Final Rule Material:
Overview - 46.101-46.115

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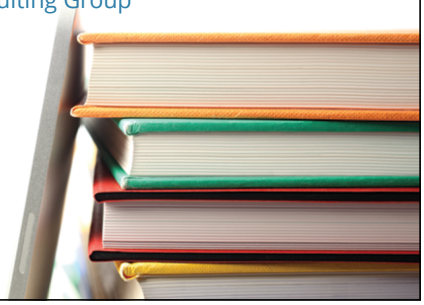

CITI Program Final Rule Materials

- We invite you to use this presentation to introduce those involved in the research enterprise to 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 - 46.101-46.115

This presentation reviews Final Rule regulatory sections 46.101-46.115 and covers changes to the following:

- *Definitions*
- *Exempt, Expedited, and Secondary Research*
- *IRB Membership, Operations, Review, and Records*
- *Cooperative Research*

Other presentations available for the **Final Rule Materials: Overview** material are**:**

- **Overview – Comprehensive** 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 – 46.116-46.124** presentation covers changes to those sections, including the informed consent document and process.

Introduction

- The Common Rule numbering scheme and section titles remain largely intact, but with some movement of text and subsection numbering revisions.
- For consistency and clarity, this presentation will use citations to 45 CFR 46, Subpart A, version of the Final Rule.
- The regulations themselves should be read and understood before implementing changes.
  - *Note - the Final Rule's preamble is a good source for further explanation.*

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."

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.*

Final Rule Delay

- On 19 June 2018, HHS and 16 other agencies published a Final Rule ("2018 Final Rule") to delay the general compliance date until 21 January 2019, but allow for three provisions from the revised Common Rule (2018 requirements) to be available in the delay period (HHS 2018).
- Regulated parties are allowed to implement three specific provisions from the 2018 requirements during the delay period (19 July 2018 – 20 January 2019), including:
  - *The definition of "research" at 46.102(l) of the 2018 requirements*
  - *Elimination of continuing review requirement for no more than minimal risk research at 46.109(f)(1)(i) and (iii) of the 2018 requirements*
  - *Elimination of IRB requirement to review grant applications at 46.103(d) of the 2018 requirements*

Note: If an institution chooses to implement any or all of the three burden-reducing provisions for research during the delay period, then the affected research must comply with all of the 2018 requirements after the general compliance date of the revised Common Rule. Institutions or IRBs must document and date each determination to transition an ongoing research study to the 2018 requirements.

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*

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.*

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.*

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

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

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.*

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)

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).*

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.*

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.*

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.

45 CFR 46.105 and 45 CFR 46.106, "Reserved"

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

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.

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.

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."

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.

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).

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.*

Burden-Reducing Provisions from 2018 Final Rule

- Institutions that voluntarily transition ongoing research during the delay period of 19 July 2018 – 20 January 2019 to the 2018 requirements of the Common Rule are allowed to employ the provision listed in 46.109 (f)(1)(i) and (iii) of the 2018 requirements (exceptions to mandated continuing review).
- This removes the requirement for continuing review for certain research (HHS 2018).

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.*

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.
  - *The reviewer must agree that the research activity is minimal risk.*
- 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.*

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.

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

- These two sections are unchanged.

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.*

45 CFR 46.115, Records

- Previous wording in this section is largely intact.
- New requirements for record retentions:
  - *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.

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 Invesitgator Responsibilities FAQs.