Welcome

PRIM&R's Primer on the Advance Notice of Proposed Rulemaking

August 10, 2011
1:00-2:00 PM ET

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ANPRM
Human Subjects
Research Protections
Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators

Goals of this Webinar
- Some sense of urgency: comments due by 5 pm Monday, September 26, 2011
- Review contents of the ANPRM
- Encourage you to submit comments
- Encourage you to spread the word to other stakeholders

Agenda
- How does the ANPRM figure into the process?
- Review of the ANPRM Sections that provide:
  - Context
  - Specific proposals for consideration
The Process


Open Comment period
Comments reviewed

Open Comment period
Comments reviewed

NOTE: All comments will be posted without change to http://www.regulations.gov

Sections of the ANPRM

- Section I
  - Background – why and why now
- Sections II – VIII
  - The meat of the notice
- Section IX
  - Request for information and comment
  - How to submit comments

Section I: Background

- History of regulations
  - 1947 Nuremberg Code
  - 20 years since Common Rule
- The evolving face of research
  - Increased volume
  - Heterogeneity of sites
  - Multi-site research
  - Different focus; e.g., genetics with huge focus on biospecimens and data
Section I: Background

In this context, 7 concerns are identified:

1. Inadequate calibration of risk to type of review
2. Inefficiencies of multiple IRB review for multisite
3. Questions about informed consent form/practice
4. Change in nature of risks/benefits in research
   a. Genetic information, biospecimens, data
5. Monitoring and evaluation of current system
6. All research subjects not protected
7. Lack of regulatory harmonization

Two themes:

- “Variety of bureaucratic procedures that seem to do little to protect research participants, yet consume substantial resources”
- “…current regulations could be doing a significantly better job in protecting research subjects”

Section I: Background

Seven proposals to respond to these seven concerns:

- Sections II-VIII
- “Fundamental goal to enhance the effectiveness of the research oversight system by:
  - Improving the protection of human subjects while also reducing burdens, delays, and ambiguity for investigators and research subjects”
  - Focus on higher-risk research
Sections II-VIII

II. Ensuring risk-based protections
III. Streamlining IRB review of multi-site research
IV. Improving informed consent
V. Strengthening data protections to minimize information risks
VI. Data collection to enhance system oversight
VII. Extension of Federal Regulations
VIII. Clarifying and harmonizing requirements and Agency guidance

Proposals are presented
☐ Remember, these are only proposals
☐ List of questions for your consideration
☐ Total of 74 questions
☐ Respond to as many as you like

NOTE:
Your comments do NOT have to be limited to the questions

Section II
Ensuring Risk-Based Protections
Section II
Ensuring Risk-Based Protections
5 potential refinements

- Goal: ensure that protections are commensurate with the level of risk
- The refinements
  - Establishing mandatory data security and information protection standards
  - Revising the rules for continuing review
  - Revising the regulations regarding expedited review
  - Revising the rules for exempt studies
  - Requiring consent for biospecimens

Section II
Ensuring Risk-Based Protections
2 Specific Proposals

II.A. A new mechanism for protecting subjects from informational risk
II.B. Calibrating the levels of review to the level of risk
  1. Full convened IRB review
  2. Revised expedited review
  3. Moving away from the concept of Exempt

Section II.A.
New mechanism for protecting subjects from informational risks

- “Standardized data protections, rather than IRB review, may be a more effective way to minimize informational risks”
  - “Establishing mandatory data security and information protection standards for identifiable information and rules protecting against inappropriate re-identification...to minimize informational risks and thereby eliminate the need for IRBs to review informational risks of research.”
Section II.A.
New mechanism for protecting subjects from informational risks

**Proposed:**
- Mandatory standards for data security and information protection whenever data are collected, generated, stored, or used
- Level of protection:
  - Calibrated to level of identifiability and
  - Based on HIPAA Privacy Rule standards
    (see Section V)

Section II.A.
New mechanism for protecting subjects from informational risks

**Proposed:**
- IRB would not be responsible for assessing adequacy of study’s procedures for protection against informational risks
- Risk assessment for determining level of review would NOT include consideration of informational risk

