



Final Rule Material: New and Revised Definitions



Content Author

Gary L. Chadwick, PharmD, MPH, CIP
University of Rochester (Emeritus) and HRP Consulting Group

Introduction

On 19 January 2017, the U.S. Department of Health and Human Services (HHS) issued a Final Rule to update the current regulations at 45 CFR 46, Subpart A - "Federal Policy for the Protection of Human Subjects" (the Common Rule).

Overall, the substantive revisions made in the Final Rule are intended to “modernize, strengthen, and make more effective” the current system of oversight as required by the Common Rule, which was largely unchanged since 1991. The revisions are intended to better protect human subjects involved in research, facilitate research, remove ambiguity, and reduce regulatory burden. This resource covers changes and additions to definitions used in the rule, which affect research institutions, Institutional Review Boards (IRBs), and investigators.

Most definitions remain the same as before; however, there are some important changes and additions. Some important terms are undefined in the regulations, but are clarified in the Final Rule’s preamble. Many undefined terms already appear in the current regulations, and IRBs and institutions have placed appropriate definitions in their standard operating procedure (SOP) and policies.

Overview of the Final Rule Revisions

The Common Rule numbering scheme and section titles remain largely intact, but with some movement of text and subsection numbering revisions. While CITI Program recognizes that each Common Rule agency has different citations for its human subject protection regulations, for consistency and clarity, this resource will use citations to HHS 45 CFR 46, Subpart A version of the Final Rule.

Unchanged Definitions

The definition of “minimal risk” has not changed. The concept of minimal risk is key to numerous provisions of the Common Rule. It affects the type of review required, the frequency of review, considerations for IRBs in the review process, and the permissibility of waiver of informed consent. Two other definitions have also remained the same - “IRB” and “IRB approval.”

New Terms Added

The definitions have been reordered alphabetically and new terms are defined including clinical trial, public health authority, and written or in writing.

Clinical Trial

“Clinical trial” means 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. The Final Rule’s preamble notes that, while not implementing the Notice of Proposed Rulemaking’s (NPRM) proposed extension of the Common Rule to all clinical trials, the definition of clinical trial should be used for determining which studies require posting of the IRB-approved consent form used to enroll subjects. The definition is intended to harmonize with the definition of clinical trial in the ClinicalTrials.gov Final Rule (HHS 2016).

Public Health Authority

“Public health authority” means an agency or authority that is responsible for public health matters as part of its official mandate. Adding this definition is important because certain public health surveillance activities are now excluded from the definition of research. The excluded public health activities are limited to activities necessary for a public health authority to “identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products)” [HHS 2017, 7149-274].

Written or In Writing

The new definition of “written or in writing” is included in the Final Rule to clarify that these terms include electronic formats, which aligns the Common Rule with U.S. Food and Drug Administration (FDA) and the International Council for Harmonisation (ICH) initiatives to promote electronic consent. The Final Rule’s preamble notes that the definition does not preclude the possibility that consent forms could be in media other than paper or electronic formats and still meet the requirements of the Common Rule.

Terms Not Added to Definitions

It is important to take note of terms used in the Final Rule that are not defined, as word selection and usage are extremely important in regulations. It can be challenging trying to determine how the federal regulation is using a term and what the significance or meaning is, and how it is applicable to research practice. There may be clues in the context of the regulation -- when the term is used, how it is used, and sometimes an explanation is provided. Also, federal guidance can help provide direction on how to understand and comply with undefined terms in research practice.

Vulnerable (to Coercion or Undue Influence)

The definition of “vulnerable” is not included in the definitions section, but it has been updated in both 46.107 (IRB membership requirements) and 46.111 (criteria for approval of research). Adopting a suggestion from NPRM public comments and the Secretary’s Advisory Committee on Human Research Protections (SACHRP), the Final Rule no longer includes pregnant women or handicapped and physically disabled individuals as examples of populations that are potentially vulnerable to coercion or undue influence. The Final Rule uses the term “individuals with impaired decision-making ability” to replace the term “mentally disabled persons.”

The Final Rule’s preamble states that the possibility of coercion or undue influence could affect the ability to make an informed decision about participating in research. Therefore, the vulnerability of the subjects in research studies should be considered as a function of the possibility of coercion or undue influence. The preamble states that this type of vulnerability alone should be the IRB focus of concern in determinations about vulnerable populations.

The preamble also notes that the assessment of the equitable selection of subjects (46.111[a][3]) should include factors like societal marginalization or discrimination. Likewise, the preamble discusses that the criterion at 46.111(a)(1) includes risks that some might term “vulnerabilities,” which are not covered by the regulatory term.

Deception

The definition of “deception,” like “vulnerable,” is not included in the definitions section, but it is specified in 46.104(d)(3)(iii) and the Final Rule preamble, which states, “authorized deception would be prospective agreement by the subject to participate in research where the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.”

Generalizable Knowledge

The term of “generalizable knowledge” remains undefined and unaddressed in the Final Rule. Each institution should define, in its standard operating procedures (SOPs) or other institutional documentation, what standard is used. Typically, this involves some variation of the thought that the results are intended / expected to be applied to a larger population beyond the site of data collection or the population studied.

