



# Final Rule Material: Overview of the Final Rule Revisions



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## Content Author

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## Introduction

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The Final Rule to update the current regulations at 45 CFR 46, Subpart A - "Federal Policy for the Protection of Human Subjects" (the Common Rule) was published by the U.S. Department of Health and Human Services (HHS) on 19 January 2017 in the *Federal Register*. The most significant Final Rule changes that affect research institutions, Institutional Review Boards (IRBs), and investigators are covered in this resource. Some changes in the Final Rule were made for clarity and do not change the application of the pre-2018 Common Rule.

Other CITI Program resources will cover the most extensive and important changes in more detail (such as, changes to revised definitions, informed consent and waiver regulations, secondary research, expedited and exempt process revisions, IRB operations, and changes relevant to different roles in research).

### **The Final Rule differs in significant ways from the 2015 Notice of Proposed Rule Making (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, these include:**

- *Require that research involving non-identified biospecimens be governed by 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*
- *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*

The substantive revisions are intended to “modernize, strengthen, and make more effective” the current system of oversight that has been the federal “Common Rule” since 1991. The revisions are intended to:

- *Better protect human subjects involved in research*
- *Facilitate research*
- *Remove ambiguity*
- *Reduce regulatory burden*

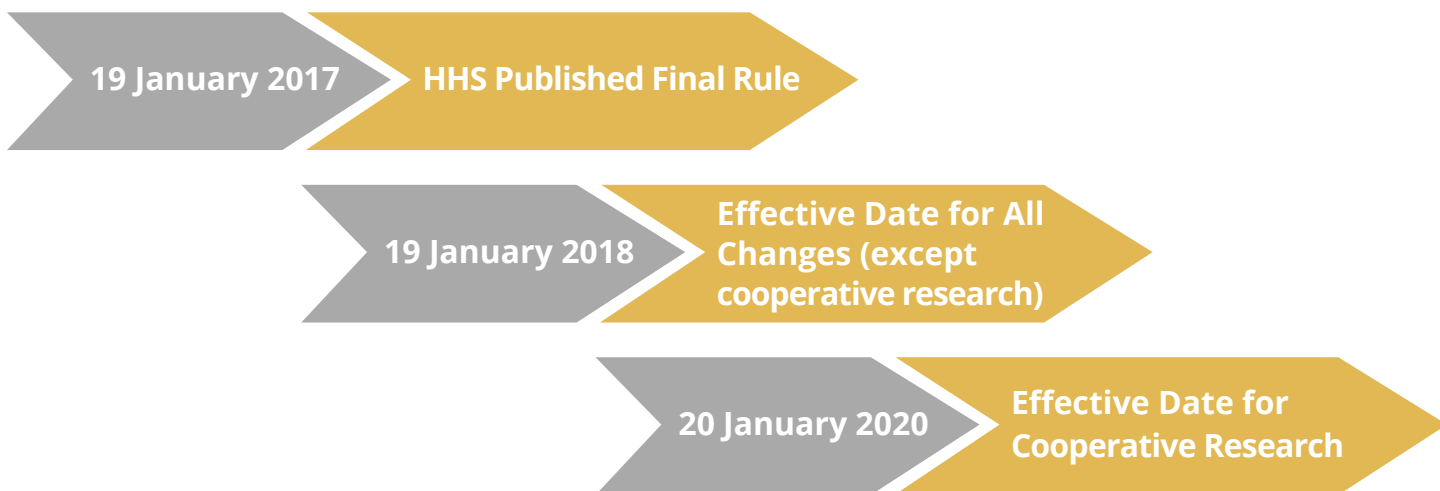
The Final Rule is intended to better manage the broader types of research (specifically including behavioral and social science research) conducted and supported by all the Common Rule departments and agencies. One of the Final Rule’s main purposes is to facilitate the conduct of minimal risk research. It also recognizes the evolving technologies including mobile technologies, the Internet, and the growth in computing power, which have changed the scale and nature of information collected in modern research activities. Large databases, biospecimen repositories, electronic health records, and clinical research networks have spurred new kinds of research.

## Compliance Dates and Transition Provisions

The new Final Rule does not immediately go into effect. There are implementation dates and transition provisions.

### *Implementation Dates*

Research organizations, institutions, IRBs, and investigators will have some time to revise forms, documents, and practices to comply with the revisions. The new rules are effective one year from publication. That means that all regulated parties must be in compliance from that date onward. One exception is the compliance requirement for single IRB (sIRB) review of cooperative research, which is set at 20 January 2020 (three years from publication).