Section II
Ensuring Risk-Based Protections
2 Specific Proposals

II.B. Calibrating the levels of review to the level of risk
  1. Full convened IRB review
  2. Revised expedited review
  3. Moving away from the concept of Exempt
Section II.B.  
Calibrating the levels of review to the level of risk

1. Full convened IRB review
2. Revised expedited review
   a) Eligibility
   b) Eliminating continuing review
   c) Streamlining documentation
3. Moving away from the concept of Exempt
   a) Types
   b) Tracking and auditing
   c) Consent rules
   d) Overall consequences for current review practices

Section II.B.1  
Calibrating the levels of review
Full Convened IRB Review

- Maintains the requirement that research that is greater than minimal risk must be reviewed by a convened IRB

- Proposed change:
  - Default of no continuing review when remaining activities are limited to:
    - Data analysis (even if identifiers retained)
    - Collecting follow-up clinical data from procedures that subjects would undergo as part of clinical care for their medical problems
Section II.B.2(a)(i)
Calibrating the levels of review
Revised expedited review: Eligibility

- Currently: Eligibility for expedited review informed by existing list of allowable activities
  - Concern: List too narrow and too dated

- Proposed
  - Promptly updating current list of activities
  - Mandating standing Federal panel to periodically review and update

Section II.B.2(a)(ii)
Calibrating the levels of review
Revised expedited review: Eligibility

- Currently: Expedited review allowed if all activities appear on the list of eligible research activities and the study is found to be no more than minimal risk
  - Concern: use of the ‘list’ in risk assessment too variable

- Proposed
  - Default presumption that a study that includes only activities on the list is a minimal risk study
    - IRB justification for convened IRB review

Section II.B.2(a)(iii)
Calibrating the levels of review
Revised expedited review: Eligibility

- Currently: Expedited review includes all of 45CFR46.111 criteria

- Proposed
  - Consideration of whether or not all criteria should be required for expedited review
Section II-B.2(b) Calibrating the levels of review
Revised expedited review: Continuing review

- Currently: Continuing review required for all approved studies
  - Concern: Is this necessary for expedited reviews?

- Proposed
  - Consideration of no continuing review for studies that qualify for expedited review
  - Note: this would not change required:
    - IRB approval of study changes
    - Reporting of unanticipated problems and other required reporting

Section II-B.2(c) Calibrating the levels of review
Revised expedited review: Streamlining documentation

- Currently
  - Researchers typically submit same documents for convened IRB review as well as expedited

- Proposed
  - Consideration of templates for protocols and consent forms with sample versions specifically designed for use in the most common types of expedited review studies

Section II.B.3 Calibrating the levels of review to the level of risk

1. Full convened IRB review
2. Revised expedited review
   a) Eligibility
   b) Eliminating continuing review
   c) Streamlining documentation
3. Moving away from the concept of Exempt
   a) Types
   b) Tracking and auditing
   c) Consent rules
   d) Overall consequences for current review practices
Section II.B.3
Calibrating the levels of review
Moving away from the concept of exempt

- Goals of revising category of exempt
  - Increase protections
    - Subject to new data security and information protection standards
    - In some cases consent would be required
  - Broaden the types of studies that would qualify for the exempt category

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Section II.B.3
Calibrating the levels of review
Moving away from the concept of exempt

- NOTE:
  - FDA's statute requires IRB approval of any clinical device investigation; therefore, FDA-regulated studies involving biospecimens will not be eligible for the new Excused category and remain subject to IRB oversight

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Section II.B.3
Calibrating the levels of review
Moving away from the concept of exempt

- “Excused” rather than exempt
  - “Excused” from being required to undergo some form of IRB review
  - But requires:
    - Data security and information protection standards
    - In some situations informed consent
Section II.B.3
Calibrating the levels of review
Moving away from the concept of exempt

Subsections

- Types of excused research
- Tracking and auditing
- Consent rules for excused research

Section II.B.3(a)
Calibrating the levels of review
Moving away from the concept of exempt

Types of excused research

Currently: Six exemption categories
- Concern: criteria are not standardly applied and may be too narrow
- Proposed:
  - Review of the 6 categories with clarification so that investigators could readily apply
  - Consideration of expansion of categories
  - Note: all expansions subject to data security and information protection standards

Section II.B.3(a)(1)
Calibrating the levels of review
Moving away from the concept of exempt

Types of excused research

Currently: Category 2
- Research involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
  1. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
  2. Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
Section II.B.3(a)(1)
Calibrating the levels of review
Moving away from the concept of exempt
Types of excused research

- Proposed:
  - Expansion of Category 2
    - If study limited to competent adults*, then delete limitations

* Adults able to provide “legally effective informed consent”

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Section II.B.3(a)(1)
Calibrating the levels of review
Moving away from the concept of exempt
Types of excused research

- Category 2 changed to:
  - Research involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
    1. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
    2. Any disclosure of the human subjects’ responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, or reputation.

