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HIGHLIGHTS IN THIS ISSUE

Deployment of a Comprehensive CRC-centric 5-Prong Recruitment, Engagement, Enjoyment, Advancement, and Retention (REEAR) Operational Model to Augment the Overall Job Satisfaction of a Clinical Research Workforce: A Single Health System-based Clinical Research Institute Experience

Evaluating the Protocol: Can the Clinical Research Site Really Do this Study?

Research with Respect: Advocacy in Pediatric Clinical Trials

Understanding the Revised Common Rule (45 CFR 46)

Resolving and Preventing Repetitive Problems in Clinical Trials

Remaining OPTIMISTIC: Project Management for New Funding Mechanisms

Study Finds Need for Less Paper, More Automation in Clinical Research

Updates to ICH E6 Good Clinical Practice

Challenges and Opportunities in Integrative Medicine Research

quality education

peer recognition

professional certification

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Understanding the Revised Common Rule (45 CFR 46)

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Abstract: *The Common Rule provides the institutional review board (IRB) and informed consent requirements for research funded by the Department of Health and Human Services and fifteen other federal agencies. In 2017, a revised Common Rule (45 CFR 46) was released. This article summarizes the major changes to informed consent and the single IRB requirement as well as other changes that impact researchers, research staff, and clinical research organizations. The potential ramifications of these changes are highlighted.*

Introduction
The Common Rule provides the IRB and informed consent requirements for research funded by the Department of Health and Human Services and fifteen other federal agencies. The revised Common Rule does not, however, cover research overseen by the U.S. Food and Drug Administration (FDA). The FDA has not signed on to this version of The Common Rule (as of January 2018), and it plans to make changes later.

The revisions to the Common Rule are the first substantial revisions to the human subject protection regulations since 1981. Work on the revised Common Rule started in 2011, with an Advance Notice of Proposed Rulemaking. In 2015, a Notice of Proposed Rulemaking was released. The Revised Final Common Rule was released in January 2017.

Theoretically, the revised Common Rule may never be effective. It was released on the last day of the Obama Administration and has been under review by the Trump administration. The effective date is supposed to be January 2018. If the revised Common Rule is released, the implementation date is likely to be extended.

The FDA has been working on revising its regulations to adopt and harmonize as closely as possible to the new version of the Common Rule, so the regulations will be as in-sync as possible. It will probably take a year for the FDA to finish revising its regulations after the Common Rule becomes effective.

Changes to Informed Consent
The revised Common Rule includes significant changes to informed consent, including the reorganization of existing language (Table 1). The biggest change is the new requirement to start the informed consent process with a presentation of key information. The regulation states:

> "Informed consent* must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally-authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension." (.116(a)(5)(i))

** Not applicable to broad consent*

"Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate." (.116(a)(5)(ii))

This sounds good, but unfortunately the terms "key information," "concise," and "focused" are not defined or described. How to provide information that "facilitates comprehension" is also unclear. Some people say that the purpose section of the informed consent form already does this. Other people say that this must be presented in a new three- to five-page pre-consent document, followed by the regular informed consent form. Still other people say that the government will provide bullet points for use in the informed consent form.

The author's best guess is that there will be a one- to three-page pre-section to the informed consent document. The difficulty is that prospective subjects come to a study with different clinical backgrounds. Some people have failed previous treatments and others have not. It is difficult to develop language tailored to an individual subject or group.

New elements of informed consent include a required statement about identifiable private information/ biospecimens and other new elements that must be used when appropriate (Table 2). The requirement for identifiable private information/ biospecimens states the consent form must include:

"(i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally-authorized representative, if this might be a possibility; or

(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies." (.116(b)(9))

Clause (i) reflects the current regulatory framework and what often happens with information and biospecimens. If the identifiers are stripped from information, it is no longer human subjects research, and consent is not necessary. Just about everyone—sponsors, government agencies, and researchers—will want to use this statement. In earlier versions of the Common Rule, there was a great deal of movement toward making human tissues automatically identifiable, thereby requiring consent and IRB review. The negative reaction from the public about this led to its removal from the current version of the Common Rule.

A new additional element of informed consent, to be used when appropriate, is:

"(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;" (.116(c)(7)-(9))

Figure 1: Changes to Informed Consent

- Be aware that ethics affects everything clinical research professionals do (big and small):
- An ethical mindset is necessary in daily practice
- Know the available resources in the event of an ethical dilemma
- Understand what the participant and family is facing:
- Imagine how difficult decisions about pediatric clinical research can be
- Consider the possible struggles of the individual or family

The author believes that most researchers and funding agencies will say that the biospecimens might be used for commercial profit and the subject will not share in the profit.

