The Final Rule: Changes to Human Subject Regulations

HRPP website

http://research.ku.edu/hrpp

Health and Human Services (HHS) –

Office of Human Research Protections (OHRP)

http://www.hhs.gov/ohrp/

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Final Rule Changes: Outline

- 45 CFR 46 Changes: Overview
- Human Subjects Research Definition
- Categories of Review
- Informed Consent Changes
- Screening, recruiting, determining eligibility
- Single IRB Review
- Clinical Trials

45 CFR 46 Changes: Overview

45 CFR 46: The Common Rule (1981)

- Federal Policy for the Protection of Human Subjects.
- The main elements include:
  - Requirements for assuring compliance by research institutions
  - Requirements for researchers' obtaining and documenting informed consent
  - Requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.
- Codified in the HHS regulations, 45 CFR part 46 (1991)

Final Rule (effective July 2018)

- Published on January 19, 2017 –effective **January 21, 2019**
  - Single IRB Implementation Date: January 20, 2020
- Federal Register states, “The final rule is designed to more thoroughly address the broader types of research conducted or otherwise supported by all of the Common Rule departments and agencies such as behavioral and social science research.” (Vol 82; No. 12 p. 7150)
- Adopted by 15 federal agencies so far (not FDA, DOJ, CDC)
- You can find additional information on our website: http://research.ku.edu/irb-reg-revisions
- You can read/find the published rule and the press release by clicking here.

Final Rule – Important Details

- Changes to the exempt categories
  - Inclusion of “benign behavioral interventions” category
  - Changes to “Educational Settings” category
  - Limited IRB Review
- Clarification on some “not human research” activities
- Requirement of Single IRBs for multi-site research projects
- No annual Continuing Review requirements for Expedited research
- Clinical Trial definition and new requirements
  - Posting of consent forms
- Changes to human research definitions
  - Inclusion of biospecimens in human subject definition
- Changes to informed consent requirements
  - Inclusion of “Key Information” at the beginning of consent form
  - Electronic signatures requires written copy given to participants

Delay Period: 3 burden-reducing provisions July 2018 – January 20, 2019

- Revised definition of “Research”
- Elimination of annual Continuing Review for certain projects:
  - Expedited projects
- Elimination of the requirements for the IRB to review grant applications or other funding proposals related to research
  - Will not affect researchers – internal processes only

Impact on projects approved before July 2018

- University must outline IF they will be applying Final Rule to old studies
  - KU is requiring expedited and committee review projects adapt to the Final Rule within 3 years of the January 2019 implementation date.
  - Any project that meets the new criteria for an exempt category will be re-categorized at Continuing Review

Human Subject Research Definition

Do I need to apply?

- IRB approval is required only when the activities being conducted are *Research* Involving *Human Subjects*

Current Definition: Research

- Research is defined in 45 CFR 46 as: *A systematic investigation designed to develop or contribute to generalizable knowledge.*

□ **Is the activity an investigation?**	Investigation: A searching inquiry for facts; detailed or careful examination.
□ **Is the investigation systematic?**	Systematic: Having or involving a system, method, or plan.
□ **Is the systematic investigation designed to develop or contribute to knowledge?**	Designed: planned with a specific purpose in mind (developing or contributing to knowledge). Develop: to form the basis for a future contribution. Contribute: to result in. Knowledge: truth, facts, information.
□ **Is that knowledge generalizable?**	Generalizable: Universally or widely applicable.

- The study activities are *research* only if **all** the boxes are checked.

Final Rule: "Research" Definition

- Definition Unchanged
  - "…a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge" (p 7260)
- Following activities that are not deemed to be research:
  - **Scholarly and journalist activities that focus directly on the specific individuals about whom the information is collected**
    - **Oral history**, journalism, biography, literary criticism, legal research, and historical scholarships
  - Public health surveillance conducted, supported, requested, ordered, required or authorized by a public health authority
  - Collection/analysis of data/information by or for a criminal justice agency
  - Authorized operational activities of intelligence, homeland security, defense, or other national security missions

Current Definition: Human Subjects

- A living individual about whom an investigator (whether professional or student) conducting research obtains
  - (1) Data through intervention or interaction with the individual, or
  - (2) Identifiable private information.

