Not Just Another Acronym:

What the NPRM Could Mean for You

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October 27th 2015
What is the NPRM?

• **Notice of Proposed Rulemaking:**
  – Revisions to the Common Rule for the Department of Health and Human Services and 16 other federal agencies
  
  – Revisions intended to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators

http://www.hhs.gov/ohrp/humansubjects/regulations/nprmhome.html
The Process

Fall 2011
- Advanced Notice of Proposed Rulemaking (ANPRM)
- 90-day comment period and then OHRP review of comments

Fall 2015
- Notice of Proposed Rulemaking (NPRM)
- 90-day comment period and then OHRP review of comments

????
- FINAL RULE
There’s A Lot!!!

• What’s **REVISED**?
  – 2° Use of Biospecimens/Data
  – Exemptions
  – Elements of Consent
  – Waivers of Consent
  – Continuing Review
  – Minimal Risk Definition /Expedited Review
  – IRB Operations
  – IRB Review of Grant Applications

• What’s **NEW**?
  – Exclusions
  – Privacy Safeguards
  – Broad Consent
  – Public Posting of Consent Forms
  – Single IRB Review for Multi-Site Research
  – Extend the Common Rule to all Clinical Trials
2° Use of Biospecimens

• Current
  – De-identified/Anonymous – not human subjects
  – Identified – exemption or expedited with waiver of informed consent

• NPRM Proposal
  – Change definition of human subject to add “obtaining, use, study, or analysis of biospecimens”

• Why?
  – Growing body of literature shows that in general people prefer to have the opportunity to consent (or refuse to consent) for research involving their biological material
# 2° Use of Biospecimens

<table>
<thead>
<tr>
<th>Current</th>
<th>NPRM</th>
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<tbody>
<tr>
<td>Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains:</td>
<td>Human subject means a living individual about whom an investigator (whether professional or student) conducting research:</td>
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<tr>
<td>1) Data through intervention or interaction with the individual</td>
<td>1) Obtains data through intervention or interaction with the individual, and uses, studies, or analyzes the data;</td>
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<tr>
<td>2) Identifiable private information</td>
<td>2) Obtains, uses, studies, analyzes, or generates identifiable private information;</td>
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<td></td>
<td>3) Obtains, uses, studies, or analyzes biospecimens</td>
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2° Use of Biospecimens

• Require consent for any 2° use of biospecimens, regardless of identifiability
  – Consent does not need to be specific, can be **BROAD CONSENT** for storage and future unspecified research

• **What does this mean for you?**
  – Storage and 2° use of biospecimens collected during research…broad consent documented through research consent
  – Storage and 2° use of clinical samples…more complicated
    • Broad consent implemented in clinical setting?
    • Other mechanism?
2° Use of Biospecimens

• NPRM Alternative Approaches
  – A biospecimen is only considered a human subject for whole genome sequencing
  – A biospecimen is only considered a human subject for particular technologies

• Lots of questions remain in the NPRM
Exclusions

• Current
  – Determination either **not** human subjects and/or **not** research
  – Does not require IRB review, but can be confirmed by an IRB

• NPRM Proposal
  – Outlines 11 specific exclusions, but there may be others
  – No regulatory requirements and no review
    • Investigators self-determine whether their research is excluded

• Why?
  – Common Rule criticized for not being specific, and leaving interpretation to the many IRBs
  – Reclassify certain research from exemption to exclusion
  – Proposed rule would eliminate the need for any administrative/IRB review
  – Research is “Low-risk”: no physical risk and low probability and magnitude of other risks, once required protections are applied
Exclusions

**NOT Research**

1. Program improvement activities
2. Oral history, journalism, biography, and historical scholarship
3. Criminal justice activities
4. Quality assurance and quality improvement activities
5. Public health surveillance
6. Intelligence surveillance - defense, national, or homeland security