## Transition Provisions

Per 45 CFR 46.101(l)(3), actions taken before the compliance dates are “grandfathered;” this means that ongoing research studies that were initially approved by an IRB, or determined to be exempt before 19 January 2018, will not be required to comply with the changes in the Final Rule. Such research may continue to completion or closure without change. Organizations and IRBs can voluntarily choose, on a study-by-study basis or by formally adding a requirement to their policies, to apply the Final Rule to these grandfathered studies. The intent of the transition phase is to minimize burdens associated with research that is conducted over an extended period and avoid a requirement that such research be subject to two sets of rules during the life of the research.

Research Study Initiation Date	Standards
<p>Research initially approved by an IRB, waived pursuant to [former subsection] 101(i), or determined to be exempt [under former subsection 101(b)] <b>before</b> 19 January 2018</p> <p>(Grandfathered research)</p>	<p>These studies are by default subject to the pre-2018 rule (the Common Rule as published in the 2016 edition of the CFR).</p> <p>However, an organization engaged in such research may choose to comply with the Final Rule (2018 requirements) for such a study (the grandfathered research) if the organization applies the Final Rule to the study and an IRB documents this determination.</p> <p>Further guidance is pending to determine if the IRB must document this per study even if the institution issues an institutional policy applying the Final Rule to all research.</p>
<p>Research initially approved by an IRB, waived pursuant to [former subsection] 101(i), or determined to be exempt on or <b>after</b> 19 January 2018</p>	<p>These studies are subject to the Final Rule (2018 requirements).</p>

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## Overview of the Final Rule Revisions

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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 the HHS 45 CFR 46, Subpart A version of the Final Rule.

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### 45 CFR 46.101, Applicability

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For institutions engaged in research, the revisions add a new condition that non-institutionally based IRBs reviewing research that is federally conducted or supported must comply with the Common Rule. This new statement supports the use of external IRBs and facilitates sIRB use. It also gives Common Rule departments and agencies the authority to enforce compliance directly with IRBs that are not operated by an assured institution.

The old footnote to the applicability section has been eliminated to implement a non-regulatory change to the assurance mechanism, which eliminates the voluntary extension of the Federalwide Assurance (FWA) to non-federally funded research (that is, it precludes “checking the box” as part of the FWA application). Therefore, FWAs will now only apply to research that is federally conducted or supported. Institutions may still voluntarily extend the regulations to all research conducted by the institution and apply consistent policies and procedures to all research, but this extension will no longer be part of the assurance process and, importantly, such research will not be subject to federal oversight even if the institution uses federal policy for its approval and conduct. The intent of this change is to decrease administrative burden, limit federal oversight, and to encourage institutions to explore a variety of flexible approaches to overseeing research that is not federally funded without reducing the protection of human subjects.

In the Final Rule, references that cite state or local law now include “tribal law passed by the official governing body of an American Indian or Alaska Native tribe.”

## 45 CFR 46.102, Definitions

Due to the importance of definitions to the proper application of regulations, a more in depth overview of definitions is covered in a separate resource.

Definitions have been reordered alphabetically and new terms were defined (including clinical trial, public health authority, and written or in writing). The definition of “written or in writing” is intended to clarify that these terms include electronic formats. The preamble to the Final Rule 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 Common Rule’s requirements.

### *Defining Vulnerable*

The definition of “vulnerable” is still not included in the definitions section (46.102), but it has been updated in both 46.107 (IRB membership requirements) and 46.111 (criteria for approval of research). Adopting a suggestion from public comment and the Secretary’s Advisory Committee on Human Research Protections (SACHRP), the Final Rule no longer includes pregnant women or handicapped or physically disabled individuals as examples of populations that are potentially vulnerable to coercion or undue influence. Instead, the Final Rule uses the term “individuals with impaired decision-making ability” to replace the term “mentally disabled persons.” The update also reflects that the vulnerability of the subjects in research studies should be considered a function of the possibility of coercion or undue influence. The IRB should focus concern on vulnerability to coercion or undue influence in reference to the subjects’ ability to make informed decisions about participating in research.

### *Defining Human Subject*

The 46.102(e) definition of “human subject” now references “information and biospecimens” (replacing “data”) and adds “obtaining, using, studying, analyzing, or generating identifiable private information or identifiable biospecimens (46.102[e][1][ii])” as trigger events. Further, it 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 (46.102[e][1][i]).

### *Update to Newborn Dried Blood Spots Act*

The Newborn Screening Saves 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).

Research with DBS will no longer be considered research with human subjects and IRBs can waive the requirement for obtaining informed consent.

