Network for Clinical Research Professionals

Overview of the Revised Common Rule

August 9, 2017
Khemraj Hirani, Ph.D.,
Associate Vice Provost for Human Subject Research
URIDE (University Research Informatics Data Environment)

- De-identified UChart data for research
- Interactive, searchable, user-friendly, “google-like” tool
- UChart records from January 2011 to March 2017 with more than 700,000 patients
- Medical School faculty with a UM login have access
- Access to identifiable data is possible with IRB approval

Learn more and get access
http://miamictsi.org/researchers/research-tools/uride
OneFlorida Statewide Network and Front Door Resource

- A Florida consortium: UM, UF, FSU, affiliated health systems and practices, Florida Medicaid and more
- Two parts to its research infrastructure
  - Practice Network
  - OneFlorida Data Trust: Database of HIPAA-limited EHR and health insurance data
    - 10.6 million patients
    - 168,774,799 encounters
    - 4,100 physician providers
    - 1,240 practices and clinics
    - 22 hospitals
    - 67 Florida counties
OneFlorida Statewide Network and Front Door Resource

The OneFlorida Front Door was created to provide helpful guidelines and instructions for accessing and using the consortium’s vast research infrastructure and resources.

You may want to use it for:

- Request a prep-to-research data query to help formulate research questions or learn more about the data available in the OneFlorida Data Trust.
- Obtain and use patient-level or practice-based data from the network
- Schedule a research consultation
- Get data-related support, study implementation support and research training
- Obtain a OneFlorida centralized IRB

Learn more: http://miamictsi.org/researchers/ctsi-research-services/one-florida-resources
July 19 Post Seminar Survey – Future Topics

- Using Electronic Technology in Clinical Trials: 31
- HSRO Update: 30
- Overview of Professional Certifications: 24
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- Setting up Multi-site Trials: 19
- Verbal and Nonverbal Communication in Informed Consent Process: 16
- Other topics (please describe): 4
Overview of the Revised Common Rule: Changes and Implementation of Review Process to Better Protect Human Subjects and Reduce Administrative Burden

Khemraj Hirani, Ph.D.
Associate Vice Provost for Human Subject Research

08/09/2017
I have no conflict of interest in relation to this presentation except (i) AAHRPP site assessor and (ii) HRPP education module reviewer.

The content is solely the responsibility of the presenter and does not necessarily represent the official views of my employers/alma maters, or my professional associations/affiliations.
Federal Common Rule, NPRM and Final Rule
Timeline of Implementation and transition provision
FDA Harmonization
Changes in Definitions, Exempt and Expedited Review Process
Single IRB Review Requirements
Changes to the Consent Process
  - General Requirement
  - New Subsection
  - Key Information at the beginning of Informed Consent
  - Changes in Basic and Additional Elements
  - Broad Consent
  - General Waiver or Alteration of Consent
  - Posting of Clinical Trial Consent Form
Key Challenges to Implement New Requirements

Learning Objectives
Be familiar with the requirement of Common Rule
Understand the changes to the IRB Review and Informed Consent Process
• This presentation is based on the Final Rule as published in the *Federal Register* on 19 January 2017.

• The Final Rule is still pending executive review.

• We will continue to update our approach as guidance and other official information is released.
Federal Common Rule | Since 1991
---|---
Notice of Proposed Rule Making (NPRM) | 2015 for Public Comments

**UNIVERSITY OF MIAMI**

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January 6, 2016

Submitted electronically at [www.regulations.gov](http://www.regulations.gov)

Jerry Menikoff, MD, JD  
Director, Office for Human Research Protections  
US Department of Health and Human Services  
1101 Wooton Parkway, Suite 200  
Rockville, MD 20852

Re: Docket Number HHS-OPHS-2015-0008-0001, Notice of Proposed Rulemaking:  
Federal Policy for the Protection of Human Subjects, published on September 8, 2015,  
Federal Register (80 FR 53933)

Dear Dr. Menikoff:

The University of Miami (UM) appreciates the opportunity to respond to the Notice of Proposed Rulemaking (NPRM), entitled Federal Policy for the Protection of Human Subjects. Founded in 1925, the UM (fondly known as “the U”) was South Florida’s first university. Today UM is a national research university, comprising 11 schools that house 11 schools and colleges. With