Another new additional element of informed consent, to be used when appropriate, is:

"(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions" (.116(c)(7)-(9))

There has been a great deal of movement toward disclosure of general and individual research results to subjects. Merck, Pfizer, and some other big companies have initiatives to disclose research results. The Secretary's Advisory Committee on Human Research Protections has issued a series of recommendations on this issue as well.

Disclosing research results gets tricky when there are incidental findings, such as discovering a brain mass or something else that has clinical implications but was not part of the research. Whether that fits into the new regulatory disclosure requirement is an open question.

The third new additional element of informed consent, to be used when appropriate, is:

"(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e.,

Figure 2: New Elements of Informed Consent

Required information about identifiable private information/ biospecimens:

"(i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies." (.116(b)(9))

Additional elements of informed consent, when appropriate:

"(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;
(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germ line or somatic specimen with the intent to generate the genome or exome sequence"

sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)." (.116(c)(7)-(9))

Some academic IRBs plan to roll out the new informed consent requirements for all research, regardless of funding, because this will be more administratively efficient for them. Thus, researchers may be forced into using the Common Rule for all research early on. The author believes that it would be better to do a test run with research funded by the National Institutes of Health and other government agencies, but wait to apply the new requirements to industry-regulated research until the FDA comes out with its version of the Common Rule. The author hopes that the IRB community will have enough common sense not to apply the revised Common Rule to all research right away.

The Broad Consent Option

The revised Common Rule also has a broad consent option, as an alternative to the regular consent process, for research involving the collection of biospecimens or other identifiable private information (.116(d)). While the idea that all human tissues will be considered identifiable was removed from the regulation, this is a remnant regulation where theoretically, an institution could set up a process whereby everybody is given an informed consent form that states that the institution wants to collect the tissue or information and use it later for research. This is not very practical, however, because if a subject does not provide consent, then an administrative process is necessary to ensure that the person's tissue or information is not later used in research.

Many elements of the broad consent (Table 3 on the next page) are the same as the regular informed consent. The amount of specificity that is required will determine the usefulness of the broad consent. Under element #3, for example, the broad consent requires stating the "types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens." The biospecimens will sit around for a long time. If the consent form can state that the institution expects the biospecimens to be used by researchers and commercial companies, that will be feasible. Under element #4, most people would want to state that there is no time limit on using identifiable private information or identifiable biospecimens for research purposes.

The phrase "they might have chosen not to consent to some of those specific research studies," in element #5, is puzzling. Does this mean researchers need to provide a list of the types of research that might be conducted or examples such as abortion research or genetic profiling? Elements #6, #7, and #8 are fine, and elements #7 and #8 are from the current informed consent requirements.

Both element #9 and one of the additional elements of informed consent require a statement about any research that involves the collection of identifiable private information or identifiable biospecimens that either:

- Identifiers might be removed, and the information or biospecimens could be used for future research or
- The information or biospecimens will not be used for future research.

Most people will probably tell subjects that they might strip the

Figure 3: Required Elements of Broad Informed Consent (.116(d))

"(1) Information required in paragraphs (b)(2), (b)(3), (b)(5), and (b)(8) and, when appropriate, (c)(7) and (9).

(2) A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;

(3) A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;

(4) A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which could be indefinite) as well as a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which also could be indefinite);

(5) If the subject or legally-authorized representative is not provided details about specific research studies, then the subject/representative must be provided a statement that the subject/representative will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that the subject/representative might have chosen not to consent to some of those specific research studies;

(6) Unless it is known that clinically-relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed must be provided to the subject; and

(7) An explanation of who to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and who to contact in the event of a research-related harm.

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and

(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

(i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally-authorized representative, if this might be a possibility; or

(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies."

identifiers off and use the information or biospecimens for research, thus providing flexibility for future use of the tissues.

The major change is that if someone says no to having their private information or biospecimens used in research, researchers must honor that.

General Waiver or Alteration of Consent

The revised Common Rule makes changes to the waiver of informed consent (.116(f)) (Table 4 on the next page). One of these changes is that if an individual refuses to consent under the broad consent, the IRB cannot waive consent for the storage, maintenance, or use of identifiable biospecimens. The phrase "identifiable biospecimens" is important because researchers can still obtain broad consent, strip the identifiers, and use biospecimens in research as they do now. However, researchers cannot use identifiable biospecimens if the subject said no to the broad consent.