Single IRB (sIRB) Review and Cooperative Research

“Single IRB review” is also not specifically defined in the Final Rule. However, 46.114 adds a requirement for institutions located in the U.S., that are engaged in federal cooperative research, to rely upon approval by a sIRB for the portion of research that is conducted in the U.S. “Cooperative research” is explained within the regulation as research “involving more than one institution” (in other words, essentially all federal multi-site research). Single IRB is synonymous with “reviewing IRB” and “IRB of record.” All other IRBs are “relying IRBs.” Further guidance is expected from the Office for Human Research Protections (OHRP).

Key Information

Detailed changes to the informed consent process and documentation are covered in a separate resource. One undefined, but important, regulatory term is “key information.” Key Information must receive priority by appearing at the beginning of the consent form and be presented first in the consent discussion. According to the Final Rule’s preamble, a brief description of five elements at the beginning of the consent form, and informed consent process, would encompass the required key information.

Key information elements include a concise explanation of the following Common Rule elements:



Practicably

The word “practicably,” which appears in the consent waiver and alteration sections, is intentionally left undefined. The preamble notes that a SACHRP recommendation was that “this requirement be interpreted to mean that it would be impracticable to perform the research, not impracticable to obtain consent due to financial or administrative burdens, without the waiver or alteration.”

Broad Consent

The Final Rule presents a new concept of “broad consent” in 46.116(a) and (d), which addresses elements of consent for the storage, maintenance, and secondary research use of private information or identifiable biospecimens. The preamble defines broad consent as “seeking prospective consent to unspecified future research.” Waivers and refusals of broad consent are addressed in 46.116(e). Broad consent may be obtained only for the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens.

Secondary Research Use

“Secondary research use” is not defined in the regulations, but the Final Rule’s preamble states it is “re-using [for research purposes] identifiable and non-identifiable information and biospecimens that are collected for some other ‘primary’ or ‘initial’ activity” (such as, from research studies other than the proposed research study).

The information or biospecimens that are used for secondary research would generally be found by the investigator in:

Records

Information Systems

Archives

Databanks (in the case of information)

Tissue repositories (such as, a hospital’s department for storing clinical pathology specimens or the “excess” portion of surgically removed tissue or blood that was drawn for clinical purposes).

The Final Rule has no requirement that the information and biospecimens must be pre-existing at the time that the investigator begins a research study.

Limited IRB Review

“Limited IRB review” is a condition for exemption of the research activities under:

- Identifiable and sensitive educational tests, survey procedures, interview procedures, or observation of public behavior (46.104 [d][2][iii])
- Identifiable and sensitive benign behavioral interventions (46.104 [d][3][i][c])
- Secondary research use (46.104 [d][8])

The Final Rule preamble states that, for these three exemptions, a limited IRB review is making and documenting the determination required by 46.111(a)(7), to ensure that there are adequate privacy safeguards for identifiable private information and identifiable biospecimens in the proposed research.

A new limited IRB review criterion (46.111[a][8]) adds additional broad consent determinations for approval of activities that store and/or maintain private information or identifiable biospecimens for secondary research use under exemption 46.104(d)(7). This new criterion states that for storage and maintenance, “the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section.”

Therefore, limited IRB review uses a single criterion, either 46.111(a)(7) or 46.111(a)(8).

To clarify that IRBs have the authority needed to conduct limited IRB review, the Final Rule modifies the IRB authorities listed in 46.109 (approve, require modifications in, or disapprove research) by adding “including exempt research activities under 46.104 for which limited IRB review is a condition of exemption.”

The Newborn Screening Save Lives Reauthorization Act of 2014 (Pub. L. 113-240) required federally funded research with newborn dried blood spots (DBS) to be considered research with human subjects, and that the provisions allowing IRBs to waive consent would not apply.

By statute, the restrictions made only applied until changes to the Common Rule were promulgated. Therefore, the changes made by the DBS law will no longer apply after the Final Rule’s effective date (19 January 2018).

Benign Behavioral Intervention

“Benign behavioral intervention” is described in 46.104(d)(3) as behavioral (not biomedical) interventions in conjunction with collecting information from an adult subject through oral or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and certain conditions are met. The new exemption is for the research activities that pose little risk to subjects.

The regulations also add that benign behavioral interventions are:

Brief in duration

Painless

Harmless

Not physically invasive

Not likely to have a significant adverse lasting affect on the subjects

The investigator has no reason to think the subjects will find the interventions offensive or embarrassing

The preamble gives the following examples of benign behavioral interventions: having the subjects play an online game; solve puzzles under various noise conditions; comparing test performance of test takers in quiet or noisy surroundings; or decide how to allocate a nominal amount of received cash between themselves and someone else. An interesting note is that the Final Rule includes three of the above examples in the regulatory language.

Revisions of Existing Terms and Definitions

Even though only three new terms were added, revisions were made to existing terms and definitions.

Minor Clarifications to Wording

“Intervention,” “interaction,” “private information,” and “identifiable private information” were elevated to get their own subsection numbers and have been changed only to clarify wording.

