



Final Rule Material: Overview - Comprehensive

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CITI Program Final Rule Materials

- We invite you to use this presentation to introduce those involved in the research enterprise about the changes to the federal Common Rule made by the Final Rule published by HHS in 2017.
- All CITI Program Final Rule materials are available on the "Resources" tab of the CITI Program website, www.citiprogram.org/en/resources.
- **Note:** These resources are based on the Final Rule issued by the U.S. Department of Health and Human Services (HHS) at 45 CFR 46, Subpart A - "Federal Policy for the Protection of Human Subjects" (the Common Rule) on 19 January 2017. These resources have been updated to reflect the 19 June 2018 Final Rule. The general compliance date is now 21 January 2019.

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Overview - Comprehensive

This presentation provides a comprehensive review of the revisions to the Common Rule, including describing changes to each regulatory section from 46.101-46.124

- **Overview - Introduction** presentation provides a brief introduction and overview of the revised Common Rule, including why it was updated, when it is effective, and which research studies must comply with it.
- **Overview - 46.101-46.115** presentation covers changes to those sections, including the definitions, exempt and expedited research, secondary research, IRB membership, IRB operations, IRB review and records, and cooperative research.
- **Overview - 46.116-46.124** presentation covers changes to those sections, including the informed consent document and process.

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Introduction

- Final Rule to revise the current regulations at 45 CFR 46, Subpart A (Common Rule) was published by U.S. Department of Health and Human Services (HHS) 19 January 2017 in the *Federal Register*.
- Revisions intended to “modernize, strengthen, and make more effective” the current system of oversight under the Federal Policy for the Protection of Human Subjects that has been the federal Common Rule since 1991.
 - *Revisions aim to better protect human subjects involved in research, facilitate research, remove ambiguity, and reduce regulatory burden.*

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Need for Updates

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

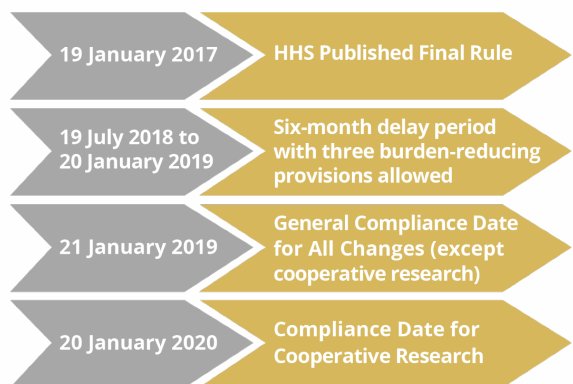
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Compliance Dates and Transition Provisions

- Final Rule does not immediately go into effect.
- Research organizations, IRBs, and investigators will have a some time to revise forms, documents, and practices to comply with the revisions.

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Implementation Dates



The general compliance date for the revised Common Rule is 21 January 2019.

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

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

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Final Rule Delay

An Interim Final Rule as published on 22 January 2018 (“Federal Policy for the Protection of Human Subjects: Delay of the Revisions to the Federal Policy for the Protection of Human Subjects”) initially delayed the general compliance date to 19 July 2018.

A Final Rule as published on 19 June 2018 (“Federal Policy for the Protection of Human Subjects: Six Month Delay of the General Compliance Date of Revisions While Allowing the Use of Three Burden-Reducing Provisions during the Delay Period”) further delayed the general compliance date of the revised Common Rule until 21 January 2019.

The cooperative research effective date was not revised.

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2018 Final Rule Allows Three Burden-Reducing Provisions

During this delay (19 July 2018 – 20 January 2019), institutions are allowed to employ three provisions from the revised Common Rule (2018 requirements) (HHS 2018) including:

- The definition of “research”
- Elimination of continuing review requirement for no more than minimal risk research
- Elimination of IRB requirement to review grant applications

Institutions that transition ongoing research studies to the 2018 requirements during the delay period must document and date their determination (HHS 2018). The research that is transitioned must also fully comply with all of the 2018 requirements beginning on the general compliance date (21 January 2019).