The Secretary's Advisory Committee on Human Research Protections has also started to think about what happens if someone goes into Hospital A and refuses to provide broad consent but then goes into Hospital B and agrees to broad consent. Can information from Hospital A go to Hospital B? Does the later consent override the earlier refusal to consent? IRBs cannot waive the key information requirements. If the broad consent is used, the IRB cannot omit or alter any of its elements. The existing waiver of consent that is used for research

Figure 4: General Waiver or Alteration of Informed Consent (.116(f))

- "When individuals refuse to consent under the broad consent, the IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable biospecimen."
- "IRB may not omit or alter any of the requirements described in paragraph (a) of this section:
  - E.g., the 'key information' requirements"
- "When a broad consent procedure is used, the IRB may not omit or alter any of the elements from (.116(d))."
- Current waiver requirements:
  - Research involving no more than minimal risk to the subjects.
  - Research that could not practicably be carried out without the requested waiver or alteration.
  - The waiver or alteration will not adversely affect the rights and welfare of the subjects.
  - Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
- New criterion for research involving identifiable private information or identifiable biospecimen:
  - "The research could not practicably be carried out without using such information or biospecimens in an identifiable format."

funded by the Department of Health and Human Services or regulated by the FDA states that the IRB can waive consent if:

- The research involves no more than minimal risk to the subjects
- The research could not practicably be carried out without the requested waiver or alteration
- The waiver or alteration will not adversely affect the rights and welfare of the subjects
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The revised Common Rule adds a new criterion for research involving identifiable private information or identifiable biospecimen:

- "The research could not practicably be carried out without using such information or biospecimens in an identifiable format."

Posting of Informed Consent Forms, Document of Consent, and Other Changes

For all clinical trials conducted or supported by a federal department or agency, a version of the informed consent form must be posted on a federal website after the clinical trial is closed to recruitment, and it must be posted no later than 60 days after the last study visit by any subject as per (.116(h)). This requirement will not apply to commercial sponsors until the FDA adopts it.

The goal of this requirement is to increase transparency in clinical research by allowing people to read informed consent forms. This will also enable researchers to access other informed consent forms that they can use as models for their informed consent forms. Pharmaceutical and device companies do not like the idea of posting informed consent forms and are concerned that trial lawyers will review the posted forms to look for things that might be questionable.

The revised Common Rule made some minor changes to documentation of informed consent, including explicitly recognizing electronic signatures. There has been a great deal of movement toward eConsent, and the FDA and the Office for Human Research Protections have published a joint guidance on eConsent.

There is a new waiver option for "members of a distinct cultural group or community in which signing forms is not the norm."

When using the short form, researchers must indicate that "the key information required by (.116(a)(5)(i)) was presented first to the subject, before other information, if any was provided." The short form, however, is rarely used.

Changes to Exemptions from Informed Consent

The revised Common Rule made changes to five of the six existing categories of exempt research, and it added three new categories. In addition, some "exemptions" have been added to the definition of "research." Some of these changes will be used often, while others will rarely be applicable.

The overall goal of these new regulations was to reduce administrative burden on minimal risk research. The main focus in the regulations that survived the iterations was to:

- Enable more minimal risk research to be conducted without IRB review (but the research may still need an exemption review)

- Require informed consent less often
- Reduce the burden on researchers.

Many people think that the Trump administration will approve the revised Common Rule because it meets the administration's stated goals that regulations must reduce burden.

Much educational research is exempt. Research involving tests, surveys, interviews, and observation continues to be exempt. The revised Common Rule adds that the IRB must conduct a limited review, focused on privacy and confidentiality, for research with identifiers that involves potentially sensitive information. This is a new class of IRB review.

Psychological research involving benign behavioral interventions is covered in (.104(d)(3)). Benign behavioral interventions are defined as:

- "…brief in duration, harmless, painless, not physically invasive,…"
- "…play an online game, solve puzzles under various noise conditions,…"

Deception is allowed; however, researchers must inform subjects that they will be "unaware of or misled regarding the nature or purposes of the research."

Revisions to secondary research on existing samples will have a major impact on clinical research (.104(d)(4) (7)) and (8)) (Table 5). Informed consent is not required for secondary research uses of identifiable private information or identifiable biospecimens, if at least one of four criteria is met:

1. *The identifiable private information or identifiable biospecimens* are publicly available. This is what the current regulations require.
2. *"Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects."* This is the current language. The investigator must also promise not to contact the subjects or re-identify subjects.
3. *"The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164…. [HIPAA]."* Data that fall under the Health Insurance Portability and Accountability Act (HIPAA) used in research conducted by covered entities does not need a separate exemption. IRBs may still want to see the research to confirm that it qualifies for an exemption because it is covered by HIPAA. This has the potential to be a very useful exemption for many institutions. The Secretary's Advisory Committee on Human Research Protections is debating whether this criterion covers biospecimens.
4. *The research is under other privacy protection (various federal privacy laws).*

This expands the exemption and reduces the burden for minimal risk research. It also allows researchers to collect information or biospecimens in the future, after the exemption determination. This is new, as under the current regulations, the information or biospecimens have to already be in existence.