Use of biospecimens okay…still excluded!
Exclusions

Low-Risk, with other Controls

7. (old exemption #2) Educational tests, surveys, interviews, or observation of public behaviors
   • Identifiable or sensitive/risky, not both

8. (old exemption #4) Research involving the collection or study of information that has been or will be collected
   • No biospecimens

9. Research conducted by a government agency using government-generated or government collected data
   • Already subject to data security, participant privacy, and notice requirements associated with federal statutes and regulations
Exclusions

Low-Risk, with other Controls
10. Certain activities covered by HIPAA
11. Secondary use of non-identified biospecimens, if it only generates information already known about the individual:
   • Test or assay development/validation
   • Quality assurance/control activities
   • Proficiency testing
Exclusions

• What does this mean for you?
  – It will depend on UR implementation:
    • Investigators could make their own determinations, items that used to require RSRB exemption determination may no longer
  – Clearer guidance about program evaluation and QI/QA

• Lots of questions remain in the NPRM
Exemptions

• Current
  – 6 exemption categories
  – Someone other than the Investigator confirms the determination
  – No further review unless there is a change

• NPRM Proposal
  – 8 exemption categories
  – “Decision tool” created by feds, researchers enter information and exemption confirmed…move forward with their research
  – Some exemptions are subject to new privacy safeguards

• Why?
  – Common Rule criticized for inadequately calibrating the review process to the risk of research…overregulation
Exemptions

**Current**

1) Educational research conducted in educational settings
2) Surveys, interviews, standardized educational tests, observation of public behavior (identifiable or sensitive, not both)
3) Surveys, interviews, standardized educational tests, observation of public behavior in public officials
4) 2° use of existing data/specimens (can not record identifiers)
5) Evaluation of public benefit or service programs
6) Taste and food quality evaluation

**NPRM**

1) Educational research conducted in educational settings
2) Evaluation of public benefit or service programs
3) Benign interventions with collection of data from adults
4) Taste and food quality evaluation
5) Surveys, interviews, standardized educational tests, observation of public behavior (identifiable and sensitive)
6) 2° use of identifiable, private information
7) Storage or maintenance of biospecimens or identifiable private information for 2° use
8) 2° use of biospecimens or identifiable private information where broad consent has been sought and obtained
Exemptions

Documentation only

1. *(old #1)* Educational research conducted in educational settings, as long as:
   - Not likely to adversely affect the student’s learning
   - Not likely to adversely affect the teacher’s assessment
   - **NPRM Questions** about notification, parental permission, broad consent like with biospecimens???

2. *(old #5)* Evaluation of public benefit or service programs, research conducted or **supported** by a federal department or agency
   - Requires department/agency disclosure on website
Exemptions

Documentation only

3. *(new)* Research involving benign interventions (temporary and painless, with no lasting negative impact) in conjunction with the collection of data from an adult subject
   - Data collected without identifiers
   - Disclosure would not put the subject at risk

4. *(old #6)* Taste and food quality evaluation and consumer acceptance studies
NEW Privacy Safeguards

PICK ONE:

• Already complies with HIPAA
• Complies with the privacy safeguards to be created by the HHS Secretary (standards will be designed to be readily implemented by an individual investigator, and involve minimal cost and effort to implement).
Exemptions

Documentation and *New* privacy safeguards

5. *(new, but similar to old #2)* Research involving educational tests, surveys, interviews, or observation of public behavior, information can be identifiable and sensitive
   • No consent but “sufficient information”

6. *(old expedited #5 with waiver of consent)* Secondary research use of identifiable private information
   • No consent but “prior notice given”
   • Prohibitions on re-use of the information
Exemptions

Documentation, New privacy safeguards, Broad consent, Limited IRB review

7. *(old expedited #5 with waiver of consent)* Storage or maintenance of biospecimens or identifiable private information for secondary research use

8. *(old expedited #5 with waiver of consent)* Secondary research use of biospecimens or identifiable private information where broad consent has been sought and obtained
   • If individual results are returned to subjects…can not be exempt
Exemptions

