

Changes to the Regulatory Environment for Research

The Revised Common Rule

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Disclaimer

- This presentation does not constitute legal advice.
- The views expressed are the presenter's own and do not bind the U.S. Department of Health and Human Services or its operational components.

Agenda

- Regulatory background – the Common Rule
- Recent publication of final rule revising the Common Rule

Highlight Reel:

- Changes in scope
- Streamlining IRB oversight
- Informed consent requirements
- Effective and compliance dates



- What now?

IRB Regulatorz



**COMMON RULE REGULATORY
BACKGROUND**

The Belmont Report (1978)



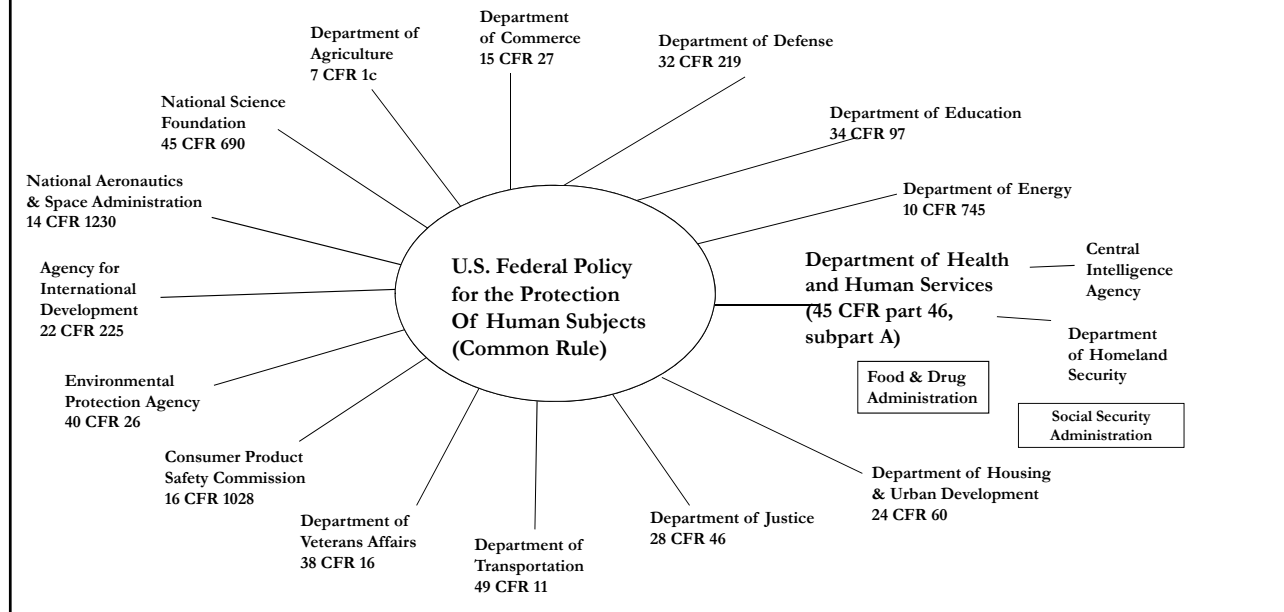
National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

- Respect for Persons
 - Promote individual autonomy
 - Protection of individuals with reduced autonomy
- Beneficence
 - Don't harm; maximize benefits and minimize harms
 - Obligations on investigators (consider benefit/risk of specific project) and society (consider long-term benefits/risks of improving knowledge and advancing science)
- Justice
 - Equitable distribution of research costs and benefits

U.S. Federal Protection of Human Subjects regulations

- U.S. Federal Policy for the Protection of Human Subjects – “Common Rule” (1991)
 - Applies to 18 Federal Departments and Agencies
 - FDA adopted own IRB and informed consent regulations at 21 CFR parts 50 and 56
 - Some Common Rule agencies have adopted additional regulatory protections
 - E.g., HHS human subjects regulations include Subparts B (pregnant women, fetuses and neonates), C (prisoners), D (children), E (IRB registration)