Final Rule: Human Subjects

- "…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**

Activities that are HSR

- Surveys/interviews/focus groups/interventions completed in order to contribute to generalizable knowledge
- Studies involving private information that could identify an individual subject
- Studies involving the collection of bodily materials
- Studies involving non-invasive procedures (Example: EEGs)

Activities that *may* not be HSR

- Class projects completed specifically for educational/teaching purposes or an assignment/grade
- Research involving deceased individuals or cadavers
- **Oral Histories that focus on the individual and do not plan to generalize findings**
- **Scholarly/Journalistic Activities**
- Deidentified biospecimens
- Gathering information about business practices, policies, products
- Quality improvement within a department
- Research involving publicly available, de-identified data (e.g. census data)
- **Public Surveillance activities**
- **Collection/analysis of data/information by or for a criminal justice agency**
- **Authorized operational activities of intelligence, homeland security, defense, or other national security missions**

Multi-Site or Collaborative Research

- Any KU-Lawrence personnel who are **engaged** in non-exempt* human subjects research must have IRB oversight, which can be accomplished in either of the following two ways:
  - Receive HRPP approval for the human subjects reseach activities, through a new study submission in eCompliance
  - Request KU IRB rely on another institution's IRB review by signing an IRB Authorization Agreement
    - HRPP must be contacted in order to initiate an IRB Authorization Agreement
    - **Another institution's IRB approval does not provide IRB oversight for KU personnel unless an IRB Authorization Agreement is signed.**

*Please note that non-exempt determinations should be made by the HRPP office.

Final Rule: Categories of Review

Final Rule: Review Categories

- Exempt Research
  - Not subject to MOST federal regulations
    - EXCEPT in cases where Limited IRB Review is Required
  - No CR
    - KU implementing 5 year approval period
  - Most categories have been revised
  - Subpart C allowed if research involves broader subject population, which only incidentally includes prisoners

Final Rule: Review Categories (cont.)

- Expedited Research (Categories Unchanged)
  - Subject to federal regulations
  - No more than “Minimal Risk” research
  - No annual CR
    - KU implementing 3 year approval period
- Board Review
  - Requirements mostly unchanged – CR still required
  - Subject to federal regulations
  - More than “Minimal Risk” or does not fit into Expedited category

§__.104 Exempt research.

- "…research activities in which the only involvement of human subjects will be in one or more of the categories in paragraph (d) of this section are **exempt from the requirements of this policy**, except that such activities must comply with the requirements of this section and as specified in each category" (p 7261)
  - Limited IRB Review
- HRPP must determine if your project meets criteria for an exempt category

Exempt Categories

- 1: Educational Settings
  - Revised existing category
- 2: Educational Tests, survey procedures, interviews procedures, or observation of public behaviors
  - Revised existing category
- 3: Benign Behavioral Interventions
  - New category
- 4: Secondary Research
  - Revised existing category
- 5: Public benefit/service projects
  - Revised existing category
- 6: Taste & Food quality evaluation
  - Category UNCHANGED
- 7: Storage/maintenance for secondary research
  - New category
  - KU HRPP will not be implementing broad consent at this time.
- 8: Secondary research w/ broad consent
  - New category
  - KU IRB will not be implementing broad consent at this time.

§__.104 (d)(1) Educational Settings

Revised existing category

- Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that **are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction**.
- This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

§__.104 (d)(2) Educational tests, survey procedures, interviews procedures, or observation of public behaviors

Revised existing category

- Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if **at least one** of the following criteria is met:
  - (i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects
  - ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
  - (iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination.[1]

§__.111(a)(7) Limited IRB Review: Privacy & Confidentiality

- Must be completed by HRPP office
- Checking if there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

§__.104 (d)(3) Benign Behavioral Interventions

New category!

