

PRIM&R's Primer on the Notice of Proposed Rulemaking (NPRM)

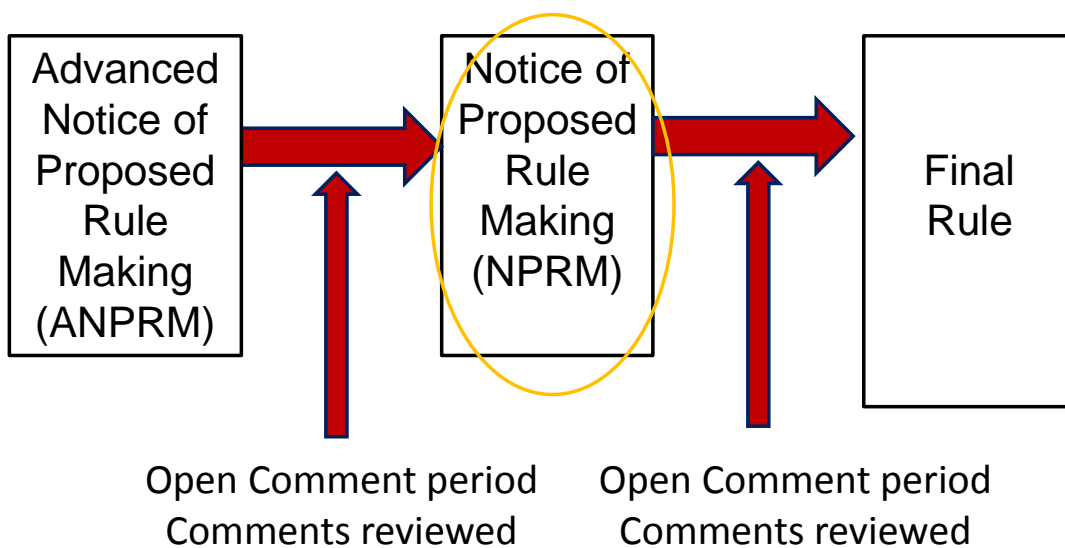
**September 15, 2015
1:00-2:30 PM ET**

The logo for PRIM&R, featuring the letters 'PRIM&R' in a serif font. The ampersand is stylized with a white outline and a small figure of a person inside it. The logo is centered on a dark red background.

PRIM&R

**PUBLIC RESPONSIBILITY IN
MEDICINE AND RESEARCH**

The Process



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

PRIM&R
PUBLIC RESPONSIBILITY IN
MEDICINE AND RESEARCH



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Goals of the Webinar

- General overview of the process, the document and the proposed rule itself
- Highlight some of the major elements
- Identify need for clarification
- Encourage everyone to submit comments
- To start a conversation regarding your reactions to the NPRM
- **CAUTION!**
 - This is NOT the definitive guide to the NPRM
 - Such proposed regulation require detailed comprehensive review
 - We do NOT have the answers - we have many questions

REMEMBER

- This is only a proposal!!!

Agenda

- Introduction to the NPRM
- Scope
 - Jurisdiction over IRBs and institutions
 - Expansion to all clinical trials regardless of funding
 - Transition/implementation
 - Exclusions
- Changes in IRB review
 - Exempt research
 - Continuing review
 - Limited IRB review
 - Single IRB
- Privacy/Security
- Informed consent and Waivers
- Effect on biospecimen research
- Effect on PHI research

Overview of the NPRM

- 80 Fed. Reg. 53933-54061 (September 8, 2015)
- Executive Summary (p. 53933)
- Discussion of Major Proposals (p. 53942)
 - NPRM Goal
 - Current Rule
 - NPRM Proposal
 - What would change?
 - Specific questions for public comment (88 in all)
- Regulatory Impact Analysis (p. 53993)
- Summary of ANPRM Comments (54033)
- Regulatory Text (p. 54045)

Scope of the Proposed Rule

Jurisdiction over IRBs and all clinical trials ___101(a)

- “Institutional Review Boards (IRBs) reviewing research that is subject to this policy” must comply with the regulations
- All clinical trials, irrespective of funding source, if:
 - At an institution that receives *any* federal funding for non-excluded, non-exempt human subject research
 - Not regulated by the FDA
 - Conducted at an institution in the U.S.