## No Changes to Minimal Risk Definition

The definition of “minimal risk” has not changed. The concept of “minimal risk” is key to numerous aspects of the Common Rule; it affects the type of review required, the frequency of review, considerations for IRBs in the review process, and permissibility of waiver of informed consent. The preamble to the Final Rule (2017) states that HHS intends to publish guidance on the definition of minimal risk to continue to decrease burden, improve efficiency, and calibrate the review process to the risk of the research, and the Secretary of HHS could still create and publish a list of activities that qualify as minimal risk in the future.

### Other Important Changes to Definitions

- *“Intervention,” “interaction,” “private information,” and “identifiable private information” are elevated to get their own subsection numbers and have been changed only to clarify wording.*
- *Three definitions have been changed in significant ways.*



*“Legally authorized representative” now adds specific authorization to use institutional policy when there is no applicable law that addresses this issue.*



*“Human subject” now references “information and biospecimens” (replacing “data”)*



*“Research” has been expanded to list activities that are specifically deemed not to be research (for example, journalism, certain scholarly activities such as oral history, public health surveillance, criminal justice or criminal investigative activities, and activities in support of intelligence, homeland security, defense, or other national security missions).*

## 45 CFR 46.103, Ensuring Compliance

The revision moves the list of written procedures formerly needed for FWAs out of this section; most of these procedural requirements now appear in the “IRB Operations” section (46.108). This conforms to the placement in the U.S. Food and Drug Administration (FDA) IRB regulations (21 CFR 56.108) because FDA does not issue FWAs. Responding to concern that the assurance process was unduly burdensome and some requirements did not provide meaningful protections, FWAs will no longer require:

- *A declaration of ethics principles to be followed*
- *An IRB roster*
- *A list of reviewing IRBs*
- *IRB grant review*

The elimination of the ethical principles statement may seem odd, but the former requirement gave some international institutions the erroneous impression that they needed to modify their internal procedures to follow the *Belmont Report*. The deletion is intended to clarify that such modification is not required. It is anticipated that most research institutions in the U.S. will continue to follow the *Belmont Report* principles.

For research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, a requirement has been added to 46.103(e) to have documentation of the reliance agreement between the institution and external IRB, which allocates responsibilities between the two. This requirement is more flexible than what was proposed in the NPRM. It does not require that the institution and organization operating the IRB establish and follow written procedures. Therefore, compliance could be achieved in a variety of flexible ways, such as:

- *Through a formal written agreement (“reliance agreement”) between the institution and reviewing IRB*
- *Through language contained in the protocol of a cooperative research study (projects that involve more than one institution)*
- *By implementation of an institution-wide policy stating the allocation of responsibilities*

An additional requirement has been added that documentation of reliance must be maintained as part of the IRB records.

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## 45 CFR 46.104, Exempt Research

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This section was previously “reserved” but has now been assigned to exemptions. It contains many new requirements, primarily due to added regulations when using human-derived biospecimens in research. Several categories of activities proposed as “exclusions” in the NPRM appear in this section of the Final Rule as “conditional exemptions.”

The Final Rule does not restrict or direct how exemptions are determined by institutions; however, the Office for Human Research Protections (OHRP) continues to recommend that investigators not be given the authority to make an independent determination that their own human subject research is exempt because of the potential for conflict of interest.

### *New Exempt Categories and “Limited IRB Review”*

The Final Rule establishes new exempt categories of research. Under some of the new categories, exempt research would be required to undergo limited IRB review. Limited IRB review is needed in four of the eight exempt categories.

In two of the categories, limited IRB review is required to ensure there are adequate confidentiality and privacy safeguards. In the other two categories, limited IRB review is required for “broad consent” in studies involving identifiable private information or identifiable biospecimens.



The pre-2018 rule’s exemptions, at 46.101(b)(1-6), have been moved to this new section and new restrictions have been added to each of them with the exception of the taste and food quality study exemption (so that the exemption is still congruent with FDA regulations). Section 46.101(b) is now reserved (that is, unused), which should help avoid confusion when implementing the new Common Rule, especially in the transition period.

New exemptions with conditions that were proposed in the NPRM as “excluded” have been added. Re-classifying these proposed exclusions as exemptions was accompanied with a requirement for administrative or IRB review.

Section 46.104(b) specifically states the applicability of the exemption categories to 45 CFR 46, Subparts B, C, and D, and changes the current policy to allow the exemptions at this section to apply to Subpart C in a specific instance.

