What is an ANPRM?

• An Advance Notice of Proposed Rulemaking
• Is a published notice in the Federal Register used by the agency to test out a proposal or solicit ideas before it drafts its Notice of Proposed Rulemaking (which announces the intent of an agency to promulgate a particular rule). An agency is not required to publish an ANPRM but may choose to do so.

Overview of Rulemaking Process

RFI → ANPRM → NPRM → Final Rule

public comment → public comment → public comment
Why an ANPRM?

- To solicit input from the public on proposed changes to the regulations.
- Seeks comment on how to better protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators.
- The strategies outlined in the ANPRM are proposals, and will not be implemented without further notice and comment.
- Comments received in response to ANPRM will be posted publically on the web.

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I. Background

- Twenty years have passed since the "Common Rule," was adopted
- Brief history of contemporary human subjects protections
- Since the Common Rule was developed, the landscape of research activities has changed dramatically; marked increase in the volume of research.
- The rapid growth and expansion of human subjects research has led to questions about whether the current regulatory framework is adequate and appropriate.
I. Background

Indications of a need for revision
• Institute of Medicine
• U.S. Government Accountability Office
• 2001 report of the National Bioethics Advisory Commission
• Others

II. Risk Based Protections
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Current regulatory framework: tiers of review:

• Review by a convened IRB—Most studies greater than minimal risk (and some that are minimal risk)
• Expedited review --categories of research eligible for such review, and no more than minimal risk.
• Exempt --six categories exempted from IRB review altogether

II. Risk Based Protections

Criticism of this framework for review

• Attempts to match the level of review to the type of risks posed by a study in a less than ideal manner. (surveys unlikely to lead to any harm to subjects undergo review by a convened IRB.)
• Some of the lines drawn between review categories are vague and difficult to apply.
• Different levels of review are sometimes required by different IRBs for the same study.

II. Risk Based Protections
Potential Refinements

• Establishing mandatory data security and information protection standards
• Revising the rules for continuing review
• Mandatory regular updating of the list of categories of research that may be reviewed in an expedited manner
• Revising the regulations regarding studies currently considered exempt
• Generally requiring written consent for research use of any biospecimens collected for clinical purposes
II. Risk Based Protections
A New Mechanism for Protecting Subjects From Informational Risks

- Mandatory standards for data security and information protection whenever data are collected, generated, stored, or used.
- Level of protection required by these standards would be calibrated to the level of identifiability of the information.
- Based on the standards of identifiability under the HIPAA Privacy Rule.
- IRB would no longer be responsible for assessing the adequacy of a study's procedures for protecting against informational risks.

II. Risk Based Protections
Calibrating the Levels of Review to the Level of Risk

- Convened IRB Review--The requirement that greater than minimal risk research be reviewed by a convened IRB would not be changed --continuing review not required for certain data analysis or f/u activities.
- Revise Approach to Expedited Review-proposals: (1) Revising the criteria that make research studies eligible for expedited review, (2) eliminating the requirement of routine annual continuing review of expedited studies, and (3) streamlining submission requirements.

Eligibility for Expedited Review-proposal:

- Update list of research activities that qualify for expedited review; mandate periodic review and update of list.
- Presumption that a study which includes only activities on the list is a minimal risk study and should receive expedited review (reviewer option to send to convened IRB).
- Considering whether a study eligible for expedited review should be required to meet all of the criteria for IRB approval at 45 CFR 46.111.
II. Risk Based Protections
Calibrating the Levels of Review to the Level of Risk

Eliminating Continuing Review of Expedited Studies
- Default -- no continuing review for studies that qualify for expedited review.
- Researchers would still be obligated to obtain IRB approval for changes to a study and to report to the IRB unanticipated problems, etc.
- Reviewer could make a specific determination (w/justification) about why continuing review is appropriate for that minimal risk study, and frequency

Streamlining Documentation Requirements for Expedited Studies
- Current: same documents for review of expedited as convened IRB studies
- Proposed: standard templates for protocols and consent forms and sample versions of those documents that are specifically designed for use in the most common types of studies would facilitate expedited review; eliminate elements relevant only in studies that pose greater than minimal risks

Moving Away From Concept of Exempt
- Although still not subject to IRB review, these studies would be subject to:
  - new data security and information protection standards
  - in some cases, informed consent would be required.
Given that these studies would no longer be fully exempt from the regulations, they could more accurately be described as "Excused"
II. Risk Based Protections
Moving Away From Concept of Exempt Types of Research Studies That Qualify for the Excused Category

Existing six exemption categories would be retained but expansions considered:

• Limitations specified in the current exempt category 2 would no longer be necessary when conducted with competent adults.
• Include certain types of SBER, conducted with competent adults involving specified types of benign interventions that are known to involve virtually no risk to subjects.
• Limitations specified in the current exempt category 4 would be eliminated.