Transition Provisions

- Ongoing human subjects research initiated prior to effective date would not need to apply new provisions related to exempt categories, privacy and security, continuing review, single IRB, new required informed consent elements
- Existing collections of biospecimens may be used for research and are not covered by the regulations if non-identified

Proposed Implementation Timeframe

- HHS anticipates that effective date and compliance date will be one year from the final rule publication
- Exceptions:
 - Voluntary application of provisions providing “regulatory flexibility” 90 days after publication
 - Three years to implement consent for all biospecimens and single IRB provisions

Application of the Proposed Rule

Exclusions .101(b)

Three categories of “excluded” activities:

1. Excluded because the activity is “deemed not to be research”
 - An institution’s operational monitoring and program improvement
 - Oral history, journalism, biography, historical scholarship
 - Criminal Justice and criminal investigation activities
 - Quality assurance or improvement activities involving the implementation of an accepted practice to improve health care delivery
 - Public health surveillance
 - Defense and homeland security

Application of the Proposed Rule

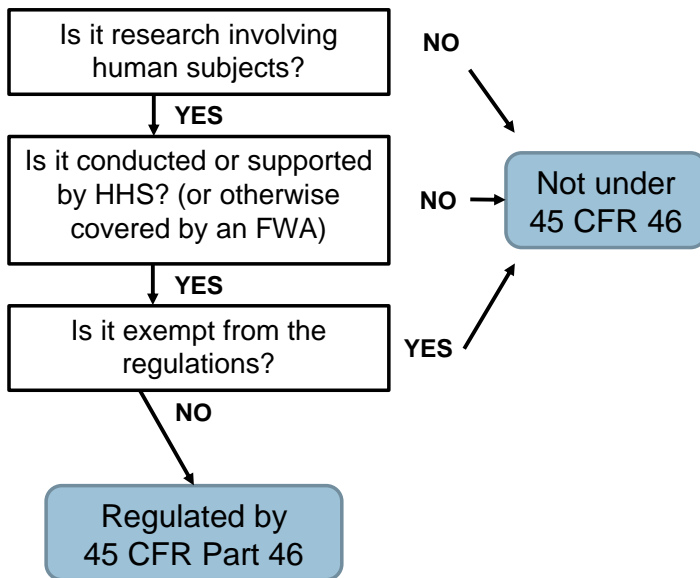
Exclusions __.101(b) (continued)

2. Excluded because they are “considered to be low-risk human subjects research when already subject to independent controls”
 - Tests, surveys, interviews or observation, if subjects cannot be identified OR disclosure would not put subjects at risk OR subject to the Paperwork Reduction Act of 1995/Privacy Act of 1974 (*previous exempt category 2*)
 - Collection or study of information gathered for non-research purposes if the sources are publically available OR not identifiable (*previous exempt category 4, modified*)
 - Research conducted by a Federal agency and subject to the Paperwork Reduction Act of 1995/Privacy Act of 1974
 - Use of identifiable health information regulated under HIPAA Privacy Rule
3. Excluded as a low-risk activity that does not “meaningfully diminish subject autonomy”
 - Secondary use of non-identified biospecimens “to generate information about an individual that already is known” (including validation tests, assays)