This change is aimed at human subjects 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 analysis is not seeking to examine prisoners as a population or subpopulation. It will also reduce burden by allowing subjects to continue participation in exempt research if they become prisoners during the course of an exempt study.

### Can Research Regulated by the Subparts Be Exempt?

*Section 46.104(b) specifically states the applicability of the exemption categories to 45 CFR 46, Subparts B, C, and D, and changes the current policy to allow the exemptions at this section to apply to Subpart C.*

Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research	Yes, all exemption categories.
Subpart C - Additional Protections Pertaining to Biomedical & Behavioral Research Involving Prisoners as Subjects	Only for research aimed at involving a broader subject population that only incidentally includes prisoners.
Subpart D - Additional Protections for Children Involved as Subjects in Research	Yes, for exemptions at paragraphs 46.104 (d)(1), (4), (5) (6), (7), and (8).
	Only for research involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed for paragraphs (d)(2)(i) and (ii).
	No, for exemption at paragraph 46.104 (d)(2)(iii) of this section.

**NEW** *Benign Behavioral Interventions*

New subsection 46.104(d)(3)(i) includes an exemption for research involving benign behavioral interventions in conjunction with the collection of information from adults (note: this is only for behavioral research, not biomedical research). Subsection 46.104(d)(3)(i)(C) allows collection of potentially sensitive or harmful identifiable private information from adults if an IRB conducts a limited IRB review and makes a determination that there are adequate provisions for protecting privacy and maintaining confidentiality. This exemption allows for both intervention and information collection.

**“Benign behavioral interventions”** are defined as “being 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 (46.104).”

Per 46.104(d)(3)(C)(iii), deception about the research’s nature or purposes is allowed if the subject authorizes the deception.

**UPDATED** *Educational Tests, Surveys, Interviews, or Uninfluenced/Unmanipulated Observation of Public Behavior*

The Final Rule continues the former exemption for non-interventional educational tests, surveys, interviews, or uninfluenced/unmanipulated observation of public behavior at 46.104(d)(2). It also adds a new subcategory at 46.104(d)(2)(iii) for educational tests, surveys, interviews, or uninfluenced/unmanipulated observation of public behavior that collects potentially sensitive or harmful identifiable private information from adults if an IRB conducts a limited IRB review and makes a determination that there are adequate provisions for protecting privacy and maintaining confidentiality.

The Final Rule removes the exemption category for research involving elected or appointed public officials or candidates for public office.

**NEW** *Exemptions for Secondary Research*

Three new exemptions apply to “secondary research” (defined in the Final Rule’s preamble as “re-using identifiable information and identifiable biospecimens that are collected for some other ‘primary’ or ‘initial’ activity”).

**1** Subsection 46.104(d)(4) covers research uses of private information or identifiable biospecimens for which consent is not required, that is, it is collected or generated for non-research purposes or from research studies other than the proposed research study.

**2** Subsection 46.104(d)(7) covers activities that involve storage or maintenance for secondary research use of private information or identifiable biospecimens.

**3** Subsection 46.104(d)(8) covers research that involves the use of private information or identifiable biospecimens that have been stored or maintained for research use.

Due to the scope of the changes to the exemptions section of the regulations, an overview of “Secondary Use” will be covered in a separate resource.

The exemption at 46.104(d)(4)(iii) applies to secondary research for which consent is not required. It includes a condition that allows research that falls under the Health Insurance Portability and Accountability Act (HIPAA) to be exempt from the Final Rule. Under HIPAA, these protections include requirements to obtain the individual subject’s authorization for future secondary research uses of protected health information, or waiver of that authorization by an IRB or HIPAA Privacy Board.

Unlike the pre-2018 rule exemption for secondary use of information and biospecimens, the Final Rule has no requirement that the information and biospecimens must be pre-existing at the time that the investigator begins the research; prospective collection is permitted.

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## 45 CFR 46.105 and 46.106, Reserved

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Although the Final Rule’s preamble recognizes that several commenters (including SACHRP and individuals) suggested adding sections to the Common Rule that would be focused on investigator responsibilities, no investigator responsibilities were added. There is one significant change; the Final Rule replaces wording in 46.103(b)(4)(iii), which was about an IRB responsibility for ensuring “changes in approved research...may not be initiated without IRB review and approval” with revised wording in 46.108(a)(3)(iii) stating, “investigators will conduct the research in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB.” This is a subtle step toward developing investigator responsibilities. However, it is still up to the IRB to design a written procedure to ensure that investigators follow the rules. The preamble states that not incorporating some comments and suggestions into the Final Rule should not be viewed as a rejection of their possible merits, or an indication that they might not be explored in some future revision of the Common Rule or in guidance. Until then, the FDA regulations on drugs and devices and the International Council for Harmonization (ICH) E6 (R2) guideline can be used to guide researchers. Also, OHRP’s website includes information on investigator responsibilities.