Common Rule Departments and Agencies --current



Determining Applicability of Common Rule

- Research involving human subjects conducted or supported by Common Rule department or agency



- Non-exempt human subject research covered by a Federalwide Assurance (FWA):

- Currently, if research institution voluntarily extends FWA to all research regardless of funding source, OHRP can extend jurisdiction to privately funded research
- **Final Rule update:** Revised Common Rule preamble states plan to eliminate voluntary extension of FWA



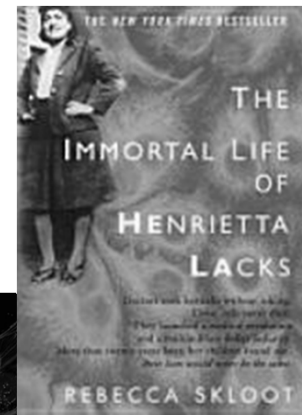
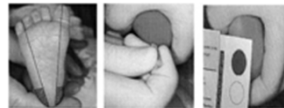
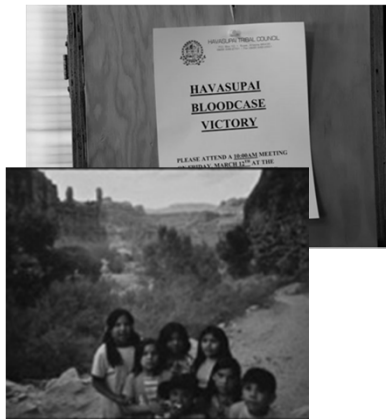
Regulatory Protections

Three basic protections for human subjects:

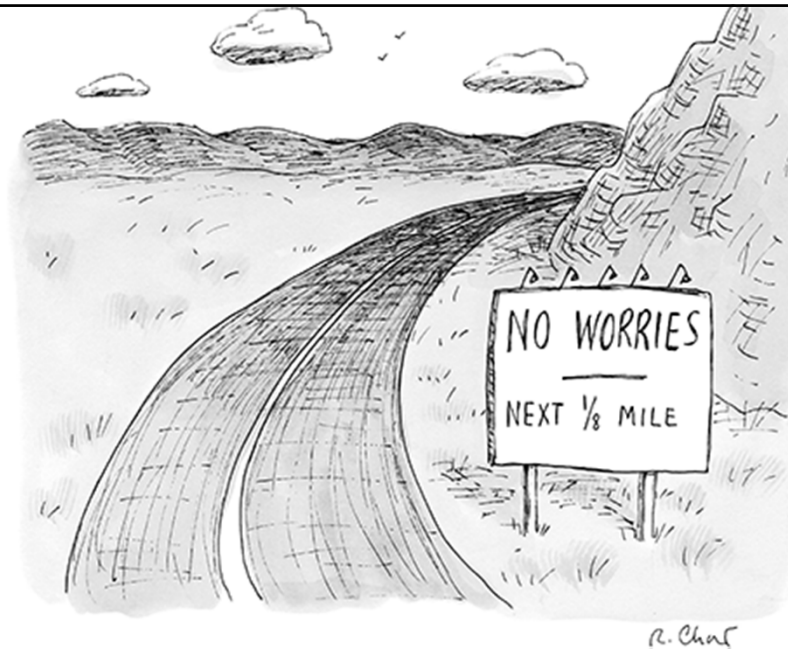
- Institutional Assurances
 - Each institution engaged in human subject research must provide an assurance to the appropriate Dept/Agency that it will comply with the regulations
- Institutional Review Board (IRB) Review
 - Approval necessary prior to beginning human subjects research
- Informed Consent
 - Prior to involvement of human subjects in research
 - May be waived in certain circumstances

Common Rule– NON applicability

- Not applicable to secondary use research involving non-identified information or non-identified specimens