- **The Revisions are intended to**  
  “modernize, strengthen, and make more effective”
  - Better protect human subjects involved in research
  - Facilitate research
  - Remove ambiguity
  - Reduce regulatory burden

- **University of Miami’s comment on this proposal**

**Final Rule to update “the Common Rule”** | 19 Jan 2017
Timeline

1/19/17
- Release of the Final Rule from OHRP
- First major update to the Common Rule since the 1991

1/19/18
- Effective AND Compliance date for the Final Rule
- All research APPROVED on/after this date must follow the Final Rule

1/25/18
- Effective Date for the NIH Single IRB of Record Policy

1/20/20
- Compliance Date for the Final Rule Single IRB of Record Requirement
### Terminology and Implementation

**Terms** | **Definition**
--- | ---
Current Rule: Pre-2018 Rule | Current set of Common Rule regulations that IRBs follow
Final Rule; New Rule, 2018 Rule, Revised Rule; Revised Common Rule | Updated Common Rule, effective January 19, 2018 (except for collaborative research, effective January 20, 2020)
NIH Single IRB Policy | Policy requiring Single IRB Review of multi-site research, effective January 25, 2018

*Transition date for revised Common Rule*

#### Pre-2018 Rule applies to all studies

**Studies initially “approved” before January 19, 2018:**
- **Presumption:** Pre-2018 rule applies
- Institution may elect to apply the revised Common Rule. IRB must document this in writing.

#### Studies initially “approved” on or after January 19, 2018:

The revised Common Rule applies

**January 19, 2018**
• **The effective date = the compliance date**
  - Several organizations have requested an extension of the **compliance date**.
  - For example, the AAMC, AAU, APLU and COGR jointly requested a one year extension of the **compliance date** to January 19, 2019.

• **The current version of the Common Rule still governs Human Subject Research until the effective date of the Revised Common Rule**
  - We understand that there is no provision for adopting the Revised Common Rule early.

• **On the effective date, all new research will be subject to Revised Common Rule provisions**
  - *New* research means research for which a determination has not been made prior to January 19, 2018. *(45 CFR 46.101(l)(4))*
Transition Provisions for Existing Research

• **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.

• **Determinations before compliance date (19 Jan 2018) : “Grandfathered”**
  - All research initiated prior to the effective date will remain subject to the pre-2018 requirements
  - 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.
  - If the Final Rule is applied to the grandfathered research, then all Final Rule requirements must be applied (no picking and choosing what to apply from pre-2018 and Final Rule regulations – it is all or none).

• **Research initially approved by an IRB, waived pursuant to [former subsection] 101(i), or determined to be exempt on or after 19 Jan 2018**
  - These studies are subject to the Final Rule (2018 requirements)
FDA plans to update its regulatory language.
- 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.

Expectation is that FDA will issue its own NPRM for 21 CFR 50 and 56 and eventually a Final Rule.
- Different requirements for waivers, consent process, and consent form language.

Institutions, IRBs, and investigators must comply with FDA and HHS regulations (pre-2018 or 2018 version as applicable) when both apply.
Changes to Definitions

- “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)
- “Intervention,” “interaction,” “private information,” and “identifiable private information” are elevated to get their own subsection numbers and have been changed only to clarify wording.
Following activities are not deemed as Research

- Government functions with separately mandated protections
  - Public health surveillance activities
  - Collection of information for criminal justice purposes
  - Operational activities for national security purposes

- Scholarly and journalistic activities
  - National security operations
  - Public health surveillance
  - Collection of information for criminal justice purposes

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)(iii))” 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)).
**Updates to Exempt Categories & Addition of Limited IRB Review**

**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.

<table>
<thead>
<tr>
<th>Pre-2018 Rule (Current)</th>
<th>Revised Common Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exemption 1</td>
<td>Restrictions added</td>
</tr>
<tr>
<td>Exemption 2</td>
<td>Expanded *</td>
</tr>
<tr>
<td>Exemption 3</td>
<td>Replaced with a new exemption *</td>
</tr>
<tr>
<td>Exemption 4</td>
<td>Expanded and less restrictive</td>
</tr>
<tr>
<td>Exemption 5</td>
<td>Expanded with changes</td>
</tr>
<tr>
<td>Exemption 6</td>
<td>No change</td>
</tr>
</tbody>
</table>

*New Exemption 7
*New Exemption 8
*New - limited IRB review
**Elimination of Continuing Review for Some Research**

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.