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Transition Provisions – “Grandfathered”

- Actions taken before the compliance dates are “grandfathered.”
 - *Ongoing research studies that were initially approved by an IRB or determined to be exempt before the effective date will not be required to comply with the changes.*
 - *Such research may continue to completion or closure without change.*
- Institutions and IRBs can voluntarily choose to apply the Final Rule on a study-by-study basis or by formally adding a requirement to their policies.
 - *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.*

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Transition Provisions – “Which Rule?”

Research Study Initiation Date	Standards
Research initially approved by an IRB, waived pursuant to [former subsection] 101(i), or determined to be exempt [under former subsection 101(b)] before 21 January 2019. (Grandfathered research)	These studies are by default subject to the pre-2018 requirements (the Common Rule as published in the 2016 edition of the CFR). 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. 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.
Research initially approved by an IRB, waived pursuant to [former subsection] 101(i), or determined to be exempt on or after 21 January 2019.	These studies are subject to the Final Rule (2018 requirements).

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Transition Provisions – “All or None”

- The transition phase is to minimize burdens for ongoing research.
 - *Avoids a requirement for two sets of rules during the life of the research*
 - *Two categories of studies – approved (or determined exempt) before general compliance date or approved (or determined exempt) on or after general compliance date*
 - *Studies are either subject to compliance with pre-2018 rule or Final Rule (not both)*
- After the general compliance date, institutional policy must be in full compliance with either the Final Rule or the pre-2018 Rule (for ongoing research).
- Non-federally funded research is not covered by the Final Rule because the new assurance mechanism eliminates the voluntary extension of the FWA to non-federally funded research.

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FDA Harmonization

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

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Guidance Harmonization

- All Common Rule departments and agencies are authorized to issue separate guidance for interpreting and implementing its regulations.
- To promote consistency, 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.
- Guidance may be issued without consultation when varied missions or differences in statutory authority/scope exist.

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Influencing Factors to Revisions

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

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

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Final Rule Differs from NPRM

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

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

Several NPRM proposals are not being adopted, including:

- *Require that research involving non-identified biospecimens be subject to the Common Rule, and that consent would be needed*
- *Expand the Common Rule to cover clinical trials that are not federally-funded*
- *Concept of "excluded" activities*
- *Standardized privacy and security safeguards for IRB records and identifiable private information and identifiable biospecimens*
- *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*

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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.
- The regulations themselves should be read and understood before implementing changes.
 - *Note - the Final Rule's preamble is a good source for further explanation.*

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45 CFR 46.101, Applicability

- Former applicability requirements have been bolstered with a new condition that non-institutionally based IRBs reviewing federally-conducted or supported research must comply with the Common Rule.
 - *Supports the use of external IRBs and facilitates single IRB (sIRB) use.*
 - *Gives Common Rule departments and agencies the authority to enforce compliance directly with IRBs that are not operated by an assured institution.*
- 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.”
- 46.101(b) (formerly exemptions) is now “Reserved.”

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Federalwide Assurance (FWA)

- The requirement that institutions designate IRBs on the FWA is deleted.
- FWA-holders are not required to routinely submit changes to IRB rosters.
- The old footnote to the Applicability section has been removed to eliminate the voluntary extension of the FWA to non-federally funded research.
 - *Precludes “checking the box” as part of the FWA application*
 - *FWAs now **only** apply to federally-conducted or supported research*
- 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.
 - *Such research will not be subject to federal oversight.*
 - *Intent is to decrease administrative burden and to permit a flexible approach to overseeing research that is not federally-funded.*

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45 CFR 46.102, Definitions

- Definitions have been reordered alphabetically and three new terms were added:
 - *Clinical trial*
 - *Public health authority*
 - *Written or in writing*
- The definition of “written or in writing” is intended to clarify that these terms include electronic formats.
- Terms were also revised, including:
 - *Vulnerable*
 - *Human subject*
 - *Legally authorized representative*
 - *Research*