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Section II.B.3(a)(1)
Calibrating the levels of review
Moving away from the concept of exempt
Types of excused research

- Result of proposal:
  - If subjects are competent adults, Category 2 excused research has no limitation based on:
    1. The identifiability of the information being collected
    2. The nature of information being collected
Section II.B.3.(a)(2)
Calibrating the levels of review
Moving away from the concept of exempt
Types of excused research

- Proposed: additional types of studies
  - Certain types of social and behavioral research
  - Conducted with competent adults
  - Involving specified types of benign interventions beyond educational tests, surveys, focus groups, interviews and similar procedures
  - That are commonly used
  - Known to have virtually no risk to subjects and
  - Prior review does little to increase protections

Section II.B.3(a)(3)
Calibrating the levels of review
Moving away from the concept of exempt
Types of excused research

- Currently: Category 4
  - “Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.”

Section II.B.3(a)(3)
Calibrating the levels of review
Moving away from the concept of exempt
Types of excused research

- Proposed consideration for Category 4
  - Clarify the definition of “existing” - collected for purposes other than the proposed research
    - Does NOT mean that all of the data or biospecimens exist at the time the study commenced
Section II.B.3(a)(3)
Calibrating the levels of review
Moving away from the concept of exempt
Types of excused research

- **Proposed consideration for Category 4**
  - Remove limitation so that retained identifiers would be allowed, unless there are plans to return research results
    - Note section II.B.3(c): consent for excused research

**Result of Proposed consideration**
- The research use of identifiable as well as de-identified data and specimens that were obtained for purposes other than the research would be in the excused category
  - Note
    - Consent requirements for excused research apply: Section II.B.3(c)
    - FDA-regulated research with biospecimens not eligible for excused category
Section II.B.3(b)
Calibrating the levels of review
Moving away from the concept of exempt
Tracking and auditing

Proposed for consideration:
- Researchers register excused research (brief form) with an institutional office
- Institution could choose to review some at the time of submission (not expected to be common)
- If not in excused category would be sent for IRB review
- Mechanism to track and audit a small number

Section II.B.3(c)
Calibrating the levels of review
Moving away from the concept of exempt
Consent rules for excused research

Currently:
- Consent for exempt research is sometimes obtained: e.g., oral consent for educational studies, surveys, etc.
- No consent required for research using a biospecimen if researcher does not possess information that would allow them to identify that person

Concern:
- Breadth of biospecimen research
- Potential for identifiability of biospecimens

Proposed:
- No change to oral consent with the understanding that at oral consent, broad use of the data collected was part of the oral consent.
Proposed:
Category 4: pre-existing biospecimens
- Written consent required regardless of:
  - Why they were collected – research or non-research purposes or
  - Identifiability of the biospecimen

Implication of proposed:
- Existing Biospecimens
  - Consent required for use of all biospecimens
  - Eliminate biospecimen research currently allowed without consent; e.g.,
    - Discarded clinical specimens without identifiers
    - Identifiable specimens from which identifiers have been removed

Proposed:
- Category 4: pre-existing data
  - If collected for non-research purposes
    - Written consent only if identifiable
  - If collected for research purposes
    - Written consent required – regardless of identifiability
### Section II.B.3(c)

#### Calibrating the levels of review

Moving away from the concept of exempt

**Consent rules for excused research**

**Implication of proposed:**

- **Existing Data**
  - ☐ Consent required for use of data originally collected for research – with or without identifiers
  - ☐ Eliminate current practice of:
    - Obtaining research data with an informed consent that specifies one purpose and then
    - Stripping the identifiers from data and using it for new purposes not covered in the initial consent

