

# Notice of Proposed Rulemaking: the Common Rule

## Summary of Changes Likely to Impact Public Health Laboratories

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### Background

A notice of proposed rulemaking (NPRM) was released by the U.S. Department of Health and Human Services (HHS) in early September 2015 to announce proposed revisions to the regulations protecting human subjects in research. The NPRM follows an advanced notice of proposed rulemaking (ANPRM) that was released in 2011 which outlined the various changes and gave an opportunity for the public to provide significant input relating to ethics, safety, and oversight of human research protections, generally referred to as the Common Rule.

The proposed changes address the need to protect individuals who participate in research as technology advances, the scope and breadth of clinical trials deepens and increased concern arises over individuals making informed decisions about participating in research.

The NPRM addresses the feedback received from the ANPRM and presents the major changes proposed. Below is a summary of the change that will likely impact public health laboratories.

The full NPRM can be found: <https://s3.amazonaws.com/public-inspection.federalregister.gov/2015-21756.pdf>

### Short Summary

- Non-identifiable biospecimens will be considered human subjects
- Secondary use of biospecimens will require broad informed consent for future unspecified research with limited exemptions
- Validation of certain tests and assays, quality assurance and control activities and proficiency testing would not require consent
- Public health surveillance activities have an exclusion from oversight of the Common Rule
- Biospecimens and private identifiable information will need broad informed consent for maintenance and storage using a form developed by HHS
- Broad informed consent must be obtained for use of biospecimens that are collected in clinical settings. Use will be permitted on biospecimens that exist at the time in which broad consent is sought and/or biospecimens that will be collected up to ten years after broad consent is obtained for adults. For children, biospecimens can be collected up to ten years after broad consent is obtained, or until the child is of legal age to consent, whichever comes first.

## Major Changes

### 1. Expanding the Definition of Human Subject to Cover Research with Non-identified Biospecimens (pg. 46)

- a. Focuses on ethical principles surrounding secondary research use of biospecimens that may have originally been collected from research or non-research settings
- b. NPRM Goals
  - i. Establish circumstances in which the Common Rule should govern what research investigators should be able to do with biospecimens that have been collected for some other purpose
  - ii. Reduce barrier to the secondary use of biospecimens to the best extent possible given that the public prefers to have the opportunity to provide consent. Concerns about privacy and autonomy
  - iii. Increase transparency in when and how a biospecimens collected in a variety of circumstances will be used for research purposes
  - iv. Increase opportunities for consent
- c. Current Rule
  - i. “Non-identifiable” has historically been interpreted as biospecimens that have been stripped of identifiers
  - ii. If biospecimens and data were collected for purposes other than the currently proposed research, it is permissible for investigators to conduct research without obtaining consent if the biospecimens and data were stripped of all identifiers (pg. 49).
- d. ANPRM Discussion
  - i. Questioned whether consent should be required for research on non-identifiable biospecimens
  - ii. Could consent be obtained for unspecified future research instead of requiring specific consent?
  - iii. What types of genomic data should be considered identifiable?
  - iv. Should human biospecimens be considered inherently identifiable?
- e. NRPM Proposal
  - i. Proposal covers obtaining, use, study, or analysis of biospecimens regardless of identifiability
  - ii. Requires broad informed consent for future unspecified research involving biospecimens with limited exemptions
  - iii. Will only apply prospectively
  - iv. Compliance will be delayed to three years after publication of the final rule
  - v. A subset of secondary research will be allowed without consent. This includes:
    1. Validation of certain tests and assays (such as research to develop a diagnostic test for a condition using specimens from individuals known to have the condition and those known not to have the condition)
    2. Quality assurance and control activities

3. Proficiency testing
- vi. **MAIN CONSEQUENCE: prospectively, informed consent would be generally required before research use of biospecimens that are not covered by an exclusion**