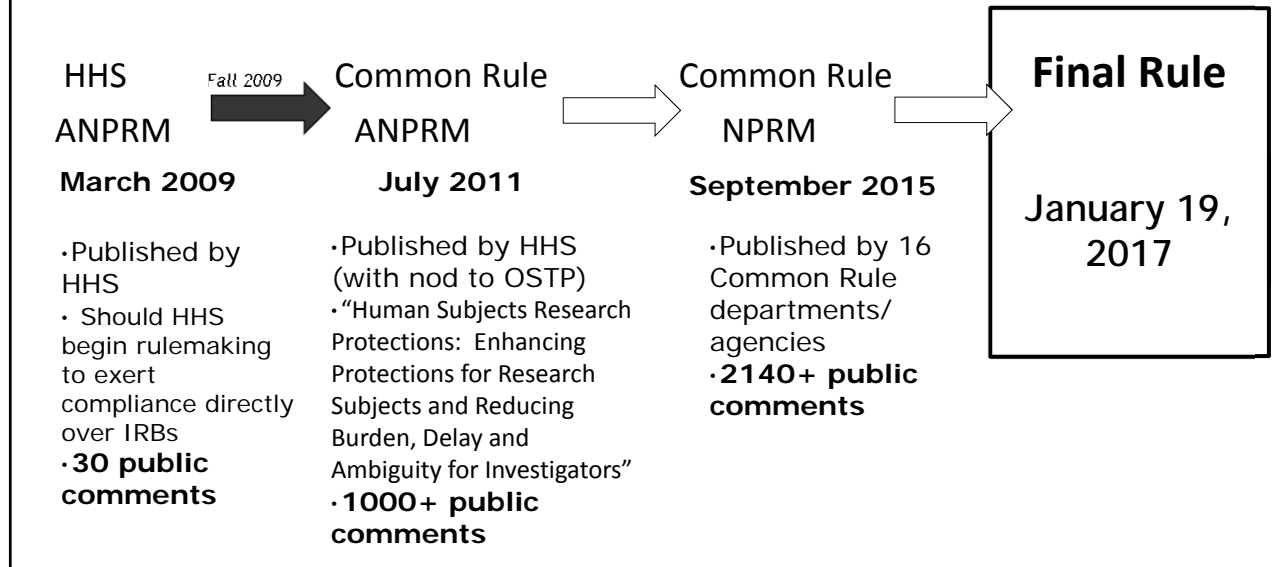
THE ROAD TO THE REVISED COMMON RULE



Why Revise the Common Rule?

- ▶ Changes in volume and landscape of research
- ▶ Revisit the appropriate protections for human subjects, while facilitating valuable research
- ▶ Consideration of how to better triage the level of regulatory protections to the risks of particular research activities
- ▶ Reduce burden, delay, and ambiguity for investigators
- ▶ Alleviate pressure on HRPPs by streamlining IRB review and reducing administrative burden

Common Rule Rulemaking Process



Major NPRM Proposals

- Expand scope to non-identified biospecimens so as to usually require consent for secondary research use
- Expand scope to some non-Federally funded clinical trials
- Explicitly exclude 11 categories of activities from regulation
- Proposed TBD data security standards, consent template, exemption decision tool, minimal risk guidance
- Required sIRB review for US sites of multisite research
- Extend compliance oversight jurisdiction to independent IRBs
- Improved informed consent
 - Allow broad consent for unspecified future research use of already-collected information and biospecimens

The role of public comment



- Specific concern: coverage of non-identified biospecimens
- General concerns expressed regarding
 - Overall complexity and length of the NPRM
 - Lack of availability of key deliverables
 - Proposals give researchers too much leeway re exempt/excluded
- Example comment of the less positive reaction:
 - “...the proposals are **virtually impenetrable** due to opaque language, unclear concepts, the overlapping nature of various elements” and recommended that “HHS conduct a comprehensive re-write of the NPRM through a concerted effort to simplify the proposed changes and to focus efforts on selected issues for which there is broad support”

The revised Common Rule!