- (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and **at least one** of the following criteria is met:
  - (A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
  - (B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
  - The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by

§__.104 (d)(3) Benign Behavioral Interventions (2)

- Benign behavioral interventions are:
  - Brief in duration,
  - Harmless
  - Painless
  - Not physically invasive
  - Not likely to have a significant adverse lasting impact on the subjects
  - The investigator has no reason to think the subjects will find the interventions offensive or embarrassing
- Examples:
  - Having the subjects play an online game
  - Having them solve puzzles under various noise conditions
  - Having them decide how to allocate a nominal amount of received cash between themselves and someone else.

§__.104 (d)(3) Benign Behavioral Interventions (3)

- Deception
  - If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable **unless:**
    - The subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he/she will be unaware of or misled regarding the nature or purposes of the research

§__.104 (d)(4) Secondary research – consent not required

Revised existing category

- Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, **if at least one** of the following criteria is met:
  - The identifiable private information or identifiable biospecimens are publicly available;
  - Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
  - The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E [HIPAA], for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
  - The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq. [1]

§__.104 (d)(5) Public benefit/service projects

Revised existing category

- Research and demonstration projects that are conducted **or supported by** a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to:
  - study, evaluate, improve, or otherwise examine public benefit or service programs
    - including procedures for obtaining benefits or services under those programs;
    - possible changes in or alternatives to those programs or procedures;
    - or possible changes in methods or levels of payment for benefits or services under those programs.
  - Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants.
  - Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

§__.104 (d)(6) Taste & Food quality evaluation

Category unchanged

- 6) Taste and food quality evaluation and consumer acceptance studies:
  - (i) If wholesome foods without additives are consumed, or
  - (ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Review Categories: Expedited Research

Expedited Categories

- An IRB may use the expedited review procedure to review the following:
  - Some or all of the research appearing on the expedited list
  - Minor changes in previously approved research during the period for which approval is authorized; or
  - Research for which limited IRB review is a condition of exemption
- **Expedited categories are unchanged**
- Annual Continuing Review is no longer required
  - KU is implementing 3 year approval period for Expedited studies

Final Rule: Informed Consent (IC) changes

New additions to informed consent (IC) [1]

- Information in consent must be what a **reasonable person** would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.
- IC must begin with a concise and focused presentation of the **key information section**
  - Include info most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research.
  - This part of the informed consent must be organized and presented in a way that facilitates comprehension.

Key Information Section: Example 1

KEY INFORMATION

- This project is studying_____.
- Your participation will take _____ minutes/hours/days.
- You will be asked to do the following procedures: *[List procedures here]*. More detailed information on the procedures can be found below.
- *[List possible risks or discomforts related to the study. If none, add statement explaining no risks or discomforts.]*
- *[List possible benefits to subjects or others. If none, add statement explaining no benefits.]*
- *[List alternatives to participating. For SONA, this may be an alternative assignment or alternative research study. If no alternative, state "Your alternative to participating in this research study is not to participate."]*

Key Information Section: Example 2

KEY INFORMATION

The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

Why am I being invited to take part in a research study?

What should I know about a research study?

Why is this research being done?

How long will the research last and what will I need to do?

Is there any way being in this study could be bad for me?

Will being in this study help me any way?

What happens if I do not want to be in this research?

IC Changes (cont.)