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45 CFR 46.103, Ensuring Compliance

- The list of written procedures formerly needed for FWAs now appear in the IRB Operations section (46.108).
 - *Conforms to the placement in the FDA regulations (21 CFR 56.108).*
- FWAs will no longer require a declaration of ethics principles to be followed. They will also no longer require a list of reviewing IRBs, an IRB roster, or IRB grant review.
- Documentation of the reliance agreement between institutions and external IRBs is required.
 - *Allocates responsibilities between the institution and the IRB.*
 - *Documentation must be maintained as part of the IRB records.*

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45 CFR 46.104, Exempt Research

- This section (previously “Reserved”) has now been assigned to exemptions.
 - *Exempt categories were previously listed in 46.101(b)*
- Contains many new requirements, primarily due to added regulations when using human-derived biospecimens in research and “conditional exemptions.”
- Final Rule does not restrict or direct how exemptions are determined by institutions.
 - *Due to the potential for conflict of interest, OHRP continues to recommend that investigators not be given the authority to make an independent determination that their own human subject research is exempt.*

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45 CFR 46.104(b)(1-3), Subpart Applicability

- Specifically states the applicability of the exemption categories to Subparts B, C, and D.
 - *Changes the former policy to allow the exemptions to apply to Subpart C for research involving a broader subject population, which only incidentally includes prisoners.*
 - *This change will permit the exempt secondary research use of information or biospecimens from subjects who are prisoners, if that research is not seeking to examine prisoners as a population or subpopulation.*
 - *Intended to allow subjects to continue participation in exempt research if they become “prisoners” during the course of an exempt study.*
- Exempt categories of research allow inclusion of Subpart B (pregnant women) research, and limited inclusion with Subpart D (children) research.

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45 CFR 46.104(d)(1-3 and 5-6), Former Exemptions

- Exempt categories were previously listed in 46.101(b)(1-5) but are now in 46.104 with new restrictions added to each.
- The former exemption for elected or appointed officials or candidates for public office (formerly 46.101[b][3]) was dropped.
- The taste and food quality study exemption (formerly 46.101[b][6]) is unchanged.
 - *Maintains congruence with FDA regulations.*

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45 CFR 46.104, New Exemptions

- Benign behavioral interventions (Category 3)
- Storage or maintenance for secondary research for which broad consent is required (Category 7)
- Secondary research for which broad consent is required (Category 8)

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45 CFR 46.104(d)(2), Revisions

- This is the former exemption for tests, surveys, interviews, or observation of public behavior.
- 46.104(d)(2)(iii) adds a new subcategory for potentially sensitive or harmful identifiable private information from adults if an IRB conducts a limited IRB review.
 - *Application to Subpart D- Children is specifically excluded by 46.104(b)(3).*

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45 CFR 46.104(d)(3)(i), Benign Behavioral Interventions

- Exemption for research involving benign behavioral interventions for collection of information from adults.
 - *Only for behavioral research, not biomedical research.*
 - *Children are specifically excluded by 46.104(b).*
- 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."
 - *Allows for both intervention and data collection.*
- 46.104(d)(3)(ii) defines "benign behavioral interventions."
 - *"Brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing."*
- 46.104(d)(3)(iii) defines "deception about the nature or purposes of the research."
 - *Allows deception if the subject prospectively authorizes it.*

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45 CFR 46.104(d)(4), Secondary Research For Which Consent is Not Required

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

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45 CFR 46.104(d)(7-8), Activities Where Broad Consent is Required

- These two exemptions are related to the secondary research use and storage or maintenance of identifiable private information and identifiable biospecimens and **require** broad consent.
- 46.104(d)(7) covers activities that involve **storage or maintenance** for secondary research use of private information or identifiable biospecimens.
- 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.

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45 CFR 46.105 and 45 CFR 46.106, “Reserved”

- As in the prior regulations, these sections are unused.