Excluded Research

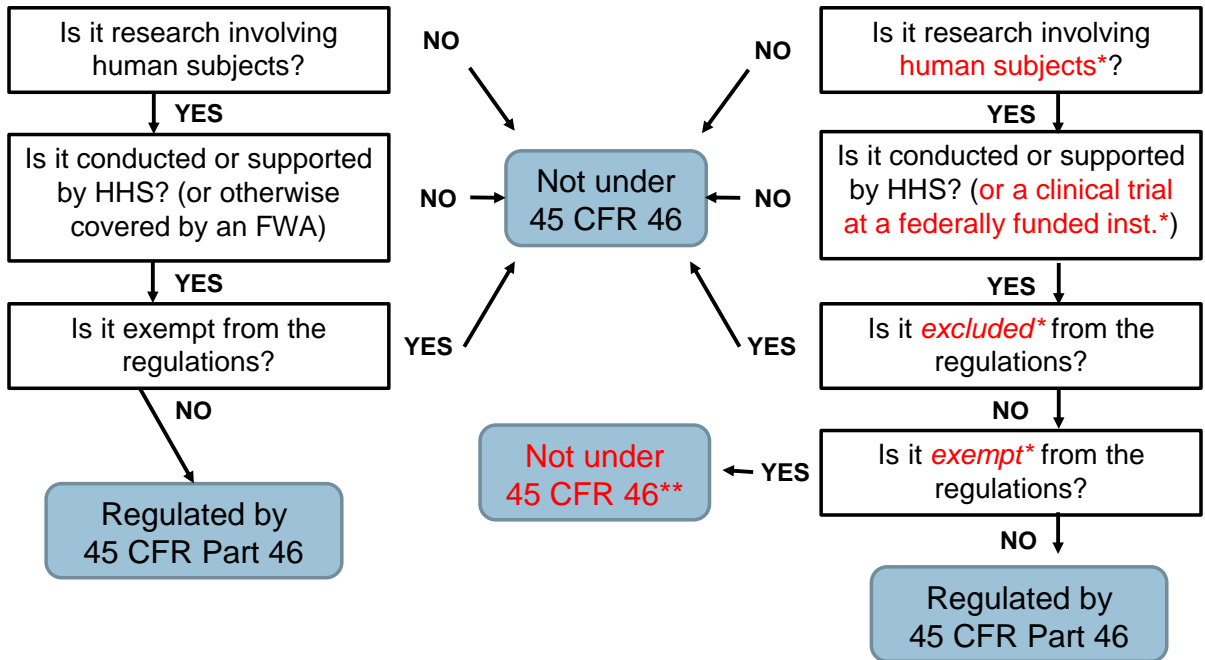
- Excluded from all procedural, recordkeeping, and other requirements of the rule
- Generally excluded even if subject to Subparts B, C, or D
 - Exception: Category 2 (low-risk, when already subject to independent controls)
 - Exclusion at (b)(2)(i) only applies to Subpart D “for research involving educational tests, or observations of public behavior when the investigator does not participate in the activities being observed”

Exclusions and Exemptions



Common Rule Today

Exclusions and Exemptions



Common Rule Today

** may not be entirely excluded from the rule...

Proposed Rule

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Changes to IRB Review Activities

- Exempt research
 - Expansion of categories
 - Determination of exempt status
- Limited IRB review
- Continuing review
- Cooperative research and single IRB

Exempt Research

- Must consider in combination with new category of excluded activities
- Three exempt subcategories
 - Low risk intervention *__.104(d)*
 - Collection of sensitive information *__.104(e)*
 - Biospecimens or identifiable private information for storage or maintenance for secondary research *__.104(f)*

Exempt Research:

Low risk intervention ___104(d)

- **Activities:**
 - Normal educational practices in accepted educational settings
 - Revised version of existing 1st category
 - Federal dept/agency research and demonstration projects designed to evaluate public benefit (must be posted)
 - Benign interventions in conjunction with data collection in adults
 - Subject agrees prospectively and
 - Recorded data not identifiable *or* disclosure would not reasonably place subjects at specified risks
 - If deception – subject must be prospectively informed
 - Taste and food quality/consumer acceptance
- **Note:**
 - Standards for information/biospecimen protection not required
 - Informed consent not required

Exempt Research:

Collection of sensitive information __.104(e)(1-2)