f. Alternative Proposals

- i. Expand the definition of “Human Subject” to include whole genome sequencing (pg. 59)
  1. Would not consider all research using biospecimens as constituting human subject research
  2. Would limit the definition of human subjects only to whole genome sequencing data (sequencing human germline or somatic biospecimens with the intent to generate the genome or exome sequence of that biospecimens)
  3. Applies to research that would generate WGS data, the use of any part of the data and to research involving secondary use of any part of WGS data that was originally generated for other purposes than the proposed research
  4. Potential for exemptions to allow research if consent to secondary future research use were obtained
  5. Under this alternate proposal, secondary research use of non-identified information or non-identified biospecimens would fall outside of the scope of the Common Rule with the exception of WGS data
  6. MAIN DIFFERENCE BETWEEN PRIMARY PROPSOAL AND ALTERNATE
    - a. Under the primary proposal, data collected from WGS could continue to be used for research without additional consent as long as it does not meet the definition of identifiable private information
    - b. Under the alternate proposal, consent would be required before using WGS data for research
- ii. Classifying Certain Biospecimens Used in Particular Technologies as Meeting the Criteria for “Human Subject” (pg. 61)
  1. Expands definition of “human subject” to include the research use of information that was produced using a technology applied to a biospecimens that generates information unique to an individual that when used in combination with publicly available information, the individual could be identified
  2. Similar to previous alternate proposal, but the scope is broader and not limited to WGS
  3. Would require consent for genomic sequencing of even small portions of a person’s genome and other technologies that would generate identifying information

- g. Request for feedback (pgs. 63-64)
  - i. *Would providing a definition of a biospecimens be helpful?*
  - ii. *How would this definition draw a line between when a biospecimens is covered by the Common Rule and when processing of biological material has sufficiently altered the materials so that they should not be subject to the regulations?*
  - iii. *Would only covering biospecimens that include nucleic acids draw an appropriate line?*
  - iv. *Does the language need to be clearer and more direct about the definition of “identifiable private information”?*

## **2. Explicit Exclusions of Activities from the Common Rule**

- a. Program Improvement Activities (pg. 69)
  - i. Excluded from the proposed NRPM, 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 purpose other than the currently proposed activity, or is obtained through oral or written communications with individuals.
  - ii. Example: survey of hospital patients to evaluate and improve quality of meals delivered to hospital patients
  - iii. *Request for feedback sought for whether biospecimens should not be included in any of these exclusion categories*
- b. Quality Assurance and Quality Improvement Activities (pg. 74)
  - i. Excludes activities that cover quality assurance or improvement activities involving the implementation of an accepted practice to improve the delivery or quality of care or services
  - ii. Purpose is limited to altering the utilization of an accepted practice and collecting data or biospecimens to evaluate the effects on the utilization of the practice. Cannot be used to evaluate an accepted practice itself
  - iii. This exclusion category is intended for activities that are designed only to improve the implementation of a practice that is already accepted, not to evaluate the effectiveness and value of the practice itself
- c. Public Health Surveillance (pg. 77)
  - i. Pertains to activities involved in 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 [...] or a sudden increase in injuries from using a consumer product, or conditions of public health importance
  - ii. Definition of public health surveillance: the collection, analysis, and use of data to target public health prevention.

iii. Examples of activities covered under this exclusion

1. Safety and injury surveillance to monitor potential safety signals for a specific product (AERS, VAERS, Medical Product Safety Network);
2. Surveillance activities designed to enable a public health authority to identify unexpected changes in the incidence or prevalence of a certain disease in a defined geographic region;
3. Surveillance activities designed to enable a public health authority to identify the prevalence of known risk factors associated with a health problem in the context of a domestic or international public health emergency;
4. Surveillance activities designed to enable a public health authority to locate the range and source of a disease outbreak or to identify cases of a disease outbreak;
5. Surveillance activities designed to enable a public health authority to detect the onset of disease outbreaks or provide timely situational awareness during the course of an event or crisis that threatens the public health, such as a natural or man-made disaster
6. Activities that would NOT fall under this exclusion and therefore subject to the Common Rule:
  - a. Understanding risk factors for chronic diseases
  - b. Exploratory studies designed to elucidate relationships between biomarkers of exposure and biomarkers of disease
7. Request for feedback (pg 80):
  - a. *Are the parameters of the exclusions sufficiently clear to provide the necessary operational guidance or whether any additional criteria or parameters should be applied to clarify or narrow any of these exclusions.*

**3. Exclusion of Activities that are Low-risk And Already Subject to Independent Controls (pg. 81)**

These activities do not entail physical risk and are non-intrusive. They will not be required to receive any form of determination or IRB approval. Consent is not required. Deemed to be low-risk research activities

- a. Educational Tests, Survey Procedures, Interview Procedures, or Observation of Public Behaviors (pg. 84)
- b. Research Involving the Collection of Study of Information that has been or will be Collected (pg. 91)
  - i. Current exemption category applies to research involving the use of existing data, documents, records, and pathological or diagnostic specimens, but only if the sources are publicly available or if the information is recorded by investigators in such a manner that subjects cannot be identified
  - ii. Proposed change by ANPRM: proposes retaining this exemption, but removes the word “existing” in order to broaden the use of information or biospecimens

that were or will be collected for purposes other than the suggested research, rather than requiring all of the information or biospecimens already exist at the time the study is suggested for exemption