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45 CFR 46.107, IRB Membership

- This section was only slightly revised.
- The specific stipulation that IRB membership should not consist entirely of individuals of one sex or profession was removed because the requirement that IRB membership reflect members of varying backgrounds and diversity accomplishes the same goal.
- Other IRB membership requirements are unchanged.

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45 CFR 46.108, IRB Operations

- 46.108(a) is significantly changed, but no new requirements are added.
- Requirement for meeting space and sufficient staff to support the IRB in old section 46.103(b)(2) is now in 46.108(a)(1).
- IRB roster requirements formerly in old section 46.103(b)(3) are now found at 46.108(a)(2).
- The Final Rule deletes the requirement that institutions designate IRBs on the FWA.
- FWA requirements for written procedures in the pre-2018 rule have been included in Final Rule as requirements for IRB operation.
 - *Subsections 46.108(b)(2-4) now agree with FDA regulatory wording.*
- FWA-holders are not required to routinely submit changes to that roster to funding departments or agencies.

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45 CFR 46.109, IRB Review

- Former requirements remain the same as before, with some additions.
- The most substantial changes to this section include:
 - *Addition of “limited IRB review”*
 - *Elimination of continuing review for expedited studies*
- To clarify that IRBs have the authority needed to conduct limited IRB review, the IRB’s authorities (approve, require modifications in, or disapprove research) are modified by adding “including exempt research activities under section 46.104 for which limited IRB review is a condition of exemption.”

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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.
- Limited IRB review has no continuing review requirement.

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Eliminate Continuing Review

- Continuing review is **not** required for research reviewed under limited IRB or approved by expedited review (minimal risk studies).
 - *Unless the reviewer explicitly justifies that it would enhance protection of subjects.*
- Annual or other periodic confirmation to the IRB for exempt research is **not** required.
- Investigators still have the obligation to report certain events (such as unanticipated problems).

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45 CFR 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 involves either one or both of the following:
 - a) *Data analysis, including analysis of identifiable private information or identifiable biospecimens; or*
 - b) *Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.*

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45 CFR 46.110, Expedited Review

- Significant changes have been made to this section in order to allow greater use of this review procedure and help relieve burden on IRBs.
- Except for limited IRB review, all of the determinations for the 46.111 approval criteria must be made.
 - *Only eliminates the need for consideration by a convened IRB.*
- Revised to permit expedited “limited IRB review” for exempt activities related to secondary use.
 - *Most exempt activities do not require any type of IRB review, so “administrative review” could suffice.*

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Expedited Review List

- Under the revised Final Rule, a research study is automatically eligible for expedited review if the study only involves activities on the HHS’ Secretary’s list.
 - *No separate determination of minimal risk is required.*
- Activities on the HHS Secretary’s List are deemed to be minimal risk, unless the reviewer determines and documents why the study involves greater than minimal risk.
 - *There is a regulatory federal agency commitment to evaluate the expedited review category list at least every eight years and amend it as appropriate.*

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45 CFR 46.111, Criteria for Approval

- This section survives largely intact.
- Limited IRB review is solely to make the determination required by section 46.111(a)(7).
 - *Ensure that there are adequate privacy safeguards for identifiable private information and identifiable biospecimens.*
 - *Under limited review, the IRB does not make the determinations in (a)(1) through (6).*
- 46.111(a)(8) defines a “limited IRB review” procedure.
 - *Used for exemptions 46.104 (d)(2)(iii), (d)(3)(i)(C), and (d)(7), and (d)(8).*
- 46.111(a)(8) adds new broad consent determinations for approval of activities that store and/or maintain private information or identifiable biospecimens for secondary research use.

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

- These two sections are unchanged.

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45 CFR 46.114, Cooperative Research

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

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45 CFR 46.115, Records

- Previous wording in this section is largely intact.
- New additions:
 - *Documentation of the rationale for conducting continuing review of research that otherwise would not require continuing review.*
 - *Documentation of an 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.*
- As in the pre-2018 rule, the Final Rule requires IRBs to maintain an accurate roster of IRB members (roster), but FWA-holders are **no longer** required to submit roster changes to funding departments or agencies.