<table>
<thead>
<tr>
<th>Does an IRB have to make a “minimal risk” determination for expedited review?</th>
<th>Not under the Final Rule; however, all human subject research that is greater than minimal risk must be reviewed at a convened meeting.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which studies can be reviewed via expedited review?</td>
<td>Research that fits into one or more of the broad categories in the Secretary's list and does not pose greater than minimal risk.</td>
</tr>
</tbody>
</table>
Updates to Multi-Site Research Using Cooperative Review and Single IRB (sIRB) Review

- The Final Rule creates a new requirement for U.S. institutions engaged in multi-site (more than one) cooperative research to use a sIRB for that portion of the research that takes place within the U.S., with certain exceptions.
- This requirement becomes effective three years after publication (20 January 2020).

Note: For studies that must comply with the National Institutes of Health (NIH) policy on sIRB review, the effective date is 25 January 2018.
Exception to the NIH sIRB Policy

• Exceptions to the sIRB policy made when
  o review by the proposed sIRB would be prohibited by federal, tribal, or state laws, regulations or policies.
  o requests for exceptions that are not based on a legal, regulatory, or policy requirement will be considered if there is a compelling justification for the exception.
  o NIH will determine whether to grant an exception following an assessment of the need.
21st Century Cures Act and sIRB Implementation

- Requires US government to reduce “duplication of effort” in human subject protections, suggesting centralized IRB review as one way to do that. Removes “local” from “institutional review board” references for device studies, aligning device regulations with established drug research regulations.

- Published: Dec 13, 2016

- Compliance: Deadline for harmonization of HHS (Common Rule) and FDA regulations to avoid regulatory duplication and unnecessary delays: December 13, 2019
The goal of 46.116 (and 46.117) in the Final Rule is to facilitate a prospective subject's or LAR's understanding of the reasons why an individual might or might not want to participate in the research.

A new approach to consent is requiring that the “key information” essential to decision making receive priority by appearing at the beginning of the consent form and being presented first in the consent discussion.
Key Revisions to Consent

- **New process requirements** for the content, organization, and presentation of information and the process to facilitate a prospective subject’s decision about whether to participate in research.

- **New requirements** for the basic and additional elements of consent.

- **Electronic consent is allowed**, but must provide written copy.

- **New broad consent** elements for the storage, maintenance, or secondary research use of identifiable private information and identifiable biospecimens.
Key Revisions to Consent

- **Changes in the waiver and alteration criteria** for consent.

- **New consent provision** that allows IRBs to approve a research proposal without individuals’ informed consent for screening, recruiting, or determining eligibility.

- **New requirement to post**, to a federal website, a copy of an IRB-approved version of the consent form that was used for enrollment purposes for each clinical trial conducted or supported by a federal department or agency.
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.116(a)</td>
<td>General conditions for consent are now numbered, new addition of reasonable person standard, and key information requirement for informed consent presentation</td>
</tr>
<tr>
<td>46.116(b)</td>
<td>New additional requirement to basic elements of informed consent if research involves collection of identifiable private information or identifiable biospecimens</td>
</tr>
<tr>
<td>46.116(c)</td>
<td>Contains three new additional elements (&quot;when appropriate&quot;)</td>
</tr>
<tr>
<td>46.116(d)</td>
<td>New broad consent section</td>
</tr>
</tbody>
</table>
• **General requirements** for informed consent remain essentially intact.

• **Broad consent** may be obtained in place of informed consent obtained in accordance with the basic and additional elements, but only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens. This is not a waiver, but an alternative.

• **Waiver or alteration of consent** in research involving public benefit and service programs conducted by or subject to the approval of state or local officials is described in 46.116(e).