- iii. NPRM modifies this category such that it does not include secondary research use of biospecimens
- iv. The proposed exclusion does not require that the data exist as of the time the study commences and is expanded to include the secondary research use data collected in the future for non-research purposes
- c. Research Conducted by a Government Agency using Government-Generated or Government-Collected Data (pg. 93)
  - i. Limited to research conducted by a federal department or agency using government-generated or government-collected information obtained for non-research purposes
  - ii. Applies to both original data collection and secondary analysis when data is subject to data security, participant privacy and notice requirements of other federal statutes and regulations
- d. Certain Activities Covered by HIPPA (pg. 95)

#### **4. Secondary Research Use of Identifiable Private Information (pg. 137)**

- a. Current rule outlines secondary research using identifiable private information is required to undergo IRB review and approval. In some cases, the IRB may waive the requirement for informed consent.
- b. ANPRM proposed if the investigator used pre-existing data, written consent or a waiver of consent would be required if the investigator obtains information that identifies the subject. If data was originally collected for research purposes, then consent would be required regardless of whether the investigator obtains identifiers
- c. NPRM proposal: a new exemption covering the secondary research use of identifiable private information that has been or will be acquired for non-research purposes if:
  - i. Prior notice has been given to the individuals to whom the identifiable private information pertains that such information may be used in research
  - ii. The privacy safeguards of §\_\_.105 are required; and
  - iii. 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

#### **5. Exemptions Subject to Documentation Requirements and Privacy Safeguards, Limited IRB Review and Broad Consent (pg. 146)**

- a. The current rule requires IRB review and approval of research involving private information, including individually identifiable biospecimens. Waiver of informed consent is allowed if it satisfies certain criteria. The current Rule also allows research without consent if a biospecimens is used for research under conditions where the

investigator does not possess information that would allow him or her to identify the person whose biospecimens is being studied (pg. 147)

- b. ANPRM discussion posed requiring written general consent for secondary research use of biospecimens originally collected in research or non-research settings regardless if they include identifiers. An exemption was proposed if written broad consent for research use was obtained at the time of the original collection. The ANPRM posed questions on whether specific types of research could be consented to or declined by subjects.
- c. The NPRM proposes requiring that consent be obtained for the research use of non-identified biospecimens, but that consent can be broad (pg. 149). Study-specific consent for research using biospecimens would not be required
  - i. Two exemptions to facilitate storage, maintenance and secondary research use of biospecimens and identifiable private information.
    1. The first exemption (pg. 150) relates **to 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 non-research 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 using the broad consent template that the Secretary of HHS will develop
      - b. The reviewing IRB conducts a limited IRB review of the process in which broad consent will be sought. For most institutions, this will be a one-time event. The IRB would review an overall general institutional protocol for the manner in which people can provide broad consent for the maintenance or storage of their biospecimens for future secondary research (pg. 153). If, over time, there is a change in the way biospecimens and information will be maintained for secondary research purposes, then a limited IRB review must be conducted to ensure standards are still met.
      - c. In the case when a research study involves the actual collection of new biospecimens (such as in a clinical trial), the informed consent process could cover both the original study and for secondary research use of the biospecimens
      - d. NOTE: the use of the informed consent form developed by the Secretary of HHS is critical to qualify for this exemption
      - e. Oral broad consent is allowed in certain situations for certain types of research. This will largely not impact the activities conducted by public health laboratories.

2. The second exemption permits secondary research use of biospecimens or identifiable private information where broad consent has been sought and obtained as described above (pg. 153)
  - a. This exemption only applies to biospecimens and identifiable private information that have been stored or maintained for secondary research use using the broad consent template that the Secretary of HHS will develop
  - b. If the investigator anticipates that the research results will be provided back to the research subject, this exemption does not apply.
  - c. This exemption does not include additional analyses being conducted to support or augment the original research study for which the information or biospecimens were originally collected.
  - d. This exemption requires the following criteria to be met:
    - i. Privacy safeguards at §\_\_.105
    - ii. Broad consent for storage and maintenance has already been obtained using the Secretary's template. **It is presumed that research involving newborn blood spots would frequently take place using this provision (pg. 155)**
- ii. Questions for public comment (pg. 157):
  1. *Public comment is sought on whether the NPRM's proposal of this exemption is the best option, or whether there is a better way to balance the respect for persons with facilitating research*
  2. *Public comment is sought on whether and how the provision regarding the return of research results in the proposed exemption should be revised*
  3. *Public comment is sought on whether there should be an additional exemption that would permit the collection of biospecimens through minimally invasive procedures (e.g., cheek swab or saliva)*