II. Risk Based Protections
Moving Away From Concept of Exempt Tracking and Auditing Excused Research

Proposed:

• Requirement that researchers register their study with an institutional office by completing a brief form.
• Institution could choose to review some of the submissions at the time they are filed (small %) and if deemed appropriate, require that the study be sent for expedited review or, in exceptionally rare cases, convened IRB review.

II. Risk Based Protections
Moving Away From Concept of Exempt Consent Rules for Excused Research

• Consent practices for studies currently exempt largely unchanged for new Excused category.
• Some changes for Excused research on the use of pre-existing data or biospecimens:
  • written general consent would be required for research use
  • use of pre-existing data
    • collected for non-research purposes, written IC only if identifiable
    • collected for research purposes, written IC always required
II. Risk Based Protections
Moving Away From Concept of Exempt Consent Rules for Excused Research

• In most cases, these consent requirements would have been met when the specimens or data were initially collected.
• Subject would have signed a standard, brief consent form allowing for broad, future research.
• This standardized general consent form would permit the subject to say no to all future research.
• Handful of special categories of research for which subjects could opt out.
• Prospective (collected after reg)
• Waiver of consent may be allowed

II. Risk Based Protections
Moving Away From Concept of Exempt Overall Consequences for Current Review Practices

• Would eliminate the current practice of not allowing researchers to begin conducting such minimal risk studies until a reviewer has determined the study does indeed meet the criteria for being exempt
• Regulations would not require, and in fact, would discourage, having each of these registration forms undergo a comprehensive administrative review prior to commencing the study or even afterward.

III. Streamlining IRB Review of Multi-site Studies
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Current Practice

Common Rule requires that each institution engaged in a multi-site research study obtain IRB approval, but does not require that a separate local IRB at each institution conduct such review. However, in many cases, a local IRB for each institution does independently review the research, resulting in hundreds of reviews for one study. The choice to have multi-site research reviewed by a central IRB, or by another IRB, is voluntary. But institutions have been reluctant to replace review by their local IRBs with review by a central IRB.

Proposal

• Mandating that all domestic sites in a multi-site study rely upon a single IRB as their IRB of record for that study.
• Would only affect which IRB would be designated as the IRB of record for compliance with the IRB review requirements of the Common Rule.
• Would not relieve any site of its other obligations to protect human subjects.
• Would not prohibit institutions from choosing to conduct additional internal ethics reviews (and may be discouraged).

Note:

• Appropriate accompanying changes would be made in enforcement procedures to hold external IRBs directly accountable for compliance with certain regulatory requirements.
• Being considered only for domestic sites in multi-site studies.
• Wouldn’t apply for device studies.
IV. Improving Informed Consent

Current Practices
• Generally must obtain and document the subjects’ informed consent to participate in research.
• ICDs must include at least eight specific items of information.
• Criticism of the amount of time IRBs devote to editing ICDs and the failure to include some of the most important information that a person would need to make an "enlightened decision" to enroll in a research study.
• Some have excessive length and reading level.

Improve Consent Forms—Proposal
• Prescribing appropriate, specific content that must be included in consent forms;
• Restricting content that would be inappropriate to include in consent forms;
• Limiting the acceptable length of various sections of a consent form;
• Prescribing how information should be presented in consent forms;
• Reducing institutional "boilerplate" language in consent forms; and
• Making standardized consent form template available.
### IV. Improving Informed Consent

#### Waiver of IC or Documentation of IC in Primary Data Collection

- Currently: CR allows for waiver of IC or documentation of IC but many find the criteria vague, applied haphazardly, or inadequately flexible.
- ANPRM requests comments on the waiver criteria and improvements

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#### Strengthening Consent Protections

Re Reuse or Additional Analysis of Existing Data and Biospecimens

- Criticism of current rules: confusing and consume substantial amounts of researchers' and IRBs' time and resources; concern about research performed on a person's biospecimens without consent.
- Potential changes described in the Excused section (written general consent required for research use; use of pre-existing data collected for non-research purposes, written IC only if identifiable; use of pre-existing data collected for research purposes, written IC always required)

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### V. Strengthening Data Protections To Minimize Information Risks
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Current Rules
- The HIPAA Privacy and Security Rules— but only apply to researchers if part of a HIPAA covered entity and to some researchers that are business associates of a covered entity.
- Privacy Act of 1974 and "Confidential Information Protection and Statistical Efficiency Act of 2002,"(CIPSEA)—but don’t generally apply to grant-funded investigators who are neither Federal employees nor contractors.
- Certificates of confidentiality—do not require investigators to refuse to disclose identifying information and do not protect against unauthorized or accidental disclosures.