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45 CFR 46.116, Informed Consent Process

- The informed consent section was extensively modified, primarily due to added regulations for the use of biospecimens in research.
- New subsections are added.

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Goal of 45 CFR 46.116 and 45 CFR 46.117

- Facilitate subjects' understanding of the reasons to participate (or not) in the research.
- Requires that "key information" essential to decision making receive priority by:
 - *Being presented first in the consent discussion.*
 - *Appearing at the beginning of the consent document.*

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45 CFR 46.116, Informed Consent Changes

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

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45 CFR 46.116(a)(4), “Reasonable Person” Standard

- The prospective subject (or LAR) must be provided with the information that a **reasonable person** would want to have in order to make an informed decision about whether to participate, and be given an opportunity to discuss that information.
 - *Investigators remain responsible for providing more information when requested by subjects or to improve a particular subject’s understanding.*
 - *Controversial research (if some subjects will find the research objectionable) need a substantial description of the future research in order to meet the “reasonable person” standard.*

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45 CFR 46.116(a)(5)(i)

- Informed consent must begin with a “concise and focused” presentation of “key information.”
 - *Information most likely to assist in understanding why to participate (or not) in the research.*
- Informed consent must be organized and presented in a way that facilitates comprehension.

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“Key Information”

- The preamble lists five elements that cover “key information:”
 - *The fact that consent is being sought for research and that participation is voluntary.*
 - *The purposes, the expected duration of participation, and the procedures to be followed.*
 - *The reasonably foreseeable risks or discomforts to the prospective subject.*
 - *The benefits to subjects or others that may reasonably be expected.*
 - *Appropriate alternatives, if any, that might be advantageous.*
- Essentially, the first four basic elements of consent plus “#8.”

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45 CFR 46.116(a)(5)(ii)

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

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45 CFR 46.116(a), Caution

- “Broad consent” may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) only for storage, maintenance, and secondary research uses of private information and identifiable biospecimens.
- This is an optional/alternative avenue for consent.

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45 CFR 46.116, “Down-shift”

- Inserting a new 46.116(a) means that 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 information or identifiable biospecimens for future research.*
- 46.116(c) now contains the **additional** applicable elements.
 - *Three new additions: biospecimen use, commercial profit, and return of results.*
- 46.116(d) adds broad consent for future research as an alternative.
 - *Replaces old 46.116-d waiver (moved to [f]).*
- Waiver for state/local public benefit/service programs is in 46.116(e).

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45 CFR 46.116(f)

- General waiver or alteration of informed consent is now 46.116(f).
 - *Old 116 (d).*
 - *New criterion added to require that the research could not practicably be carried out without accessing or using the information or biospecimens in an identifiable format.*
- Caution: If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use and **refused** to consent, an IRB **cannot waive** consent for the use of identifiable private information or identifiable biospecimens, nor can they be de-identified and used.
 - *Is asking again permissible? This has not been addressed in guidance or regulation.*

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45 CFR 46.116(g) and (h)

- 46.116(g) allows waivers of informed consent to obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects.
- 46.116(h) adds new requirements for posting “clinical trial” consent forms on a publicly available federal website.

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45 CFR 46.117, Consent Forms, Signatures, and Waivers

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

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“Documentation” in Section 46.117

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

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45 CFR 46.118 through 45 CFR 46.124

- These sections have remained essentially unchanged except for some minor clarifying wording.

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References and Additional Resources

References

- [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.](#)"
- [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.
- U.S. Department of Health and Human Services (HHS). 2018. "Federal Policy for the Protection of Human Subjects: Delay of the Revisions to the Federal Policy for the Protection of Human Subjects." *Federal Register* 83(14): 2885-2894.
- U.S. Department of Health and Human Services (HHS). 2018. "Federal Policy for the Protection of Human Subjects: Six Month Delay of the General Compliance Date of Revisions While Allowing the Use of Three Burden-Reducing Provisions During the Delay Period." *Federal Register* 83(118):28497-520.

Additional Resources

- 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](#).

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