<table>
<thead>
<tr>
<th>Assumption</th>
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<tbody>
<tr>
<td>☐ Standard, brief general consent form allowing for broad future research</td>
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<tr>
<td>- Would allow a person to say no to all research</td>
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<tr>
<td>- May have to consider &quot;check-off boxes&quot; for particular areas of research</td>
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<tr>
<td>- NOTE: if oral consent allowed at initial collection – envision that broad consent also obtained</td>
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### Section II.B.3(d)

**Calibrating the levels of review**

Moving away from the concept of exempt

**Overall consequences**

- Eliminate current practice of reviewer determining exempt status
  - ☐ Not required by Common Rule
  - ☐ Results in delays without added significant protections
- **New process**
  - ☐ Researchers file with institution or IRB brief registration form (e.g., investigator, purpose)
  - ☐ Researcher can then begin
  - ☐ Administrative review of forms discouraged
Section II
Ensuring Risk-based Protections

II.A. A new mechanism for protecting subjects from informational risk
II.B. Calibrating the levels of review to the level of risk
   1. Full convened IRB review
   2. Revised expedited review
      Questions 1 - 13
   3. Moving away from the concept of Exempt
      Questions 14 - 29

Section III
Streamlining IRB review of multisite studies

Currently:
- Each institution engaged in the research must have IRB approval – BUT – it does not have to be local review
- Multi-site research is often/routinely reviewed by multiple IRBs

Concern:
- Unnecessary duplication without added benefit
- Delay of research
Section III
Streamlining IRB review of multi-site studies

 Proposal

 Mandate that all domestic sites in a multi-site study* rely upon a single IRB as their IRB of record for the study

* Would not apply to FDA regulated device trials: FDA statute requires local IRB review

NOTE:
- Relevant local contextual issues (e.g., investigator competence, site suitability) can be addressed through mechanisms other than local IRB review
- This would not relieve any site of its other obligations under the regulations to protect human subjects
- Local sites could perform ethical review – but this would NOT be the formal IRB regulatory review

QUESTIONS 30 – 34
Section IV
Improving informed consent

THREE Subsections

A. Improving consent forms
B. Waiver of informed consent or documentation of informed consent in primary data collection
C. Strengthening consent protection related to reuse or additional analysis of existing data and biospecimens

Section IV.A.
Improving informed consent

Improving consent forms

- Concerns:
  - Too long
  - Too legalistic
  - Too high a reading level
  - Not informative
Section IV.A.
Improving informed consent
Improving consent forms

- Considering:
  - Prescribing content that must be included
  - Restricting content that is inappropriate
  - Limiting the length of various sections of the form
  - Prescribing how information should be presented
    - E.g. At the beginning vs an appendix
  - Reducing institutional boilerplate
  - Making available standardized consent form templates

- Questions 35 - 40

Section IV.B.
Improving informed consent
Waiver of informed consent or documentation in primary data collection

- Currently:
  - 45CFR46.116(d) - 4 criteria for waiver of IC
    - Concern: Too vague and no standard application
  - 45CFR46.117(c) – waiver of documentation
    - Concern: Not flexible enough

- Comments and recommendations requested
  - Q41: What changes to the regulations would clarify the current four criteria for waiver of IC and facilitate consistent application
  - Q42: When oral consent is permitted, what information should be presented? Are all elements of IC (45FR46.116) necessary?
Section IV.B. Improving informed consent
Waiver of informed consent or documentation in primary data collection

- Comments and recommendations requested
  - Q43: Are there additional circumstances under which it should be permissible to waive the usual requirements for obtaining or documenting IC?
  - Q44: Are there types of research involving surveys, focus groups, or other similar procedures in which oral consent without documentation should not be permitted? What principles or criteria distinguish these cases?