- Published January 19, 2017
- **Not yet effective**
- **NOTE:** Current rule applies until revised rule becomes effective

June 1, 2017

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"Give me a couple years, and I can answer your simple question about the new regulations."

#134970409

SCOPE OF THE REVISED COMMON RULE

Changes to "Research": §__.102(l)(1)-(4)

- ▶ Certain carve-outs from definition of research §__.102(l)(1)-(4)
 - ▶ §__.102(l)(1): certain scholarly and journalistic activities
 - ▶ §__.102(l)(2): public health surveillance activities
 - ▶ §__.102(l)(3): collections/analyses for criminal justice or criminal investigative purposes
 - ▶ §__.102(l)(4): authorized operational activities in support of specified missions

Changes to “Human Subject”: §__.102(e)

- New definition of “identifiable biospecimen”
- Reexamination of meaning of identifiable private information and identifiable biospecimens:
 - Consultation with appropriate experts
 - Within 1 year and regularly thereafter (at least every 4 years)
 - Collaboration by Common Rule departments and agencies
 - Interpretation of terms may be changed
- Assessment of whether there are analytic technologies or techniques that should be considered to generate identifiable private information or identifiable biospecimens:
 - Consultation with appropriate experts
 - Within 1 year and regularly thereafter (at least every 4 years)
 - Collaboration by Common Rule departments and agencies
 - Any identified technologies/techniques will be included on list published after notice and comment

New Exemptions Related to Secondary Use Research

- ▶ **Secondary use research** = research using identifiable private information (IPI) or identifiable biospecimens already obtained from the subject for other purposes (e.g., different research, clinical purpose)
- ▶ Exemptions: .104(d)(4), .104(d)(7), .104(d)(8)

Exemptions for secondary use research (no consent required): §__.104(d)(4)

- Secondary use research of IPI or identifiable biospecimens
- New .104(d)(4) [expanded from current exemption .101(b)(4)]:
 - Publicly available;
 - Information recorded by the investigator such that identity cannot readily be ascertained directly or through identifiers; investigator does not contact subjects; investigator will not re-identify subjects;
 - Research involves only information collection and analysis regulated under HIPAA as “health care operations,” “research,” or “public health activities and purposes”;
 - OR**
 - Research conducted by Federal agencies using government nonresearch information if Privacy Act, PRA (with caveat), e-Gov of 2002 apply

New exemption for *storage* for potential secondary use research: §__.104(d)(7)

- Includes new regulatory concepts: “limited IRB review” and “broad consent”
- IRB conducts “limited IRB review” and makes the following determinations:
 - Broad consent for storage, maintenance, and secondary research use of IPI or identifiable biospecimens is obtained in accordance with .116(a)(1)–(4), (a)(6), and (d);
 - Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with .117; **AND**
 - If there is a change made for research purposes in the way the IPI or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and maintain confidentiality of data

New exemption for secondary research *use* of materials for which broad consent was obtained: § __.104(d)(8)

- Broad consent was obtained in accordance with .116(a)(1)-(4), (a)(6), and (d);
- Documentation of informed consent or waiver of documentation obtained in accordance with .117;
- IRB conducts “limited IRB review” and makes the following determinations:
 - when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data (under .111(a)(7)), **AND**
 - research to be conducted is within the scope of the broad consent obtained;
- **AND**
- Investigator does not include returning individual research results to subjects as part of the study plan
 - Note the caveat: “This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.”