Figure 5: Secondary Research

- Revised:
  - Secondary research (.104(d)(4))
- New:
  - Storage and maintenance for secondary research (.104(d)(7))
- New:
  - Use of information or biospecimens in secondary research (.104(d (8))

Storage and maintenance for secondary research for which broad consent is required is new (.104(d)(7)). Research conducted under broad consent can now be done as an exemption.

Changes to Definitions

The revised Common Rule changed the definitions of "research," "legally authorized representative," "human subject," and "vulnerable," and added a definition for "clinical trial." Exemptions were added to the definition of "research," clarifying things that people were uncertain about:

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

The definition of "research" now also identifies four types of activities that are not research:

1. Much social science research
2. Public health surveillance activities
3. Collection and analysis of information, biospecimens, or records by or for criminal justice or criminal investigative purposes
4. Authorized operational activities for intelligence, homeland security, defense, or other national security missions.

Some states do not have a clear definition of "legally authorized representative." The revised Common Rule states that if there is no applicable law addressing this issue, the institution can write a policy defining a legally authorized representative.

A definition of "clinical trial" was added, since the informed consent forms for clinical trials must now be posted.

> "Clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes."

Informed consent forms do not need to be posted for other types of research, such as behavioral research.

Changes to the definition of "human subject" are important to IRBs, but they will not have much impact on researchers. The changes include uses of identifiable information and identifiable biospecimens, as well as a definition of identifiable biospecimens. The changes also require federal departments and agencies to reexamine the meaning of "identifiable private information" and "identifiable biospecimen" within one year and regularly thereafter (at least every four years).

The definition of "vulnerable subjects" is now consistent in all three references in the Common Rule. Certain examples have been removed: "pregnant women" and "handicapped." Mentally disabled persons" was changed to "individuals with impaired decision-making capacity."

Continuing Review and the Single IRB Requirement

Continuing review will no longer be required for minimal risk research that is research eligible for expedited review. IRBs still oversee minimal risk research, so if the research is changed, investigators must still obtain IRB review. IRBs, however, will have to decide how to administratively put this into effect, as the requirement for continuing review provided an opportunity for the IRB to assess whether the research was still open or not:

- Should the IRB keep every minimal risk study open forever because there is no continuing review to tell them when the study ends?
- Should investigators be required to tell the IRB when the study ends?
- Can IRBs simply give an initial approval and then wait for the submission of further information, without maintaining an open file?

The Common Rule version of the single IRB requirement has a three-year implementation date; however, in January 2018, the NIH began requiring single IRB review for any grant that involves more than one institution. IRBs are scrambling to implement this, including determining ground rules for adverse event reporting, conflicts of interest, and other issues. Also, under the new rule the Office for Human Research Projects will have authority for regulatory oversight of external (non-institutional) IRBs.

Conclusion

Transitioning research will be difficult. Research that was approved before the implementation date of the revised Common Rule (planned for January 19, 2018) complies with the pre-2018 requirements. The institution engaged in the research, however, can comply with the 2018 requirements if they determine that the ongoing research will comply with those requirements and they document that determination.

There are many questions about transitioning research. For example, if an IRB decides to apply the new regulations, does the informed consent form need to be revised to include the new concise information and other new requirements? If so, do all subjects have to be re-consented or would the revised informed consent form only be used with new subjects?

Is continuing review necessary for minimal risk research started before the implementation date? If it is no longer required, does that mean informed consent forms must be revised with the new requirements?

Since the FDA has not adopted the revised Common Rule yet, when determining whether to adopt the new requirements for research started before the implementation date, researchers will need to consider whether the research is funded by NIH or another government agency and/or under FDA oversight.

Researchers and IRBs will need to be very careful about whether the new or old rules apply to a given study and keep track of this. The transition will be most difficult for federally-funded and FDA-regulated research because researchers must apply the new requirements without violating any existing FDA requirements. The solution is to apply the stricter requirements. Over time, researchers and IRBs will get used to doing this.

The other difficulty with the transition is that different stakeholders have different needs and interests. The investigators will want one thing and academic centers and hospitals will want something different. IRBs will want to do whatever is easiest for them. Commercial sponsors will want to do what is best for them.