## 6. Proposed Changes to Obtaining, Waiving, and Documenting Informed Consent (pg. 162)

- a. Required elements of informed consent (pg. 166-174)
  - i. Essential information must be up front
  - ii. Must provide sufficient detail relating to specific research
  - iii. Must be organized to promote subject's understanding
  - iv. For research with non-identifiable data, it is proposed that a new element of informed consent be required to better ensure that subjects are informed of the possibility that identifiers that are collected as part of a research study could be removed from the data and then used for secondary research studies. This new

element would apply to all research collecting identifiable private information (pg. 171)

- b. NRPM proposes adding three additional elements of consent that would be included in the informed consent form and process (pg. 173)
  - 1. Subjects must be informed that biospecimens may be used for commercial profit and whether the subject will share in this commercial profit
  - 2. If clinical relevant research results will or will not be disclosed
  - 3. Establish an option to consent or refuse consent to investigators re-contacting the subject to seek additional information or biospecimens or to discuss participation in another research study.

**7. Broad Consent to the Storage, Maintenance and Secondary Research Use of Biospecimens and Identifiable Private Information (pg. 175)**

- a. Proposes to allow broad consent to cover the storage or maintenance for secondary research use of biospecimens and identifiable private information. Requirements for broad consent would include several of the basic and additional elements of informed consent as described in 6.a and 6.b of this outline, but not all, and would include several additional requirements (pg. 181)
- b. Consent would not be required for the secondary research use of non-identified private information, such as the use of medical records that have had all identifiers removed
- c. NPRM proposes to require that the broad consent describe the biospecimens and identifiable private information that would be covered by the consent, recognizing that the biospecimens and information to be used in future research studies might be collected after the consent was obtained.
- d. In the non-research context (e.g. biospecimens that were originally collected for clinical purposes), the NPRM proposes (pg. 182) that broad consent for the research use of biospecimens or identifiable private information obtained for non-research purposes would be limited to covering either of both of the following:
  - i. Biospecimens or identifiable private information that exist at the time at which broad consent is sought; and
  - ii. Biospecimens or identifiable private information that will be collected up to 10 years after broad consent is obtained for adult subjects, and for research involving children as subjects, biospecimens or identifiable private information that will be collected up to 10 years after broad consent is obtained or until the child reaches the legal age of consent to the treatments or procedures involved in the research, whichever comes first.
    - 1. The definition of a child is outlined in 45 CFR §46.402(a)
    - 2. At the time the child becomes an adult, the broad consent or permission would no longer be valid and either broad consent would need to be sought from the child turned adult, or the investigator would

need to seek a waiver of informed consent in order to use the individual's biospecimens or identifiable private information

- iii. The proposed element of broad consent includes a requirement that subjects be informed that they may withdraw consent, if feasible. It acknowledges however that information that has been stripped of identifiers might not be traceable (pg. 184)
- iv. If non-identifiable data is posted publicly (e.g. genomic data), there is an element of broad consent that would include an option for an adult subject to consent or refuse consent to the including of the subject's data (pg. 184)
- e. Questions for public comment:
  - i. *Public comment is sought on whether broad consent to secondary research use of information and biospecimens collected for non-research purposes should be permissible without a boundary, or whether there should be a time limitation or some other type of limitation on information and biospecimens collected in the future that could be included in the broad consent as proposed in the NPRM. If a time limit should be required, is the NPRM proposal of up to 10 years a reasonable limitation? Would a limitation related to an identified clinical encounter better inform individuals of the clinical information and biospecimens that would be covered by a broad consent document?*

#### **8. Waiver of Informed Consent or Documentation of Informed Consent (pg. 187)**

- a. NPRM proposed more stringent waiver conditions when research involving biospecimens specifically that:
  - i. There are compelling scientific reasons for the research use of biospecimens; and
  - ii. The research could not be conducted with other biospecimens for which informed consent was or could be obtained
- b. *NPRM considered that a waiver of consent NOT be permissible for secondary research involving the use of biospecimens. The purpose of such a requirement would be to encourage investigators to seek broad consent for such research. This proposal was not included in the NPRM, but public comments are requested on whether such a prohibition to waive informed consent should be included in the final rule (pg. 194)*

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