

Revised Rule Overview

Harvard University Area Institutional Review Board

HUA-IRB

Presentation adapted from CITI Overview of the Final Rule

Content

- Why a Revised Rule
- What has changed
- What is new
- Decisions that have been made

To note...

- Revised Rule
 - Final Rule
 - 2018 Rule
 - New Common Rule
- Old Rule
 - Pre-2018 Rule
 - Old Common Rule

Introduction

Final Rule to revise the current regulations at 45 CFR 46, Subpart A (Common Rule) was published by U.S. Department of Health and Human Services (HHS) January 19, 2017 in the Federal Register.

Revisions intended to “**modernize, strengthen, and make more effective**” the current system of oversight under the Federal Policy for the Protection of Human Subjects that has been the federal Common Rule since 1991.

Revisions aim to better protect human subjects involved in research, facilitate research, remove ambiguity, and reduce regulatory burden.

Need for Updates

- Large databases, biospecimen repositories, electronic health records, and clinical research networks have spurred new kinds of research
- Revised Rule intended to better manage new broader types of research
 - *Specifically including behavioral and social science research*
- Recognizes the evolving technologies including mobile technologies, the Internet, and the growth in computing power that have changed the scale and nature of information collected
- One of the main purposes of the Revised Rule is to facilitate the conduct of minimal risk research

FDA Harmonization

- The 21st Century Cures Act (2016) requires the Secretary of HHS to harmonize the differences between 45 CFR 46, Subpart A, and the U.S. Food and Drug Administration (FDA) human subject regulations.
- FDA plans to update 21 CFR 50 and 56 as part of the government-wide effort to modernize rules for the involvement of human subjects in research.
- Until an update is issued by the FDA, research organizations, institutions, IRBs, and investigators must comply with the current FDA regulations, as well as the Revised Rule (pre-2018 or 2018 version as applicable) when both sets of FDA and HHS regulations apply.

Guidance Harmonization

- All Common Rule departments and agencies are authorized to issue separate guidance for interpreting and implementing its regulations.
- To promote consistency, the Revised Rule creates a requirement that guidance on the protection of human subjects should be issued only after consultation among the Common Rule departments and agencies.
- Guidance may be issued without consultation when varied missions or differences in statutory authority/scope exist.

Influencing Factors to Revisions

Revisions to the Common Rule were based on a variety of sources, including:

- *Public, stakeholder, and expert comments (for example, SACHRP, individual researchers, and professional organizations)*
- *Advice (including guidance provided by a 2014 National Research Council consensus report, the National Academies of Science, Engineering, and Medicine 2016 report)*
- *Public discussions associated with the President's Precision Medicine Initiative and comments received on the Announced Notice of Proposed Rule Making (ANPRM) and the NPRM*
- *Medicare Access and Children's Health Insurance Program Reauthorization Act of 2015 (Pub. L. 114-10)*
- *Newborn Screening Saves Lives Reauthorization Act of 2014 (Pub. L. 113-240)*
- *National Institutes of Health (NIH) policy on the use of a sIRB for multi-site research*
- *OHRP draft guidance on the required content of consent language for research conducted within the standard of care*
- *FDA's draft guidance on "Use of Electronic Informed Consent in Clinical Investigations"*
- *NIH policy to promote sharing of large-scale human genomic data*

Revised Rule Differs from NPRM

The Revised Rule differs in significant ways from the 2015 Notice of Proposed Rulemaking (NPRM).

The 2015 NPRM received more than 2,100 public comments. The proposals receiving the most comments were those related to human-derived biospecimens (for example, expanded definition of human subject, requirement for broad consent, and tightened criteria for waiver of consent).

Several NPRM proposals are **NOT** being adopted, including:

- *Require that research involving non-identified biospecimens be subject to the Common Rule, and that consent would be needed*
- *Expand the Common Rule to cover clinical trials that are not federally-funded*
- *Concept of “excluded” activities*
- *Standardized privacy and security safeguards for IRB records and identifiable private information and identifiable biospecimens (HIPAA standard)*
- *More restrictive proposed criteria for obtaining a waiver of the consent requirements relating to research with identifiable biospecimens*
- *Require notice to exempt some secondary research including clinical data registries*

Implementation Dates



The new rules were published January 19, 2017.