- IC as a whole must present information in sufficient detail relating to the research, and must be **organized** and presented in a way that **does not merely provide lists of isolated facts**, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one might or might not want to participate.
- Biospecimens: statement on whether the identifiers might be removed and information or biospecimens could be used for future research without additional consent
- Waiver of documentation (signature) allowed now when subjects are members of a cultural group of community in which signing forms is not the norm
- Electronic signatures allowed – BUT written copy must be given to the person signing consent form
- Allows (but does not require) consent forms to be read to participants

New Additional Elements of IC [1]

- A statement that 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
- A statement regarding whether **clinically relevant research results**, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- For research involving biospecimens, whether the research will (if known) or might include **whole genome sequencing** (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

IC Exception: Screening, recruiting, determining eligibility

- An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's LAR, if **either of the following** conditions are met:
  - Investigator will obtain info through oral or written communication with the prospective subject or LAR
  - Investigator will obtain identifiable private info or identifiable biospecimens by accessing records or stored identifiable biospecimens
- This is an exception—not a waiver
- For this exception to be granted, the IRB must be approving the **entire research proposal**

Final Rule: Cooperative Research (Single IRB)

Single IRB[1]

- Requires any US institution engaged in cooperative research to rely upon approval by a Single IRB
  - For portions conducted in the US
- Not subject to this requirement
  - When required by law
    - Tribal law
  - Research for which any federal dept supporting/conducting the research determines and documents that use of Single IRB is not appropriate
- Required after January 20, 2020

Final Rule: Clinical Trials

Clinical Trials

- New Definition: "…a 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."
- Requirement to post consent forms for clinical trials conducted or supported by Federal departments
  - Posting on clinicaltrials.gov or regulations.gov
  - Only 1 consent needs to be posted
  - Posted after recruitment is closed or within 60 days of last study visit by any subject
  - Redaction is possible

NIH Information: Clinical Trials

- Clinical Trial if you answer “yes” to all of the following:
  - Does the study involve human participants?
  - Are the participants prospectively assigned to an intervention?
  - Is the study designed to evaluate the effect of the intervention on the participants?
  - Is the effect being evaluated a health-related biomedical or behavioral outcome?
- Clinical trial even if…
  - You are studying healthy participants
  - Your study does not have a comparison group (e.g. placebo or control)
  - Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
  - Your study is utilizing a behavioral intervention

https://grants.nih.gov/policy/clinical-trials/definition.htm

NIH Clinical Trial Definitions

- **Prospectively Assigned**: a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.
- **Intervention:** a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.
  - Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and diagnostic strategies.
- **Health-related biomedical or behavioral outcome:** the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life.

NIH Case Study #9

https://grants.nih.gov/policy/clinical-trials/case-studies.htm#case1

Case #9: The study involves the recruitment of healthy volunteers who will be randomized to different durations of sleep deprivation (including no sleep deprivation as a control) and who will have stress hormone levels measured. It is designed to determine whether the levels of stress hormones in blood rise in response to different durations of sleep deprivation.

- **Does the study involve human participants?** Yes, the healthy volunteer are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to an intervention, different durations of sleep deprivation followed by a blood draw.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to measure the effect of different durations of sleep deprivation on stress hormone levels.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, stress hormone levels, is a health-related biomedical outcome.

✓ **This study is a clinical trial.**

NIH Case Study #18a

https://grants.nih.gov/policy/clinical-trials/case-studies.htm#case1

Case #18a: Note: The details of Case #18 (a-f) have been revised and updated as of Jan. 17, 2018.

The study involves the recruitment of healthy adolescent volunteers followed over time to assess brain development and factors that influence brain development. Participants are administered a battery of standard measures at each visit, including blood draws, surveys, various cognitive performance measures (e.g., working memory tasks) and brain scans (e.g., fMRI) to assess the association of these measures over time.

- **Does the study involve human participants?** Yes, the healthy adolescent volunteers are human participants.
- **Are the participants prospectively assigned to an intervention?** No, not in this context. The battery of standard measures and the brain scans are being used to describe patterns and associations over time, but not to modify them.

X **This study is not a clinical trial.**

Web Resources:

- OHRP Revised Common Rule Q&As
- CITI Program Resources
- KU HRPP Revised Common Rule webpage
- NIH Clinical Trial Definition and Case Studies