Significant Revisions to Existing Definitions

Three definitions have been changed in significant ways.

Legally Authorized Representative	The definition of “legally authorized representative” now adds specific authorization to use institutional policy when there is no applicable law (state statute or regulation, case law, or an opinion of a state Attorney General) that addresses this issue. This change is intended to bring consistency to the consent process and it allows institutional policies in either the clinical context or other non-research contexts to authorize who may serve as a legally authorized representative in that institution.
Research	The definition of “research” has been expanded to list activities that are specifically deemed not to be research. The Final Rule specifies that the collection of information is permitted under public health surveillance, but subsequent research using information collected from public health surveillance activities would fall under the definition of research as secondary use.
Human Subject	The definition of “human subject” now references “information and biospecimens” (replacing “data”) and adds obtaining, storing, using, studying, analyzing, or generating identifiable private information or identifiable biospecimens as trigger events. 46.102(e)(1)(i) clarifies that investigators may “obtain” (possess) information and biospecimens without triggering the human subject definition until they use, study, or analyze the information or biospecimens.

Review of Changes to Definitions Section (46.102)

Below is the new wording in the Final Rule definitions section.

Additions are **bolded** and/or in boxes. Deleted items are shown in ~~strike-through~~.

46.102, Definitions

(a) Certification means the official notification by the institution to the supporting **Federal** department or agency **component**, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

(b)



added

Clinical trial means 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.

(c) Department or agency head means the head of any **Federal** department or agency, **for example, the Secretary of HHS**, and any other officer or employee of any Federal department or agency to whom **the authority provided by these regulations to the department or agency head** has been delegated.

(d)



added

Federal department or agency refers to a Federal department or agency (the department or agency itself rather than its bureaus, offices or divisions) that takes appropriate administrative action to make this policy applicable to the research involving human subjects it conducts, supports, or otherwise regulates (e.g., the U.S. Department of Health and Human Services, the U.S. Department of Defense, or the Central Intelligence Agency).

(e) Human subject...

(1) Human subject means a living individual about whom an investigator (whether professional or student) conducting research:

(i) Obtains ~~data~~ **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**.

(2) Intervention includes both physical procedures by which ~~data~~ **information or biospecimens** are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

- (3) Interaction includes communication or interpersonal contact between investigator and subject.
- (4) Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information **that** has been provided for specific purposes by an individual and **that** the individual can reasonably expect will not be made public (e.g., a medical record).
- (5) **Identifiable private information** is private information ~~must be individually identifiable for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information in order for obtaining the information to constitute research involving human subjects.~~

(6)



added

An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

(7) **Federal departments or agencies implementing this policy shall:**



added

(i) Upon consultation with appropriate experts (including experts in data matching and re-identification), reexamine the meaning of “identifiable private information,” as defined in paragraph (e)(5) of this section, and “identifiable biospecimen,” as defined in paragraph (e)(6) of this section. This reexamination shall take place within 1 year and regularly thereafter (at least every 4 years). This process will be conducted by collaboration among the Federal departments and agencies implementing this policy. If appropriate and permitted by law, such Federal departments and agencies may alter the interpretation of these terms, including through the use of guidance.



added

(ii) Upon consultation with appropriate experts, assess whether there are analytic technologies or techniques that should be considered by investigators to generate “identifiable private information,” as defined in paragraph (e)(5) of this section, or an “identifiable biospecimen,” as defined in paragraph (e)(6) of this section. This assessment shall take place within 1 year and regularly thereafter (at least every 4 years). This process will be conducted by collaboration among the Federal departments and agencies implementing this policy. Any such technologies or techniques will be included on a list of technologies or techniques that produce identifiable private information or identifiable biospecimens. This list will be published in the Federal Register after notice and an opportunity for public comment. The Secretary, HHS, shall maintain the list on a publicly accessible web site.

Under the Final Rule, secondary research with nonidentified newborn dried blood spots will be treated in the same way as secondary research with any other type of non-identified biospecimen because such research would not be considered to be “research with human subjects.”

(f) Institution means any public or private entity, **or department** or agency (including federal, state, and other agencies).

(g) IRB means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) IRB approval means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) **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.**

The Final Rule replaces references to a “subject’s representative” throughout the regulations with references to a subject’s “legally authorized representative.”

(j) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(k)



added

Public health authority means 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.

(l) Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities **that** meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program **that** is considered research for other purposes. For example, some demonstration and service programs may include research activities. **For purposes of this part, the following activities are deemed not to be research:**

- (1)  *added* **Scholarly and 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.**
- (2)  *added* **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, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases 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).**
- (3)  *added* **Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.**
- (4)  *added* **Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.**

(m) **Written, or in writing, for purposes of this part, refers to writing on a tangible medium (e.g., paper) or in an electronic format.**

References

- U.S. Department of Health and Human Services (HHS). 2017. "Federal Policy for the Protection of Human Subjects." Federal Register 82(12):7149-274.
- U.S. Department of Health and Human Services (HHS). 2016. "Clinical Trials Registration and Results Information Submission." Federal Register 81(183):64981-5157.