The new rules are effective one year from publication on January 19, 2018.



All regulated parties must be in compliance from that date onward.



One exception is the compliance date for single IRB (sIRB) review of cooperative research.

Two years are added to the overall transition period for this requirement (January 20, 2020).

Transition Provisions – “All or None”

The transition phase is to minimize burdens for ongoing research.

- *Avoids a requirement for two sets of rules during the life of the research*
- *Two categories of studies – approved (or determined exempt) before effective date or approved (or determined exempt) after effective date*
- *Studies are either subject to compliance with pre-2018 rule or Revised Rule (not both)*

Transition Provisions – “Grandfathered”

Actions taken before the compliance dates are “grandfathered.”

- *Ongoing research studies that were initially approved by an IRB or determined to be exempt before the effective date will not be required to comply with the changes.*
- *Such research may continue to completion or closure without change .*

Harvard University has voluntarily chosen to apply the Revised Rule to pre-2018 **EXPEDITED and **CONVENED IRB** studies on a study-by-study basis. Evaluation will occur at time of continuing review (*a system limitation*)**

Exempt research determinations before revised rule implementation will be left “as is”

Equivalent Protections

- New assurance mechanism eliminates the voluntary extension of the FWA to non-federally funded research
- Non-federally funded research is not covered by the Revised Rule
- Harvard University has chosen to apply the Rule to all research regardless of funding.
 - *Maintains equivalent protections*
 - *Accreditation standard*
 - *Comports with historical practice*

Levels of Review



Definitions

Three new terms were added...

- Clinical Trial
- Written or in writing
- Public Health Authority

Clinical trial

Research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes

- *Harmonizes with NIH*
- *Posting “clinical trial” consent forms on a publicly available federal website (TBD).*

Written or in writing

Refers to writing on a tangible medium (e.g., paper) or in electronic format

- *Intended to clarify that these terms include electronic formats*
- *FDA guidance on electronic consent*

Public Health Authority

An agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

- *Definition for “Public health surveillance activities”*

Revised Terms

Terms were also revised, including:

- *Legally authorized representative*
- *Human subject*
- *Research*

Legally authorized representative

Means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Human Subject

Means a living individual about whom an investigator (whether professional or student) conducting research:

- i. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or*
- ii. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens*

What is “identifiable” ...

- Upon consultation with appropriate experts (including experts in data matching and re-identification)
- A re-examination will take place within 1 year and regularly thereafter (at least every 4 years)

Research - Clarification on what IS NOT research

The core definition is the same but now includes what is NOT research. . .

- Scholarly or journalistic activities
- Public health surveillance activities
- Collection and analysis of information, biospecimens, or records by or for a criminal justice agency
- Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions

Scholarly or journalistic activities

(e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

Public health surveillance activities

Including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onset of disease outbreaks, or conditions of public importance (including trends, signals, risk factors, patterns in diseases, or increased in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man made disasters).

Levels of Review



Exempt Research

- Comprised of various categories
- Contains many new requirements, primarily due to added regulations when using human-derived biospecimens in research and “conditional exemptions” (Limited IRB review)

Subpart Applicability

Specifically states the applicability of the exemption categories to Prisoners (Subpart C) -

- *Changes the former policy to allow the exemptions to apply to Subpart C for research involving a broader subject population, which only incidentally includes prisoners.*
- *This change will permit the exempt secondary research use of information or biospecimens from subjects who are prisoners, if that research is not seeking to examine prisoners as a population or subpopulation.*
- *Intended to allow subjects to continue participation in exempt research if they become “prisoners” during the course of an exempt study.*

Exempt categories of research allow inclusion of Pregnant Women (Subpart B) research, and limited inclusion with Children (Subpart D) research.