- Activities:
 - Educational tests, surveys, interviews or observation of public behavior (no interventions) if:
 - Information recorded is identifiable directly or through links
 - Enough info for subjects to make informed decision (*commentary*)
 - Secondary research use of identifiable private information that has been or will be collected *for non-research purposes*, if:
 - Prior *notice* to subjects re: research use, *and*
 - Research use limited to specific recipient request
- Note:
 - Does NOT include biospecimens
 - Standards for information protection required

Exempt Research:

Biospecimens and identifiable data for storage/maintenance for secondary research *___104(f)*

- Biospecimens or identifiable private information
 - *___104(f)(1)* Storage or maintenance for secondary research or biospecimens and ID data that has been/will be acquired for other research or non-research purposes
 - *___104(f)(2)* Research involving the use of biospecimens or private information that have been stored

- Required:
 - Exemption must be recorded
 - Standards for information and biospecimen protection
 - Informed consent
 - Biospecimens – written consent: Broad consent with Secretary’s template
 - Data – oral consent (including template elements) adequate for data initially obtained pursuant to excluded or exempt categories; otherwise written consent
 - Limited IRB review

Exempt Research:

Use of biospecimens and identifiable data stores or maintained for secondary research ___104(f)(2)

- Exempt if: broad informed consent obtained – as noted in ___104(f)(1) – *(previous slide)*
- Note: cannot be exempt if investigator anticipates that individual research results will be returned to subjects.
 - Return of results requires:
 - IRB review
 - Routine informed consent

Exempt Research: Process

- Who makes determination?
 - Individual knowledgeable about exemption criteria (e.g., IRB person) or
 - Investigator or other person using the 'yet-to-be-developed' decision tool
- What is this 'decision tool?'
 - One or more may be developed by federal depts/agencies
- Record keeping:
 - IRB must keep records of: name of study, investigator, exemption category applied
 - Completed 'decision tool' is adequate record
 - NOTE: IRB need not review the accuracy of the tool completion

Limited Review __.111(9)(i-ii)

- Supports exemption __.104(f)(1)
- IRB must only determine the following:
 - .111(9)(i) “Procedures for obtaining broad consent for storage, maintenance, and secondary research use of biospecimens or identifiable private information will be conducted in accordance with the requirements of the first paragraph in .116 (*General requirements for informed consent*)
 - .111(9)(ii) “If there will be a change for research purposes in the way the biospecimens or information are stored or maintained, that the privacy and information protection standards at .105 are satisfied for the creation of any related storage database or repository.”
- *The other 8 IRB review criteria do NOT apply*

Continuing Review __.109(f)

- Continuing review not required for
 - Research eligible for expedited review
 - Research is at point of data analysis of identifiable information and/or involves access to follow-up clinical data from procedures undergone as part of standard of care
 - Research reviewed by limited IRB review procedure
- Annual IRB confirmation that:
 - Research is ongoing and
 - No changes that would require continuing review

Cooperative Research __.114

- Cooperative research = more than one institution involved
- Any US institution engaged in cooperative research must rely on single IRB approval for that portion of the research conducted in the US.
 - Unless otherwise required by law or supporting Dept/agency
- Who serves as the single IRB?
 - Selected by Federal department/agency funding or conducting the research
 - If no funding agency, IRB at the lead institution

Cooperative Research___.114

- Note:
 - ___.101(a) explicitly gives Common Rule Dept/agencies “authority to enforce compliance directly against unaffiliated IRBs, not operated by an assured institution.”
 - ___.103(e) “institution and the IRB should establish and follow written procedures identifying compliance responsibilities of each entity.”