Final Rule new concept of limited IRB review

- Only available for purposes of new exemptions
- Only referenced IRB determinations are required
- This is still a form of IRB review! Can’t be done by a non-member
- Can be performed through expedited review (.110(b)(1)(iii))
- No continuing review required (.109(f)(1)(ii))
- If limited IRB review conducted by an external IRB, institution and organization operating the IRB must document institution’s reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure regulatory compliance (.103(e))

STREAMLINING IRB OVERSIGHT



New Jurisdiction Over Independent IRBs (.101(a))

- “Institutions that are engaged in research . . . **and institutional review boards (IRBs) reviewing research that is subject to this policy** must comply with this policy”
 - Provides Common Rule agencies authority to enforce compliance directly against IRBs not operated by FWA
 - Anticipated to reassure institutions using independent IRB because compliance actions can be directed against the IRB responsible for regulatory noncompliance, rather than against the relying institution

New Mandated Single IRB Review: §.114(b)

- U.S. institution engaged in cooperative research must rely on a single IRB approval for the portion of the research conducted in U.S.
 - Cooperative research = research involving more than 1 institution
- The reviewing single IRB must be either:
 - identified by Federal department or agency supporting or conducting the research, or
 - proposed by lead institution , and subject to the acceptance of Federal department or agency supporting the research
 - Final Rule preamble indicates consistency with NIH sIRB policy (published June 21, 2016)

Exceptions to Mandated Single IRB Review

- Two exceptions :
 - Research for which more than single IRB review required by law (including tribal law); or
 - Research for which Federal department or agency supporting or conducting the research determines and documents use of single IRB not appropriate for the particular context

**NIH sIRB policy also includes allowance for exceptions:

- Review by the proposed sIRB would be prohibited by law, regulation, or policy
- Requests for exceptions not based on a legal, regulatory, or policy requirement will be considered if compelling justification for the exception

Changes to Continuing Review (.109(f)(1))

- *Unless IRB determines otherwise, continuing review of research is not required in the following circumstances:*
 - Research eligible for expedited review;
 - Research progressed to the point that it involves only:
 - Data analysis, including analysis of identifiable private information or identifiable biospecimens *OR*
 - Accessing follow-up clinical data from procedures subjects would undergo as part of clinical care

Changes to Expedited Review (.110)

- No change in concept of expedited review procedure
 - Performed by IRB Chair or experienced IRB member designated by Chair
 - Reviewers have all authorities of IRB except disapproval of research
- **Retains expedited review list:** list of categories of research that may be reviewed through expedited review procedure, published by Secretary of HHS
 - Prior rule: research has to be on category on list *and* reviewer had to determine involved no more than minimal risk;
 - Revised rule: research has to be on category on list, *unless* reviewer determines involved more than minimal risk

Related changes to IRB recordkeeping (.115)

- Must document rationale for conducting continuing review when not otherwise required
- Must document rationale for expedited reviewer's determination that research on expedited review list is more than minimal risk
- Must document, for cooperative research, responsibilities an institution and an organization operating external IRB each will undertake to ensure compliance

REVISED INFORMED CONSENT REQUIREMENTS



Revisions to Study-Specific Informed Consent: §.116

- ▶ Begin with key information most likely to assist subject in understanding why or why not to participate; organized and presented to facilitate comprehension
- ▶ Overall, present information in sufficient detail, organization, and presentation to facilitate understanding of why or why not participate
- ▶ Must include either statement:
 - ▶ Identifiers might be removed from IPI or identifiable biospecimens and stripped information or biospecimens could be used for future research studies or given to another investigator for future research studies without additional informed consent; **OR**
 - ▶ Subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies

Revisions to Study-Specific Informed Consent: Additional Disclosures

- ▶ Consent must include either statement:
 - ▶ Identifiers might be removed from IPI or identifiable biospecimens and stripped information or biospecimens could be used for future research studies or given to another investigator for future research studies without additional informed consent; **OR**
 - ▶ Subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies

Revisions to Study-Specific Informed Consent: Additional Disclosures (2)

When appropriate, informed consent must include the following statements:

- ▶ The subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit
- ▶ Whether clinically relevant research results will be disclosed to subjects, and if so, under what conditions
- ▶ For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing

New Allowance for Broad Informed Consent: §.116(d)

- New regulatory allowance for broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens
 - Not study specific, but not “brief” either: 10-12 required elements
- A regulatory flexibility, not an independent requirement
 - So, just waiver of “consent” – no separate waiver of “broad consent”
- Alternatives to broad consent include:
 - Study specific informed consent
 - Waiver of informed consent
 - Using an exemption that does not require broad consent

New “reasonable person” standard

- Study-specific consent: subject must be provided with information a reasonable person would want to have in order to make an informed decision about whether to participate
- Broad consent must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted



Waiver or alteration of informed consent

- Waiver limitation: if individual asked to provide broad consent and refused, IRB cannot waive consent for storage, maintenance, or secondary research use of IPI or identifiable biospecimens
- Alteration limitations:
 - Explicit statement that IRB may not omit or alter any of the requirements at .116(a)
 - IRB may not omit or alter required elements of broad consent
- New waiver/alteration criterion:
 - If research will use IPI or identifiable biospecimens, research could not practicably be carried out without using these in an identifiable format



IMPLEMENTATION OF THE REVISED COMMON RULE

Final Rule's Effective and Compliance Dates

Effective Date of Final Rule: **January 19, 2018**

General Compliance Date: **January 19, 2018**

Compliance Date for mandated sIRB review of cooperative research:
January 20, 2020

Transition Provisions under the Final Rule: §__.101(I)

Prior to January 19, 2018: pre-2018 rule continues to apply

On or after January 19, 2018:

- **Ongoing Research Begun Prior to January 18, 2018:**
 - “Begun” includes research initially approved by an IRB
 - Presumption: pre-2018 rule applies
 - Optional allowance: revised Common Rule instead can apply to a study if:
 - institution makes this determination; &
 - IRB documents this determination
- **Research Begun On or After January 19, 2018:**
 - Revised Common Rule applies

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Pragmatic Implementation Considerations for Research Institutions

- Consent
 - Broad consent process development: tracking will be necessary
 - Utilization of broad consent flexibilities
 - Consider tradeoffs (e.g., no waiver of consent if subject was asked to provide broad consent and refused)
 - Revise consent templates
- IRB review
 - Revise protocol templates
 - Draft appropriate IRB reliance agreements and consider allocation of responsibilities
 - Consider need to realign IRB resources
 - Will new flexibilities be fully implemented or will institutional policy add layers?
- Transition to revised rule
 - Transition existing studies to revised rule, or keep under prior rule?
 - Consider both advantages of new flexibilities (e.g. continuing review) vs. potential application of new requirements (e.g. new informed consent disclosures)

Harmonization Considerations: Common Rule Departments and Agencies

- Required collaboration on guidance (.101(j)):
 - “Federal guidance on the requirements of this policy **shall** be issued only after consultation, for the purpose of harmonization (to the extent appropriate), with other Federal departments and agencies that have adopted this policy, unless such consultation is not feasible”

Harmonization Considerations: FDA regulations

Preamble to revised Common Rule states:

“Finally, it is important to note that, to the extent appropriate, the intent is to ...**consider the need for updates to FDA regulations** and other relevant federal departmental or agency regulations with overlapping scope.”

21st Century Cures Act: Sec. 3023. Protection of human research subjects.

“(a) In general.—In order to simplify and facilitate compliance by researchers with applicable regulations for the protection of human subjects in research, **the Secretary of Health and Human Services...shall, to the extent practicable and consistent with other statutory provisions, harmonize differences between the HHS Human Subject Regulations and the FDA Human Subject Regulations...**

...

(d) Timing.—The Secretary shall complete the harmonization described in subsection (a) not later than **3 years after the date of enactment** of this Act.”

Stay tuned



"These new regulations will fundamentally change the way we get around them."

THANKS for your attention!

QUESTIONS?