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## 45 CFR 46.107, IRB Membership

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This section was only slightly revised. It includes a revised definition of “vulnerable” (it drops “pregnant women” and replaces “handicapped or mentally disabled persons” with “individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons”) that aligns with other mentions of “vulnerable.”

The Final Rule removes the specific stipulation that IRB membership should not consist entirely of individuals of one sex or profession because, per the preamble, “the requirement that IRB membership reflect members of varying backgrounds and diversity, including gender [sic], accomplishes the same goal.”

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## 45 CFR 46.108, IRB Operations

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46.108(a) was significantly revised, but no new requirements are added. Changes include:

- *The Federalwide Assurance (FWA) requirements for written procedures described in the pre-2018 Common Rule (sections 46.103[b][4] and 46.103[b][5]) have been included at 46.108(a)(3) and (4) as requirements for IRB operation.*
- *The IRB roster detail requirements formerly in 46.103(b)(3), are now found at 46.108(a)(2). These three subsections agree with FDA regulatory wording.*
- *The requirement for meeting space and sufficient staff to support the IRB, formerly in 46.103(b)(2) (which is not in FDA regulations), is now found at 46.108(a)(1).*

As in the past, the Final Rule requires IRBs to maintain an accurate list of IRB members, but FWA-holders are not required to routinely submit changes to that roster to funding departments or agencies. The Final Rule deletes the requirement that institutions designate IRBs on the FWA.

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## 45 CFR 46.109, IRB Review

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The most substantial changes to this section include:

- *Addition of “limited IRB review”*
- *Elimination of continuing review for expedited studies*

NEW

### *Limited IRB Review*

The new “limited IRB review” is intended to ensure that there are adequate privacy safeguards for identifiable private information and identifiable biospecimens. Limited IRB review involves making and documenting the determination that adequate provisions are in place for protecting privacy and maintaining confidentiality.

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 section 46.104 for which limited IRB review is a condition of exemption.”

NEW

### *Eliminating Continuing Review for Certain Expedited Studies*

This section also includes a new subsection (46.109[f][1][i]) eliminating continuing review for all studies that are approved by expedited review (minimal risk studies), unless the reviewer explicitly justifies why continuing review would enhance protection of research subjects.

In addition, the Final Rule states that continuing review is not required for research reviewed in accordance with the limited IRB review procedure.

The Final Rule removes the requirement to conduct continuing review of ongoing research for studies that undergo expedited review and for studies that have completed study interventions and are merely analyzing study data or involve only observational follow up in conjunction with standard clinical care.

Limited IRB review has no continuing review requirement.

➔ Per 46.109(f)(1)(ii), for greater than minimal risk studies initially reviewed by a convened IRB, continuing review is not required when the research only involves one or both of the following:

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

Investigators still have the obligation to report various events (such as unanticipated problems or proposed changes to the study) to the IRB. The Final Rule does not require investigators to provide annual or other periodic confirmation to the IRB that exempt research is ongoing and no changes have been made that would require the IRB to conduct continuing review. Institutions that choose to require some method of accounting for ongoing research, which does not require continuing review, have significant flexibility in how they implement their own requirements, policies, and procedures.

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## 45 CFR 46.110, Expedited Review

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Some significant changes have been made to this section to allow greater use of the expedited review procedure, which is intended to help relieve burden on IRBs. IRBs are reminded that, except for limited IRB review of some exemptions, all the determinations for 46.111 approval criteria must be made. Expedited review just eliminates the need for consideration at a convened IRB meeting.

Activities on the list of expeditable research categories published by the Secretary of HHS are deemed to be minimal risk, unless the reviewer determines and documents that the study involves greater than minimal risk. Also, there is a regulatory federal agency commitment to evaluate the expedited review category list at least every eight years and amend it as appropriate.

This section has been revised to permit the new limited IRB review procedure for exempt activities to be conducted through expedited review. Most exempt activities do not require any type of IRB review, so “administrative review” could suffice.

