Waiver of Consent

The additional criteria required before broad consent may be waived are intended to make waivers of the broad consent requirement for biospecimens research exceptionally rare, requiring broad consent in almost every circumstance. The criteria (compelling scientific reasons and other biospecimens for which broad consent exists cannot be used) all but remove the discretion from IRBs to determine in a given case that the failure to have obtained broad consent should not prohibit the use of the biospecimens for research purposes. Institutions commenting on this proposed change may want to consider whether identifying limited exceptions, or principles for categorical exceptions, where only the standard waiver criteria would attach is worthwhile.

Prospective Collection vs. Secondary Research

It is relatively clear that under the NPRM, the prospective *collection* of biospecimens (i.e., the actual blood draw, buccal swab, or other specimen collection) for research purposes—including for the purpose of populating a research biorepository—is not eligible for the exclusion and exemptions available for biospecimens research given the research intervention to collect the biospecimens. The exemptions apply only to the storage, maintenance and secondary research involving biospecimens, and the exclusion is only potentially applicable in the secondary research context where no new information is generated about the individual. See 80 Fed. Reg. at 53966 (September 8, 2015) (noting that the exemption applicable to storage or maintenance of biospecimens does not cover "the actual new collection of any biospecimens from a person through a research interaction or intervention" and citing as an example a circumstance where "the proposed research activities involved creating a research repository of DNA samples that would be obtained from people through cheek swabs" in which case "the creation of the research repository would require IRB review, and would not be exempt").

Where things get murky is with respect to the *storage activity*—itself considered a "research" activity—where the specimen collection was performed solely for research purposes, particularly in the context of institutional biorepositories (as opposed to the storage of biospecimens secondary to a clinical trial). The commentary indicates that the exemption in §___.104(f)(1) "is for secondary research use of biospecimens and identifiable private information and applies to biospecimens and identifiable private information that were initially collected for purposes *other than the proposed research activity*. The term 'other than the proposed research activity' here means that the information or biospecimens were or will be collected for a *different research study* or for a *non-research purpose*." 80 Fed. Reg. at 53966 (September 8, 2015) (emphasis added). However, it remains ambiguous at best whether the development of an institutional research biorepository, where biospecimens will be prospectively collected for the express purpose of inclusion in the biorepository, is a research activity "other than the proposed research activity". By way of example, the commentary cites a clinical trial, where the research-driven collection clearly occurs for the purposes of the underlying research study, not for the secondary research use. In public comments, OHRP has recognized the ability to combine informed consent for an underlying research study with the broad consent for storage, maintenance and secondary use so long as the participant can understand the two distinct activities. The commentary to the NPRM also suggests that one could

"make use of the Secretary's template" in the context of obtaining consent to secondary research uses as part of the clinical trial consent. Id.; see also 80 Fed. Reg. at 53973, September 8, 2015 ("Broad consent for the research use of biospecimens or identifiable private information that were originally collected for a research study would generally be described in the consent document for the study that would be generating the research biospecimens or information."). However, it remains unclear at what point, if any, combining these two consents might make the secondary research activity ineligible for the exemption, which *requires* that the template be used.

What is even less clear is how that would look when the "research study" for which the biospecimens are collected is the development of a research biorepository, as opposed to a specific study or clinical trial. If the development of the biorepository into which the collected specimens will be stored is *not* a different research study than the research study for which the biospecimens were collected (at least for those specimens that were collected solely for purposes of inclusion in the bank), then arguably the exemption for storage and maintenance in §___.104(f)(1) would not apply. This has the potential to create an inconsistent application of the exemption across the various materials in a biorepository based on the context of the collection (i.e., if a biospecimen was collected specifically for inclusion in the biorepository—no available exemption—vs. if it was collected for an underlying clinical trial or for clinical purposes—potentially available exemption). Although clearly the intervention to collect would not be exempt in either case, it is unclear why the *storage* of one type of biospecimen vs. another would require different levels of protection. Institutions may wish to comment on this ambiguity and, in particular, the appropriate required elements for consent when the collection of biospecimens will be limited to populating a research biorepository in which biospecimens and information will be stored, maintained, and used for secondary research purposes. If the broad consent is combined with other required elements given that the collection is not eligible for an exemption, is that type of combination a deviation from the forthcoming HHS template such that the exemptions in §___.104(f)(1) and (f)(2) are unavailable?

A New Era of "Exempt"?

Under the existing Common Rule, qualifying for a regulatory exemption means that the research is not subject to the regulations' requirements. The NPRM would change the concept of what it means to be "exempt", attaching significant conditions in order to qualify, and limiting the activities and research outside the purview of the regulations to those that qualify as *excluded*. The potential availability of the exemptions in §___.104(f)(1) and (f)(2) for certain secondary biospecimens research is cited as a balancing factor to the proposed application of the regulations to non-identified biospecimens. However, when the conditions attendant to such exemptions are explored, it becomes clear that biospecimens research—which currently, if non-identified, would not constitute human subjects research at all—is "exempt" from IRB review and standard informed consent under the NPRM's proposed changes because the conditions required to meet the exemptions standardize the floor of protections (consent, privacy, oversight, etc.) that any individual IRB review would need to confirm are satisfactory under the existing regulatory scheme. As such, the proposed regulations in effect accomplish what the IRB review process is currently intended to accomplish—provide an incentive for researchers to ensure appropriate protections are in place. It is important to recognize that under the proposed changes, meeting an exemption is not the only way to conduct secondary research with biospecimens. Institutions could reasonably conclude that the requirements to qualify for exemption are as, or even more, burdensome than proceeding with broad consent to unspecified

uses that is then reviewed for sufficiency by an IRB at the time of the secondary research use. Institutions may wish to consider (and comment on) whether these exemptions are, in fact, a preferable option to the status quo in which IRBs have discretion to identify the appropriate protections on a project-specific basis, and highlight whether or how the exemptions might be modified to create the appropriate incentives.