• **What does this mean for you?**
  – It will depend on UR implementation:
    • Investigators could make their own determinations…federal “decision tool” or ROSS
  – Items that used to **require** RSRB review and approval may no longer
  – But, what does this mean…
    • Sufficient information (Information letter)??
    • Prior notice given???
    • BROAD CONSENT???
Broad Consent

• Current
  – 2° use of biospecimens and data
    • Not human subjects
    • Exempt
    • Expedited with a waiver of consent

• NPRM Proposal
  – Biospecimens: Broad consent required (no waivers)
  – De-identified data: Excluded
  – Identified Data: Exemption with “prior notice” or “broad consent”

• Why?
  – Respect for Person: Some critics, including potential and former research subjects, object to research performed on a person’s biospecimens or information without consent.
  – Scientific Need: Investigators and patient advocacy groups concerned that obtaining individual consent for each separate research study will inhibit research and create unmanageable logistical demands, making valuable research impossible
Broad Consent

• Required for 2° storage, maintenance, and future unspecified use of biospecimens or identifiable private information

• Written broad consent required for biospecimens; Oral for private information (some cases)
  – HHS Secretary to create template…MUST USE!

• Limited IRB review of the consent process in the non-research context ("Institutional protocol")

• Must require the possibility to withdraw consent, when feasible

• Public posting of non-identifiable data
  – When relevant, individuals would be given an option to consent or refuse to consent to the inclusion of their data, with the removal of certain identifiers, in a publicly available database
Broad Consent

• Initially created through research
  – Consent will cover whatever is created as part of that research

• Initially created clinically
  – Adults: Consent will cover what is currently existing and anything for the next 10 years.
  – Children: Parental permission will cover what is existing and anything for the next 10 years or until the child turns 18, whichever comes first
Broad Consent

• **What does this mean for you?**
  – 2° use of research samples – include **written** broad consent with every study storing samples
  – 2° use of clinical samples (even discarded tissue)
    • include **written** broad consent with every study storing samples
    • URMC needs to develop mechanism to obtain, track, and maintain
  – Oral consent can be used in some situations with identifiable private information, not samples
Consent Form: Public Posting

• Current
  – Investigators create consents
  – IRBs review and approve
  – Subject’s sign and receive a copy

• NPRM Proposal
  – Copy of the final consent form for clinical trials conducted or supported by a Common Rule department or agency will be posted on a publicly available federal web site within 60 days after the trial is closed to recruitment
  – Must include the name of the clinical trial and who to contact

• Why?
  – To increase transparency and facilitate the development of more informative consent forms
Consent Form: Public Posting

• **What does this mean for you?**
  – Similar to ClinicalTrials.gov??
  – Sponsors/agencies/investigators will be required to do this
  – Do we need to audit???
Consent Form: Required Elements

• Current
  – Informed consent to participate in research is obtained
  – At least 8 specific required elements

• NPRM Proposal
  – Essential information in the beginning of the document
  – Consent only contains required elements (plus HIPAA) all other information in appendix
  – 1 new required element: Future use of data or not
  – 3 new additional elements: Commercial profit, return of results, future contact

• Why?
  – Many claim consent forms have evolved to protect institutions rather than to provide potential research subjects information needed to make an informed decision
  – Growing body of literature that suggests consent forms are too lengthy and complex, adversely affecting their ability to convey the information needed for decision-making
Informed Consent: Required Elements

• *What does this mean for you?*
  – ????????????

  – HHS Secretary to publish future guidance on improving understandability of informed consent
Informed Consent: Waivers

• Current
  – Waiver of Consent: 4 requirements
    • 2° use of identifiable biospecimens or data
    • Deception research
  – Waiver of Documentation of Consent (no signature): 2 situations
    • Telephone, Survey, Interviews, Focus Groups with oral consent/information sheet

• NPRM Proposal
  – No waivers for 2° research with biospecimens.
  – More flexibility for waivers of documentation of consent to be culturally appropriate.