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## 45 CFR 46.111, Criteria for Approval

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This section survives largely intact. Updates include the following:

UPDATED

*Updated wording for vulnerable populations*

UPDATED

*Updated wording for equitable selection of subjects to include factors (such as, societal marginalization or discrimination)*

NEW

*Subsection added to define limited IRB review procedure*

- *Limited IRB review procedure is a condition for exemption of the research activities under 46.104 (d)(2)(iii) and (d)(3)(i)(C) when the determination for 46.111(a)(7) (that is for privacy or confidentiality) must be made. Under limited review, the IRB does not need to make the determinations at paragraphs (a)(1) through (6).*
- *Limited IRB review is also a condition of exemptions 46.104(d)(7) and (8), which requires 46.111(a)(7) determination on privacy and confidentiality and the scope of broad consent included in 46.111(8).*

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## 45 CFR 46.112 and 46.113, Institutional Review, Suspension, and Termination

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These two sections are unchanged.

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## 45 CFR 46.114, Cooperative Research

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The cooperative research section adds a requirement for institutions located in the U.S. that are engaged in federal cooperative research (projects involving more than one institution) to rely upon approval by a sIRB for the portion of the research that is conducted in the U.S.

Choosing a sIRB of Record

The reviewing sIRB will be specified by the federal department or agency supporting or conducting the research; the “lead institution” may propose the reviewing IRB, but final approval will be required.

Additional Requirements

Documentation specifying the responsibilities of each entity, when research takes place at an institution in which IRB oversight is outsourced.

When does Cooperative Research become effective?

This is the only part of the regulations that will go into effect after three years from publication of the Final Rule (on 20 January 2020).

Other types of reviews either mandated by other regulations or by institutional policy (for example, Radiation Safety Board review, Privacy Board review, reporting and management of conflicts of interest, and departmental scientific review) are not included in the required sIRB review.

Note - for studies that must comply with the National Institutes of Health (NIH) policy on sIRB review, the effective date is 25 January 2018 (with certain exceptions).

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## 45 CFR 46.115, Records

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A majority of the changes proposed in the NPRM for this section are enacted in the Final Rule. Previous wording in this section is largely intact with additional requirements added on, including:

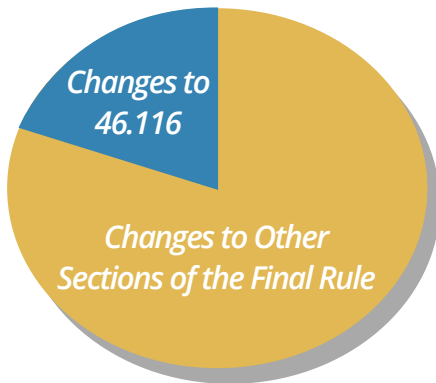
- *Documentation of the rationale for conducting continuing review of research that otherwise would not require continuing review.*
- *Documentation of expedited reviewer's more than minimal risk determination for research that appears on the HHS Secretary's list of expeditable research activities.*
- *Documentation specifying the responsibilities of each entity when research takes place at an institution in which IRB oversight is outsourced (the institution is relying on another IRB for review). This may be achieved in several ways including a description in the study plan or by separate agreement.*

As in the pre-2018 rule, the Final Rule requires IRBs to maintain an accurate list of IRB members (roster), but FWA-holders are no longer required to submit roster changes to funding departments or agencies.



## 45 CFR 46.116, Informed Consent Process

Due to the extensive changes in the informed consent and waiver regulations, a detailed overview of the informed consent revisions is provided in a separate resource.



### *Final Rule's Preamble*

*Almost 20 percent of the Final Rule's preamble is dedicated to explaining the changes to this one section of the regulation. The informed consent section was extensively modified, primarily due to added regulations for the use of biospecimens in research.*

The goal of 46.116 (and 46.117) in the Final Rule is to facilitate the understanding of a prospective subject or legally authorized representative in regards to the reasons why one might or might not want to participate in the research. Part of this includes requiring that only the key information, essential to decision making, receive priority by appearing at the beginning of the consent document and being presented first in the consent discussion.

The unnumbered list of conditions appearing in the pre-2018 rule "introduction" before basic elements of consent have been separated and the conditions that appeared there have been numbered as 46.116(a) (1-3) and (6). Subsections 46.116(a)(4-5) are new and deal with the amount and presentation of information in the consent process.

- NEW** Subsection 46.116(a) has been added, which states that broad consent may be obtained in lieu of a full informed consent only with respect to the storage, maintenance, and secondary research uses of private identifiable information and identifiable biospecimens.
- UPDATED** Subsection 46.116(b) now contains the basic informational elements of consent. Added is a requirement to include one of two statements about the collection of private identifiable information or identifiable biospecimens for future research.
- UPDATED** Subsection 46.116(c) now contains the additional elements ("if applicable"), but three additional requirements have been added for biospecimen use, commercial profit, and return of results.
- NEW** Subsection 46.116(d) addresses elements of "broad consent" (seeking prospective consent to unspecified future research) for the storage, maintenance, and "secondary research use" of private identifiable information or identifiable biospecimens.