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Privacy and Security Standards *_.105*

- Certain exempt research and all non-exempt research must implement “reasonable and appropriate safeguards” to protect biospecimens and identifiable private information
 - IRB review is generally not required
 - HHS will establish specific measures that will satisfy the requirements
 - Institutions and investigators can choose to implement HHS standards or to comply with HIPAA rules (voluntarily or as already required)
- This would apply to IRB records if they contained identifiable private information

Informed Consent and Waivers __.116

- Goal: “to facilitate prospective subjects’ decision about whether or not to participate in a research study, thereby enhancing autonomy”
- Primary changes:
 - Emphasize the need to get essential information to prospective subjects
 - Organize document to provide sufficient detail but also facilitate understanding
 - Present core information first, including only required elements and including all other information in appendices

Informed Consent and Waivers __.116

- Basic elements of informed consent are largely unchanged, with one new element:
 - A statement about whether or not the subject's data will be used for future research studies if the identifiers are removed
- Additional elements are generally unchanged and three elements have been added:
 - Discussion of commercial profit and whether the subject will share in such profit
 - Whether clinically relevant results will be returned to the subject
 - Options for consenting or refusing to consent to be contacted for more information/biospecimens or another research study
- Broad consent for biospecimens will be discussed later

Informed Consent and Waivers __.116

- IRB may approve screening, recruiting, or eligibility determinations without consent with assurance of protections
- Waiver of written informed consent related to biospecimens severely restricted
- Waiver of written informed consent possible if subjects are members of a “community in which signing forms is not the norm”
- Final consent forms must be posted on a federal website

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Effect on Research using Biospecimens and Identifiable Data

- Relevant sections scattered throughout
- General take-home messages:
 - Consent
 - Very limited use of waivers
- If the NPRM becomes the rule:
 - Major change to use of identifiable information
 - Even more major change to use of biospecimens

Biospecimens

- Biospecimens = human subjects
 - Regardless of identifiability
 - Per definition in .102(e)
- In general, consent for use of biospecimens in research is required
 - Routine consent if acquired as part of research study
 - New 'broad' consent for secondary uses of biospecimens acquired for other research or non-research purposes
- Waiver of consent is very limited

Biospecimens are Human Subjects .102(e)

Is the activity excluded from the regs?

YES  NO

.101(b)(1)(i, iii-vi)
.101(b)(3)(i)



Is the research exempt from the regs?

YES  NO

.104(d)(2)
.104(f)(1-2)

Excluded Biospecimen Activities

Deemed not Research

- Internal operational monitoring and improvement
.101(b)(1)(i)
 - Data and biospecimens not collected for this specific purpose
- Criminal justice or criminal investigation .101(b)(1)(iii)
- Quality assurance or improvement activities .101(b)(1)(iv)
 - “Limited to altering the utilization of the accepted practice”
 - “...does not cover the evaluation of an accepted practice itself.”
- Public health surveillance activities .101(b)(1)(v)
- Defense, national security, homeland security
.101(b)(1)(vi)
 - Note: does not include __.101(b)(1)(ii) oral history, biography and historical scholarship

Excluded Biospecimen Activities

Low risk HSR activities that do not meaningfully diminish subject autonomy

- “...secondary research use of a non-identified biospecimen that is designed only to generate information about an individual that already is known.” .101(b)(3)
 - E.g., “...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”

Exempt Biospecimen Activities

- Biospecimens included in 2 of the 6 exempt categories
 - Research and demonstration projects conducted/supported or otherwise subject to approval by a Federal department or agency to evaluate or examine public benefit or service programs. .104(d)(2)

Exempt Biospecimen Activities

___ .104(f)(1-2)

- “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 the proposed research study, or for non-research purposes” if:
 - Limited IRB review .113(a)(9)
 - There is “written consent for the storage, maintenance, and secondary research use” (Broad consent)
 - Oral consent allowed for identifiable data but NOT for biospecimens

Broad Consent - 1

- As in routine consent form
 - Reasonably foreseeable risks/discomforts
 - Benefits that may reasonably be expected
 - How confidentiality will be maintained
 - Whom to contact with questions and concerns
- If applicable
 - May be used for commercial profit – and if subject will/will not share
 - If and how individual results will be returned
 - Option to refuse to consent to be recontacted

Broad Consent – 2

Additional elements __.116(c)