• Why?
  – Respect for persons related to biospecimens
Informed Consent: Waivers

**Current for Waivers of Consent**

- Minimal risk
- Not adversely affect the rights and welfare of the subjects;
- Research could not practicably be carried out without the waiver
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

**Current for Waivers of Documentation of Consent**

- Only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality or
- Research presents minimal risk and no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.
Informed Consent: Waivers

**NPRM**

Waiver

- Minimal risk
- Research could not practicably be carried out without waiver
- If the research involves accessing or using identifiable biospecimens or identifiable information, the research could not practicably be carried out without accessing or using identifiers;
- Not adversely affect the rights and welfare of the subjects;
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

**NPRM**

Waiver for Biospecimens (*NOT REALLY*)

- Compelling scientific reasons for the research use of the biospecimens
- Research could not be conducted with other biospecimens for which informed consent was obtained or could be obtained.

If an individual was asked to provide BROAD CONSENT and refused, an IRB cannot waive consent for either the storage or maintenance for secondary research use, or for the secondary research use, of those biospecimens or information.
Informed Consent: Waivers

**NPRM**

Waiver of Documentation

- Only record linking the subject and the research would be the consent form and the principal risk would be potential harm resulting from a breach of confidentiality

or

- Research presents minimal risk and no procedures for which written consent is normally required outside of the research context

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

**NPRM**

- If subjects are members of a distinct cultural group or community where signing forms is not the norm, it’s minimal risk and provided there is an appropriate alternative mechanism for documenting consent was obtained. Documentation must include a description for why it’s not the norm.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

This waiver does not apply when BROAD consent required and not for FDA-regulated.
Informed Consent: Waivers

• *What does this mean for you?*
  – No more waivers of consent for research with biospecimens…must be written broad consent.
Cooperative Research: Single IRB Review

• Current
  – IRBs have the choice to perform local review or defer to another IRB
  – IRBs do not have FWAs, therefore not held to compliance requirements
    • E.g., WIRB reviews a study for UR, there is an issue with the review, OHRP comes after UR, not WIRB

• NPRM Proposal
  – Mandate all institutions in the US engaged in cooperative research (more than one site) rely on a single IRB (not international)
  – Common Rule departments and agencies have the authority to enforce compliance directly against unaffiliated IRBs that are not operated by an assured institution.

• Why?
  – To enhance and streamline the review process, reduce inefficiencies, and hold unaffiliated IRBs directly accountable for regulatory compliance, without compromising ethical principles and protections
Cooperative Research: Single IRB Review

• Only applies to studies undergoing convened or expedited review

• Only affect which IRB would be designated as the reviewing IRB for institutional compliance with the IRB review requirements of the Common Rule
  – Institutional review still applies

• Policies required to document an institution’s reliance on an external IRB

• Reviewing IRB selected by the funding agency or, if no funding, by the lead institution conducting the study
Cooperative Research: Single IRB Review

• *What does this mean for you?*
  – New processes
  – When RSRB defers:
    • OHSP will still conduct institutional review (*similar* to current WIRB process)
  – When RSRB is the Single IRB:
    • [OHSP Policy 504 - RSRB Reliance for Review](#)
    • UR lead site takes on more responsibilities (e.g. coordination centers)
    • Oversight plans to ensure compliance at other sites, responsibilities related to reporting
  – ROSS Changes???
Continuing Review

• Current
  – IRBs conduct continuing review (CR) of research appropriate to the degree of risk, but not less than once per year.