• **General waiver or alteration of informed consent** is described in 46.116(f).
• Requires that subjects be provided with the information that a “reasonable person” (undefined) would want to have.

• Responsibility remains for the investigator to:
  • Provide more information when requested by subjects
  • Make sufficient time and opportunity to discuss the research
  • Answer questions to improve a subject’s understanding

• For certain types of research (such as, research for which there is reason to believe some subjects will find the research controversial or objectionable), a robust description of the research will be required to meet this reasonable person standard.
This new requirement states that the informed consent process must begin with “key information” and that this part of the informed consent be “organized and presented in a way that facilitates comprehension.”

Currently, there is no federal (including OHRP) guidance defining these terms. Presumably, further guidance will explain what these terms mean and how to achieve the goal along with what qualifies as a concise and focused presentation.
According to the preamble of the Final Rule, a brief description of five “factors” (elements) at the beginning of an informed consent process (and consent form) would encompass the key information including a concise explanation of the following (HHS 2017, 7149-274):

1. The fact that consent is being sought for research and that participation is voluntary
2. The purposes of the research, expected duration of the prospective subject’s participation, and procedures to be followed in the research
3. The reasonably foreseeable risks or discomforts to the prospective subject
4. The benefits to the prospective subject or others that may reasonably be expected from the research
5. Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject
This new section reminds investigators to present informed consent information in sufficient detail and in a way that helps with subject comprehension, not just running down a list of risks and procedures.

The Final Rule’s preamble discusses both the consent process and consent form somewhat interchangeably, and states that “investigators would first have to present the [relatively short concise] information” and “the final rule replaces [the NPRM differentiation between the ‘body’ of the consent form and appendices] with references to material that must be at the beginning of the consent form, versus material that can appear after that beginning section.”
No changes to the eight previous basic informational elements of consent, but a new requirement was added.

New Requirement for Informed Consent Form Language

Added at 46.116(b)(9) is a new requirement to include one of two statements about the collection of private information or identifiable biospecimens for future research:

- Identifiers might be removed and the de-identified information or biospecimens used for future research without additional informed consent from the subject; or

- The subject’s information or biospecimens will not be used or distributed for future research studies even if identifiers are removed.
No changes to the six previous additional informational elements of consent, but three new requirements were added.

- 46.116(c)(7) - A statement that the subject’s biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit.

- 46.116(c)(8) - A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.

- 46.116(c)(9) - For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).
This is a new subsection that addresses broad consent (seeking prospective consent to unspecified future research) for the storage, maintenance, and secondary research use of private information or identifiable biospecimens.

Broad consent for secondary research use is permitted as an alternative to the standard informed consent requirements for a specific research study.
Final Rule added new waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials.

New and complicated section because:

- Research and demonstration projects that are conducted or supported by a federal department or agency are exempt under 46.104(d)(5).
- Restriction that an IRB may not “omit or alter” any of the general requirements (conditions) in 46.116(a).
- Carries an instruction that if an individual was asked to provide broad consent and refused to consent, an IRB cannot waive consent for the use of identifiable private information or identifiable biospecimens.
46.116(f), General Waiver or Alteration of Consent

- Reflects major revision in content, format, and organization of the general waivers or alterations of informed consent that formerly appeared in 46.116(d).

- Four existing waiver conditions are included unchanged in 46.116(f)(3).

- Additional criterion was added for research that involves accessing or using private 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.*
  - *Non-identified information should be used whenever possible to respect subjects’ interests in protecting the confidentiality of their information and biospecimens.*
46.116(f), General Waiver or Alteration of Consent

- IRB cannot waive informed consent under broad consent, or omit or alter any of the required broad consent elements.

- If an individual was asked to provide broad consent and refused to consent, the IRB cannot waive consent.

- Unlike complete waivers at 46.116(f)(1), for alterations at 46.116(f)(2) an IRB may not "omit or alter" any of the general requirements (conditions) in 46.116(a) including the new “format” requirements in 46.116(a)(5). Unless a total waiver under 46.116(f)(1) is granted, single or multiple general conditions cannot be waived/altered separately.