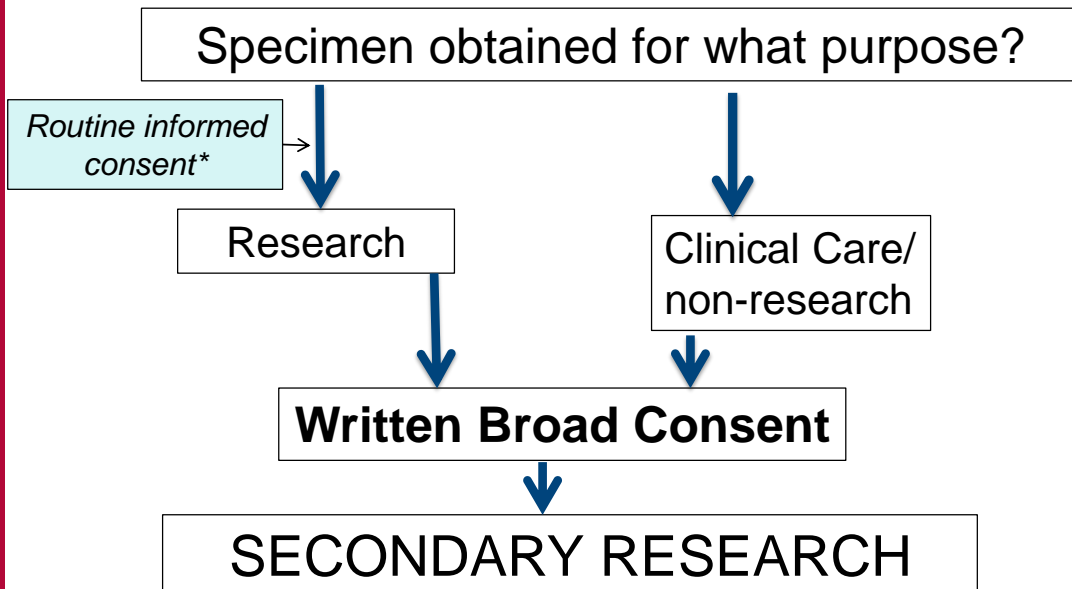
- Types of research, info to be generated by what type of specimens and by what institutions
- Scope of the consent must provide:
 - Types of biospecimens/information collected over what period of time
 - Time period cannot exceed 10 years
 - How long specimens may be used by an investigator
 - Participation is voluntary
 - If applicable –subject will not be informed of specific studies
 - If applicable –use/sharing by multiple investigators, institutions
 - Names of institutions at which specimens collected
 - If relevant, consent/decline inclusion of de-identified data into a public, open database

Broad Consent – 3

Additional elements __.116(d)

- HHS Sec to develop a template for broad consent
- For biospecimens, consent must be written
- Copy of consent given to subject
- Any declined consents must be documented
 - In rare event of an approved waiver – consent cannot be waived for any individual who when asked, declined consent