Proposal
- Mandate data security and information protection standards that would apply to all research that collected, stored, analyzed or otherwise reused identifiable or potentially identifiable information.
- Considering applying these new protections only to prospective collections of data and biospecimens after the CR changes are implemented.
- Scaled appropriately to the level of identifiability of the data.

V. Strengthening Data Protections To Minimize Information Risks

Consistently Characterizing Info With Respect to Potential for Identification
- Inconsistencies between Common Rule and HIPAA Privacy Rule re identifiability
- Proposal to adopt HIPAA standards regarding what constitutes individually identifiable information, a limited data set, and de-identified information.
- Evaluate the set of identifiers that must be removed for a data set to be considered "de- identified"
- Considering categorizing all research involving the primary collection of biospecimens as well as storage and secondary analysis of existing biospecimens as research involving identifiable information.
V. Strengthening Data Protections to Minimize Information Risks

Standards for Data Security and Information Protection Proposal

- Research involving the collection and use of identifiable data, as well as data in limited data set form, could be required to adhere to data security standards modeled on the HIPAA Security Rule.
- Data could be considered de-identified or in limited data set form even if investigators see the identifiers but do not record them in the permanent research file.
- Provide for periodic random retrospective audits, and additional enforcement too.

<table>
<thead>
<tr>
<th>Excused Research Involving Pre-Existing Information or Biospecimens</th>
<th>Standardized data protections?</th>
<th>Registration of research w/IRB or research office?</th>
<th>Prior review by IRB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written IC req’d for future research w/material collected for non-research?</td>
<td>Yes, Protections include encryption, authorized personnel, breach notification, audits</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes, usually at time of consent for initial research (could be oral for data)</td>
<td>Yes (same rule as “Identifiable info and all biospecimens”)</td>
<td>Yes, which could be obtained during initial collection</td>
<td>No, unless PI plans</td>
</tr>
<tr>
<td>Data could be considered de-identified or in limited data set form even if investigators see the identifiers but do not record them in the permanent research file.</td>
<td>Yes (same rule as “Identifiable info and all biospecimens”)</td>
<td>No consent required</td>
<td>No</td>
</tr>
</tbody>
</table>

VI. Data Collection To Enhance System Oversight
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Currently

• Research agencies collect various types of safety data with the common goal of protecting human subjects, agency requirements vary, resulting in variations between agencies regarding their policies and requirements for the reporting of such data.

• Data collected by each agency is stored in separate datasets inhibiting integrated analyses and comparative studies about the frequency and severity of adverse events.

Proposal

• Standardized, streamlined set of data elements flexible enough to enable customized safety reporting and compliance with agency reporting requirements;

• Build on prototype of a Web-based, Federal-wide portal allowing investigators to submit electronically certain safety data and automatically have it delivered to appropriate agencies and oversight bodies;

• Harmonize safety reporting guidance across all Federal agencies;

• Central Web-based repository.

VII. Extension of Federal Regulations
VII. Extension of Federal Regulations Currently
- An institution engaged in non-exempt human subjects research conducted or supported by any Common Rule agency is required to hold an assurance of compliance approved by the agency conducting or supporting the research (such as an FWA).
- The FWA mandates the application of the Common Rule only to certain Federally funded research projects.
- Most institutions voluntarily extend the applicability of their FWAs to all HS research regardless of support; not mandatory

VII. Extension of Federal Regulations Proposal
- Require domestic institutions that receive some Federal funding from a Common Rule agency for research with human subjects to extend the Common Rule protections to all research studies conducted at their institution.

VIII. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance
VIII. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

Currently

- By 1991, 15 Federal agencies had adopted the Common Rule.
- Each of the agencies that have adopted the Common Rule may issue its own guidance regarding the protection of human subjects.
- Consequently, there are variations in the guidances issued.
- Other Federal laws and regulations have been enacted that relate to the protection of human subjects, (e.g. HIPAA) and the rules are inconsistent with the Common Rule in certain areas.

Request for Comments

How do differences in guidance on research protections from different agencies either strengthen or weaken protections for human subjects or the ability to conduct research?

How to Submit Comments
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Identify by docket ID number HHS-OPHS-2011-0005
• Federal eRulemaking Portal:
  http://www.regulations.gov/
• Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions] to: Jerry Menikoff, M.D., J.D., OHRP, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852.
Comments received, including any personal information, will be posted without change to http://www.regulations.gov/

Office for Human Research Protections
THANK YOU for protecting Human Subjects!