Subsection 46.116(e) addresses waiver or alteration of consent in research involving public benefit and service programs. Subsection 46.116(f) addresses “general” waivers or alterations of the informed consent process.



Subsection 46.116(f) reflects a major revision in content, format, and organization of the “general” waivers or alterations of informed consent that formerly appeared in 46.116(d). The format is similar to 46.116(e) above. The four existing waiver conditions are unchanged (but moved to) 46.116(f)(3). An additional criterion was added for research that involves accessing or using private identifiable information or identifiable biospecimens. This new requirement is that the research could not practicably be carried out without accessing or using such information or biospecimens in an identifiable format.

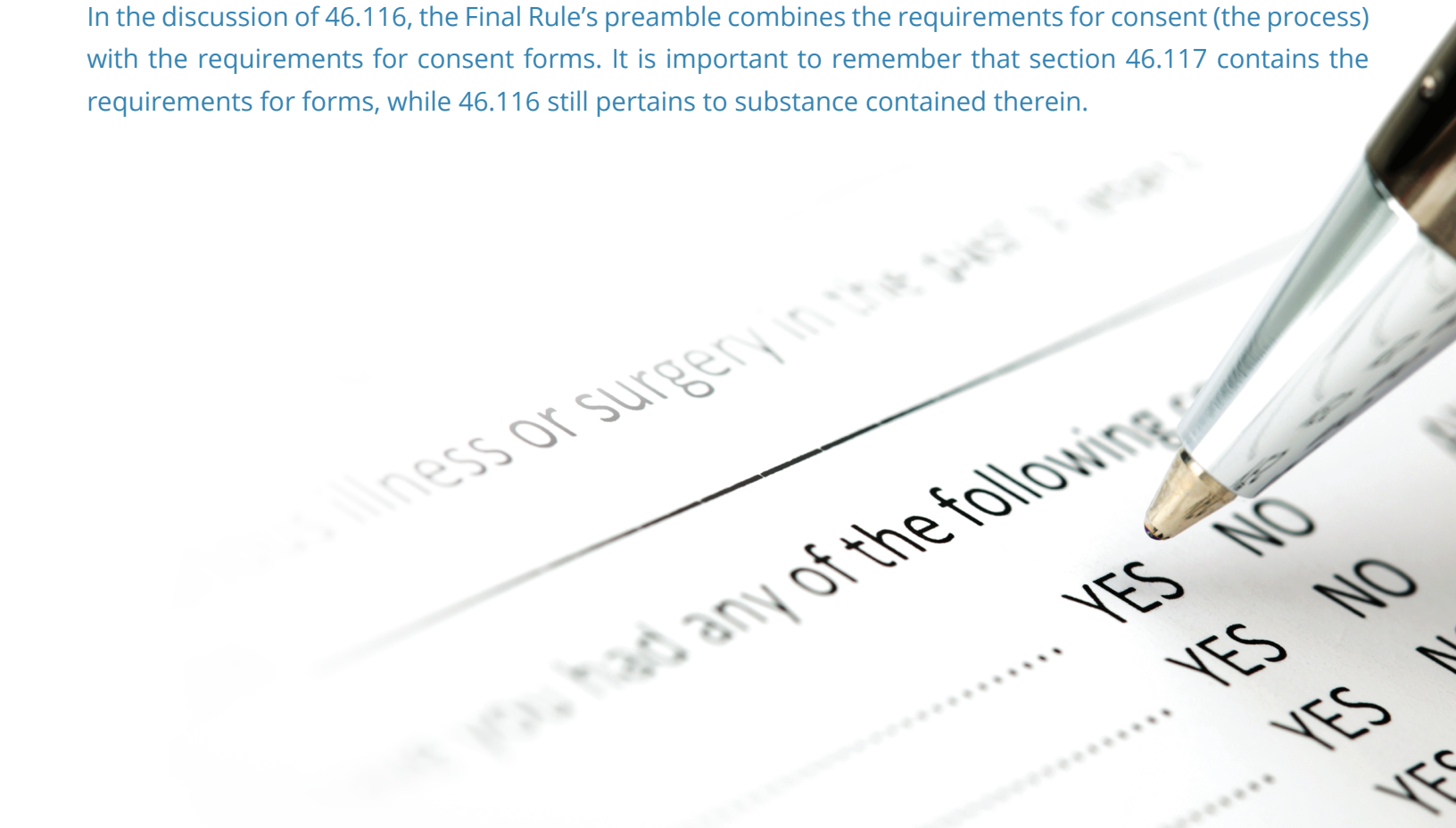


Subsection 46.116(g) addresses exceptions to the requirement for informed consent to obtain information or biospecimens for screening, recruiting, or determining the eligibility of prospective subjects.