• NPRM Proposal
  – No CR for minimal risk (expedited) unless reviewer requires
  – No CR for convened review after research/intervention is over (e.g. data analysis only or accessing follow-up clinical data)
  – No CR required when regs require “Limited IRB review”
  – REQUIRE: Annual confirmation that research ongoing
    • Institutions will have significant flexibility in how they implement this requirement

• Why?
  – to reduce or eliminate the need for continuing review in specific circumstances, thereby reducing regulatory burden that does not meaningfully enhance protection of subjects.
Continuing Review

• **What does this mean for you?**
  – No continuing review, but still confirmation research ongoing
  – Not sure exactly how this will be implemented:
    • Remove expiration dates?
    • How to ensure compliance with annual reporting?
    • More QI reviews?
  – No change for submission and review of amendments
  – No change for reporting of research events
    • How to collect summary data on research events normally submitted with continuing review?
Minimal Risk Definition/Expedited Review

• Current
  – Minimal risk is “…the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those *ordinarily encountered in daily life* or during the performance of *routine physical or psychological examinations or tests*.”
  – Minimal risk and on the list of expedited categories = EXPEDITED REVIEW

• NPRM Proposal
  – On the list of expedited categories = Minimal Risk = EXPEDITED REVIEW
  – The list will be re-evaluated at least every 8 years

• Why?
  – to help eliminate ambiguity in the definition, and improve the efficiency and consistency of minimal risk determinations for some activities.
Minimal Risk Definition/Expeditied Review

• *What does this mean for you?*
  – More studies qualify for expedited review??
  – Expedited list will be regularly updated with current technology and procedures
    • Last update was 1998
IRB Operations: Approval Criteria

• Current
  – Expedited and Full board – 8 approval criteria

• NPRM Proposal
  – Limited IRB review for 2° use limited approval criteria (*not all 8*)
  – Clarification to the language for vulnerable populations (remove #8 and clarify #3 – Selection of Subjects)
  – New #8 - if an investigator submits a plan for returning individual research results, the IRB will evaluate the appropriateness of the plan
    • IRBs do not have to determine whether there should be a plan for returning individual research results.

• Why?
  – To eliminate approval criteria determination for 2°use
  – To address an inconsistency
  – To address return of individual research results
IRB Operations: Approval Criteria

**Current**
1. Risk Minimized
2. Risks reasonable to benefits
3. Selection of subject equitable
4. Informed consent sought
5. Informed consent documented
6. Data and safety monitoring
7. Protect privacy, maintain confidentiality
8. When vulnerable, additional safeguards

**NPRM**
1. Risk Minimized
2. Risks reasonable to benefits
3. Selection of subject equitable, additional vulnerability language
4. Informed consent sought
5. Informed consent documented
6. Data and safety monitoring
7. Protect privacy, maintain confidentiality
8. If the investigator proposes a research plan for returning clinically relevant results to subjects, that the plan is appropriate.
IRB Operations: Approval Criteria

• *What does this mean for you?*
  – Not too much, except it now highlights the increasing attention on return of individual research results
Extend the Common Rule

• Current
  – Institutions have the option to apply the Common Rule to all research or just that with federal funding (Check/Uncheck “the box”)

• NPRM Proposal
  – An extension to ensure clinical trials are covered by the Common Rule at US institutions receiving federal money for research, regardless of the study’s funding source

• Why?
  – to ensure studies that pose the most risk to potential subjects are covered by the Common Rule
    • Clinical trials not already covered by the FDA (e.g. surgical trials) will be covered.
Extend the Common Rule

• *What does this mean for you?*
  – Not too much…we already apply the Common rule to all research regardless of funding, so no anticipation of major impact
IRB Review of Grant Applications

• Current
  – IRBs are required to review grant applications

• NPRM Proposal
  – Remove this requirement

• Why?
  – The grant application is often outdated at the time of IRB review and contains detailed information not pertinent to the mission to protect human subjects
IRB Review of Grant Applications

• What does this mean for you?
  – You will not have to submit them
  – We will not have to review them
Questions
References

• OHRP Website: NPRM for Revisions to the Common Rule
  – http://www.hhs.gov/ohrp/humansubjects/regulations/nprmhome.html

• PDF of the NPRM