General waiver applies to:

- 46.116(a) - General requirements of informed consent
- 46.116(b) - Basic elements of informed consent
- 46.116(c) - Additional Elements of Informed Consent
New addition that addresses privacy issues regarding waivers of informed consent to obtain information or biospecimens for screening, recruiting (contacting), or determining the eligibility of prospective subjects.

- The previous requirement for IRBs to waive informed consent was viewed as burdensome and unnecessary for protecting subjects, and is not consistent with FDA regulations.

Now in 46.116(g), one of two conditions must be met for an exception:

1) The information will be obtained by communicating with the prospective subject.
2) The information will be obtained by accessing records or stored biospecimens.

This is not a waiver of the consent requirement but rather an exception to the requirement.
New requirements for posting clinical trial consent forms on a publicly available federal website that will be established as a repository for clinical trial consent forms.

The Final Rule’s preamble states “ClinicalTrials.gov might be an appropriate choice as the website … the fact that these trials already have a record in the database will mean that the burden of submission of the informed consent document will be substantially lower.”

Consent forms must meet the requirements of 46.116.

• The Final Rule’s preamble specifically states that posted consent forms will need to comply with the requirement in 46.116(a)(5), such that a concise presentation of key information is at the beginning of consent forms.
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>46.116(h)(1)</td>
<td>The responsibility for posting is on the awardee or the federal department or agency component conducting the study. The posting can take place any time after the trial is closed to recruitment, so long as the posting is no later than 60 days after the last study visit by any subject (as required by the protocol).</td>
</tr>
<tr>
<td>46.116(h)(2)</td>
<td>The redaction of proprietary or institutionally sensitive information of portions of consent forms is allowed.</td>
</tr>
<tr>
<td>46.116(h)(3)</td>
<td>Only one version (not necessarily the final) of the consent form (absent any signatures) for each clinical trial must be posted on the federal website after the clinical trial is closed to recruitment. In accord with the new “single IRB review” requirement, only one posting is required for each multi-institution study. There is no expectation that a version would need to be posted for each study site nor even for each class of subjects in the study (for example, a posting both for adults and for children).</td>
</tr>
</tbody>
</table>
46.116(i), Preemption & 46.116(j), Emergency Medical Care

- These sections were renumbered and clarified, but otherwise unchanged.

- Preemption: Informed Consent requirements do not preempt applicable federal, state, local or tribal laws

- Emergency Medical Care: Nothing in this policy is intended to limit the authority of a physician to provide emergency care
### 46.117, Consent Forms, Signatures, and Waivers

<table>
<thead>
<tr>
<th><strong>Electronic Signatures</strong></th>
<th>Now specifically allows electronic signatures and specifies that a written copy must be given to the person signing the consent form.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Form Requirements</strong></td>
<td>Requires that, when using the short form, the consent form must begin with a concise and focused presentation of the key information to assist a prospective subject in making a decision. This subsection requires that this part of the consent form must be organized in a way that facilitates comprehension.</td>
</tr>
<tr>
<td><strong>Additional Waiver of Documentation</strong></td>
<td>Allows a waiver of requiring subject’s signature on the consent form if the subjects are members of a cultural group or community in which signing forms is not the norm.</td>
</tr>
</tbody>
</table>
Key Challenges to Implement Newer Requirements

- **Technology**
  - Evaluate the institution’s current IRB management software to determine changes required

- **SOPs**
  - Revise the checklists, worksheets and guidance documents

- **Resources**
  - Assess the capacity of current human subject research office to address unique requirements from changing regulations

- **Communication**
  - Engage with research community
  - Local and National HRPP Partners
References and Special Thanks to...

- www.citiprogram.org (CITI) @ BRANY
- www.aahrpp.org/ (AAHRPP)
- HRPP Partners at University of Miami/Jackson Health Services
- www.nihcollaboratory.org (NIH)
- www.ncats.nih.gov (NCATS)
- www.ctsacentral.org (CTSA)
- www.ctti-clinicaltrials.org (CTTI)
- www.FDA.gov (FDA)
Timeline

1/19/17
- Release of the Final Rule from OHRP
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Questions and Discussions