Biospecimen research

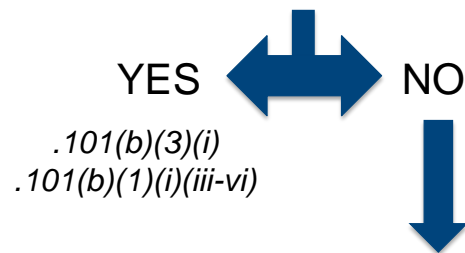


**initial consent could include elements required for Broad Consent*

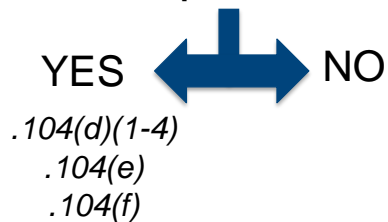
*** rare approval of waivers*

Private Identifiable Data

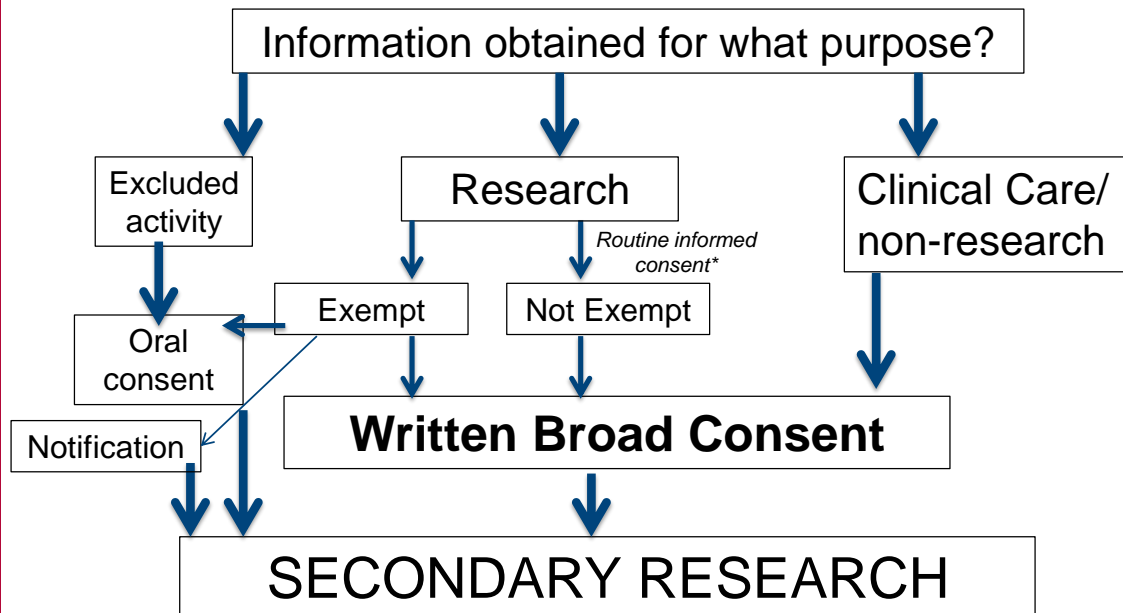
Is the activity excluded from the regs?



Is the research exempt from the regs?



Identifiable Private Information



** initial consent could include elements required for Broad Consent*

*** rare approval of waiver*

What will change?

- For clinical biospecimens and identifiable private information:
 - Broad consent
- For research specimens
 - For primary research question
 - Routine consent
 - For secondary research uses
 - Routine consent with elements of Broad consent
 - Additional broad consent

Rare approval of waivers

On the HHS Secretary's 'To-Do' List

- Maintain guidance re: no more than minimal risk
 - And re-evaluate at least every 8 years .102(j)
- Establish and publish reasonable and appropriate safeguards re: privacy protections
 - And re-evaluate at least every 8 years .105(a)
- Establish and publish list of research for expedited review
 - And re-evaluate at least every 8 years .110(a)
- Templates for 'broad' consent .116(d)(1)

Federal Dept/Agency 'To-Do' Lists

- Scope determinations
 - Final judgment re: what is covered .101(c)
 - Determine what activities require additional protections .101(d)
 - When to substitute foreign procedures .101(h)
- Develop decision tool for exemption determinations .104(c)
- Provide public list of exempt demonstration projects .101(i)
- If funding the research – select reviewing IRB for cooperative research .114(b)(1)
- Provide and post to federal Website copy of final version of the informed consent form .116(h)(1-2)

REMEMBER

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Discussion

To submit a comment for discussion,
simply click on the Q&A menu
at the top of the screen.

Share your comments on the NPRM

- Directly to HHS:
<http://www.regulations.gov/#!docketDetail;D=HHS-OPHS-2015-0008>
- With PRIM&R's Public Policy Committee:
<http://www.primr.org/publicpolicy/nprm/>
(Please note you must be logged in as a PRIM&R member to view this content.)

Thank you!!



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