Revised Exemptions

Category 1 Revision

- Wording has been modified – research impact on standard classroom experience.
 - “...not likely to adversely impact students’ opportunity to learn required educational content or the assessment of educators who provide instruction.”
- “When appropriate, investigators may provide notice in a manner that is appropriate to the research activity and the cultural context in which it occurs.” §__.101(f)

Category 2 Revision

- This is the former exemption for tests, surveys, interviews, or observation of public behavior.
- Adds “observation of public behavior (including visual or auditory recording)”
- Clarifies “no intervention”

Category 2 Revision Cont'd

- Adds a new subcategory for potentially sensitive or harmful identifiable private information from adults if an IRB conducts a **limited IRB review**.
- So, if you are collecting data that is:
 - 1) not identifiable, OR
 - Children **OK**: educational tests, observation **OK**. No interaction.
 - 2) not damaging, OR
 - Children **OK**: educational tests, observation **OK**. No interaction.
 - 3) identifiable (may include potentially sensitive or harmful)
 - **Limited review** –additional data considerations to protect rights/welfare
 - **NO** children

Category 4, Secondary Research For Which Consent is Not Required

- Adds to the former “publicly available and de-identified” category.
 - *Collection and analysis of identifiable health information regulated by HIPAA.*
 - *Certain federal research using government-generated or government-collected information obtained for non-research activities.*
- Unlike the pre-2018 rule exemption for secondary use, there is now **no** requirement that the information and biospecimens must be pre-existing at the time that the investigator begins the research.
 - *Prospective and ongoing collection for secondary use is permitted.*

New Exemptions

- Benign behavioral interventions (Category 3) – *this is a replacement of a previous category*
- Storage or maintenance for secondary research for which **broad consent** is required (Category 7)
- Secondary research for which **broad consent** is required (Category 8)

Category 3, Benign Behavioral Interventions

- Exemption for research involving benign behavioral interventions for collection of information from adults.
 - *Only for behavioral research, not biomedical research.*
 - *Children are specifically excluded*
- “Benign behavioral interventions”
 - *“Brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing.”*
- Allows collection of potentially sensitive or harmful identifiable private information from adults if an IRB conducts a “**limited IRB review.**”
 - *Allows for both intervention and data collection.*
- Allows “deception about the nature or purposes of the research” if the subject authorizes it.

Limited IRB Review

- Intended to ensure that there are adequate privacy safeguards for identifiable private information and identifiable biospecimens.
- Involves making and documenting the determination that adequate provisions are in place for protecting privacy and maintaining confidentiality.
- Although, limited IRB review is an expedited review, it has no continuing review requirement

Category 7-8, Activities Where Broad Consent is Required

- These two exemptions are related to the secondary research use and storage or maintenance of identifiable private information and identifiable biospecimens and **require** broad consent.
- Category 7 covers activities that involve **storage or maintenance** for secondary research use of private information or identifiable biospecimens.
- Category 8 covers research that involves the **use** of private information or identifiable biospecimens that have been stored or maintained for research use.

Broad Consent

- “Broad consent” may be obtained in lieu of informed consent only for storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens (Exempt categories 7 & 8).
- An optional/alternative avenue for consent.
- Requires tracking of decisions across the lifespan of the private identifiable data and/or identifiable biospecimen

Broad Consent

- Harvard University has chosen not to implement Broad Consent
- ~~Exempt Category 7 & 8~~
- **However**, if an individual was asked to provide broad consent for the storage, maintenance, and secondary research use and **refused** to consent, an IRB **cannot waive** consent for the use of identifiable private information or identifiable biospecimens, nor can they be de-identified and used.

Levels of Review



Expedited Review

- Comprised of various categories
- Significant changes have been made to this section in order to allow greater use of this review procedure and help relieve burden on IRBs.
- Except for limited IRB review, all of the determinations for the 46.111 approval criteria must be made.
- Revised to permit expedited “limited IRB review” for applicable exempt categories.

Eliminate Continuing Review

- Continuing review is not required for research reviewed under limited IRB or approved by expedited review (minimal risk studies).
- Unless the reviewer explicitly justifies that it would enhance protection of subjects.
- Investigators still have the obligation to report certain events (such as unanticipated problems).
- Harvard University will implement an annual reminder (Study still active?, Responsibilities of PI) for expedited review studies and convened IRB studies that do not have a continuing review requirement

Expedited Review List

- Under the Revised Rule, a research study is automatically eligible for expedited review if the study only involves activities in one of the expedited categories
 - *The reviewer must agree that the research activity is minimal risk.*
- Expedited categories are deemed to be minimal risk, unless the reviewer determines and documents why the study involves greater than minimal risk.
- There is a regulatory federal agency commitment to evaluate the expedited review category list at least every eight years and amend it as appropriate.