In a departure from the focus of 46.116 on the consent process and not on consent forms, 46.116(h) adds a requirement for posting clinical trial consent forms on a publicly available federal website that will be established as a repository for consent forms. Until a special website is developed, or further guidance is available, an option is posting the consent form for the trial to ClinicalTrials.gov.

In the discussion of 46.116, the Final Rule’s preamble combines the requirements for consent (the process) with the requirements for consent forms. It is important to remember that section 46.117 contains the requirements for forms, while 46.116 still pertains to substance contained therein.



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## 45 CFR 46.117, Consent Forms, Signatures, and Waivers

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This section has a few important changes.

- **Electronic signatures** - 46.117(a) now specifically allows electronic signatures and specifies that a written copy must be given to the person signing the consent form.
- **Reading consent forms to subjects** - 46.117(b)(1) specifically allows, but does not require, consent forms to be read to the subject.
- **Concise and focused presentation** - 46.117(b)(2) requires that, when using the short form, the consent must begin with a concise and focused presentation of the key information to assist a prospective subject in understanding the reasons why one might or might not want to participate in the research. This subsection requires that this part of the consent form be organized and presented in a way that facilitates comprehension.
- **Added category for waiver of requirement to obtain signature** - 46.117(c) still addresses waivers for the requirement to obtain a signed consent form and maintains the two pre-existing categories. A third category is added that allows a waiver if the subjects are members of a distinct cultural group or community in which signing forms is not the norm.

➔ It is important to remember that the word “documentation” in 46.117 means obtaining the signature of subjects (or authorized representatives) on consent forms. It does not mean recording that the process has taken place. This is a longstanding unique regulatory use of the word “documentation,” which has caused confusion from its first appearance in 1974.

“Waivers of documentation” only mean that no signature is obtained; it is still good research practice to document (record) occurrence of the consent process and that the subject agreed to participate in the research.

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## FDA Harmonization

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The FDA has stated that it plans to update its regulatory language at 21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (Institutional Review Boards) in concert with the government-wide effort to modernize rules governing the involvement of human subjects in research. The 21st Century Cures Act enacted in December 2016, requires that the Secretary of HHS, to the extent practicable and consistent with other statutory provisions, harmonize the differences between 45 CFR 46, Subpart A, and the FDA human subject regulations.

The expectation is that FDA will issue its own NPRM with proposed changes and eventually an update to those regulations that can be harmonized with HHS. High on that list will be the changes to informed consent (process and forms), continuing review, sIRB review, and biospecimen use. Until an update is issued by FDA, research organizations, institutions, IRBs, and investigators will have to comply with the current FDA regulations as well as the Common Rule (pre-2018 or 2018 version [as applicable]) when both sets of FDA and HHS regulations apply.

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## Guidance Harmonization

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All Common Rule departments and agencies and the FDA are authorized to issue separate guidance about interpreting and implementing the regulations protecting human subjects. In the past, this has led to concerns from institutions, investigators, and IRBs regarding navigating different sets of regulations and department or agency guidance documents.

To promote as much consistency as possible, the Final 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. It does, however, permit guidance to be issued without such consultation when consultation is not possible or desirable given the varied missions of the departments and agencies that oversee the protection of human subjects and differences in their statutory authorities. Explanation of these differences is one of the most important objectives of departmental guidance.

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## References

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- Institutional Review Boards, 21 CFR § 56 (2015).
- National Institutes of Health (NIH). 2016. "Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research." Accessed September 30.
- Protection of Human Subjects, 21 CFR § 50 (2015).
- U.S. Department of Health and Human Services (HHS). 2017. "Federal Policy for the Protection of Human Subjects." Federal Register 82(12):7149-274.

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## Additional Resources

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- FDA's 2006 guidance entitled "Using a Centralized IRB Review Process in Multicenter Clinical Trials" reinforces the FDA's support of centralized IRB review for multi-site research as described in 21 CFR 56.114. It provides researchers and IRB administrators additional clarification regarding roles and responsibilities when relying on an IRB outside the research institution.
- HHS Investigator Responsibilities FAQs available on HHS.gov.