Section IV.C. Improving informed consent
Strengthening consent protections related to reuse or additional analysis of existing data and biospecimens

- Concerns
  - Requirements for informed consent for pre-existing data and biospecimens – confusing
  - Potential and former research subjects’ concerns re: research performed on their biospecimens without consent

- Same details as described in Section II.B.3(c)
- Questions 45 - 53
Section V
Strengthening data protections to minimize information risks

A. Consistently characterizing information with respect to potential for identification

B. Standards for data security and information protection

Currently:
- HIPAA Privacy Rule standards for identifiable and de-identified information not aligned with Common Rule
Section V.A.  
Strengthening data protections to minimize information risks  
Consistently characterizing information with respect to potential for identification

- **Considering:**
  - ☐ Adopting the HIPAA standards for
    - Individually identifiable
    - Limited data set
    - De-identified
  - ☐ Categorizing research with biospecimens as research involving identifiable information
  - ☐ QUESTIONS 54 - 57

Section V.B.  
Strengthening data protections to minimize information risks  
Standards for data security and information protection

- **Considering:**
  - ☐ HIPAA data security standards required for identifiable data and limited data sets
    - Encryption, physical safeguards, audit trails and access controls
    - Breach notification
  - ☐ Data considered de-identified even if investigators see the identifiers but do not record them
  - ☐ Periodic random retrospective audits
  - ☐ QUESTIONS 58 - 66

Section VI  
Data collection to enhance system oversight
Section VI
Data collection to enhance system oversight

- Currently
  - Interagency differences in reporting of safety data
  - Lack of connectivity and interoperability that inhibits the conduct of integrated analyses and comparative studies about the frequency and severity of adverse events
  - Lack of data collection re: numbers of participants in various areas of research
    - Question 68 asks for comment

- Proposals intended to simplify and consolidate and not to expand information to be reported
  - Considering:
    - Standardized, streamlined set of data elements compliant with most reporting requirements
    - Web-based, Federal-wide portal for investigators to submit electronically certain data that would then be delivered to appropriate agencies
    - Harmonize safety reporting guidance across agencies
    - Questions 67 - 70
Section VII
Extension of Federal Regulations

Currently
- The Federalwide Assurance (FWA) mandates application of the Common Rule only to certain Federally funded research projects
  - Many institutions extend Common Rule to all research
  - Extension is NOT required

Section VII
Extension of Federal Regulations

Considering:
- Domestic institutions that receive some Federal funding for research with human subjects to extend the Common Rule protections to all research at their institution
  - Question 71

Section VIII
Clarifying and harmonizing requirements and agency guidance
Section VIII
Clarifying and harmonizing regulatory requirements and agency guidance

■ Currently
  □ Different laws and regulations that may pertain
    ■ E.g., Common Rule, FDA regs., HIPAA
  □ Different guidance from departments and agencies

Comments and recommendations requested:
  □ Questions 72 - 74

Proposed Changes

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<tr>
<th>Improving effectiveness</th>
<th>Enhancing protections</th>
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<tr>
<td>Distinction between types of risk</td>
<td>Federal oversight expanded</td>
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<td>Note informational risk</td>
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<td>Eliminating some required continuing reviews</td>
<td>Central database for adverse events</td>
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<td>Improved application of expedited review for research posing minimal risk</td>
<td>Informed consent improvements</td>
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<td>Single IRB review of multisite studies</td>
<td>Written consent for use of biospecimens</td>
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<td>Harmonization of guidance</td>
<td>Confidentiality protections</td>
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Emanuel and Menikoff. 10.1056/NEJMsa1106942
published July 28, 2011 at NEJM.org
So...What do you think?

- Do you understand the proposed changes?
  - What other information/detail do you need?
- Do the proposed changes:
  - Meet the goals of
    - Improved effectiveness
    - Enhanced protections
  - Provide solutions for some of your biggest problems/concerns?
  - Create new problems
- What did they miss?

Why submit comments

- Because your opinion matters
- Your comments will be read and will inform the next steps.
- If you like it – say so
- If you do not like it – say so
- Do remember that all comments will be posted on a publicly available website

How to submit comments

- Label comments with:
  - Docket ID number HHS-OPHS-2011-0005
- Submit by:
  - Federal eRulemaking Portal
    - http://www.regulations.gov
  - Mail/hand delivery/Courier to:
    - Jerry Menikoff, MD, JD
    - OHRP
    - 1101 Wootton ParkwaySuite 200
    - Rockville, MD 20852
Remember
5 PM ET
Monday, September 26, 2011
is closer than you think!

Questions and Comments
To submit a question, simply click on the Q & A menu at the top of the screen.
webinars@primr.org

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