Levels of Review



Convened IRB

For greater than minimal risk studies initially reviewed by a convened IRB, continuing review is not required when the research involves either one or both of the following:

- a) Data analysis, including analysis of identifiable private information or identifiable biospecimens; or
- b) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Levels of Review



Single IRB / Cooperative Research

- New requirement for institutions to rely upon approval by a single IRB (sIRB).
 - *This part of the regulations will go into effect on [January 20, 2020](#).*
- Harmonizes with NIH
- The “lead institution” may propose the reviewing IRB, but final federal approval is required.
- Additional institutional review (including IRB review) would no longer have any regulatory status in terms of compliance with the Revised Rule.
- Other types of reviews either mandated by other regulations or by institutional policy are not included in the required central review.
 - *For example, radiation safety board review, privacy board review, reporting and management of conflicts of interest, and departmental scientific review.*

Screening, Recruiting, or Eligibility

- Now allows waivers of informed consent to obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects.
- Harmonizes with FDA

Informed Consent

- Key information
- “Reasonable person” standard
- Additional elements

Investigators must present informed consent information in sufficient detail and organize and present the information in a way that does not “merely provide lists of isolated facts, but rather facilitates the prospective subject’s ...understanding.”

Key Information

- Facilitate subjects' understanding of the reasons to participate (or not) in the research.
- Requires that “key information” essential to decision-making receive priority by:
 - *Being presented first in the consent discussion.*
 - *Appearing at the beginning of the consent document.*
 - *Information most likely to assist in understanding why to participate (or not) in the research.*
- Informed consent must be organized and presented in a way that facilitates comprehension.

Key Information

The preamble lists five elements that cover “key information:”

- *The fact that consent is being sought for research and that participation is voluntary.*
- *The purposes, the expected duration of participation, and the procedures to be followed.*
- *The reasonably foreseeable risks or discomforts to the prospective subject.*
- *The benefits to subjects or others that may reasonably be expected.*
- *Appropriate alternatives, if any, that might be advantageous.*

“Reasonable Person” Standard

- The prospective subject (or LAR) must be provided with the information that a **reasonable person** would want to have in order to make an informed decision about whether to participate, and be given an opportunity to discuss that information.
- Investigators remain responsible for providing more information when requested by subjects or to improve a particular subject’s understanding.

Additional Elements

- Added is a requirement to include one of two statements about the collection of private identifiable information or identifiable biospecimens for future research.
- **Additional** applicable elements:
 - *Three new additions: biospecimen use, commercial profit, and return of results.*
- ~~Adds broad consent for future research as an alternative.~~

Consent Forms, Signatures, and Waivers

- Electronic signatures are specifically allowed.
- Reading consent forms to subjects is allowed.
- A **written** copy must be given to the person signing the consent form.
- Short form consent forms must begin with a “concise and focused” presentation of “key information.”
- Added a third signature waiver category:
 - *Members of a distinct cultural group in which signing forms is not the norm and the research is minimal risk.*

“Documentation” in Section 46.117

- Means obtaining the **signature** of subjects (or LAR) on consent forms.
- It **does not** mean recording that the process has taken place.
 - *This term has caused confusion at research sites.*
- “Waivers of documentation” only mean that no signature is obtained.
 - *Still good practice to:*
 - *Document (record) occurrence of the consent process.*
 - *Document (record) the fact that the subject agreed to participate.*
- Waivers of documentation (signature) must be documented (recorded) in IRB records.

Summary

- Implementation date –January 19, 2018
 - Studies submitted on or after will be reviewed under the Revised Rule
 - Existing studies (expedited and convened IRB) will be transitioned on a case-by-case basis
 - Revised Rule will be applied to all new research regardless of funding
- New definitions
- New and revised exempt categories, some with limited IRB review
- No broad consent
- No continuing review for expedited studies however there will be annual reminders
- No continuing review for some convened IRB studies
- Single IRB requirement – January 20, 2020
- New informed consent requirements
- New informed consent waivers

Next steps

- ESTR upgrade sessions
- Revised IRB application
- Revised informed consent form templates
- Extensive training for IRB staff to provide better assistance

We're here to help!

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Thank you!