# Clinical Researcher
# December 2019
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## *Rules and Regulations: Staying on the Straight and Narrow*

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Clinical Research—December 2019 (Volume 33, Issue 10)

PEER REVIEWED

# Opinion: Shedding Light on the Impact of the Revised Common Rule on the Informed Consent Document

Joy Jurnack, RN, CCRC, CIP, FACRP

As of January 21, 2019, updates to the Common Rule (the Federal Policy for the Protection of Human Subjects governing institutional review boards [IRBs]) were implemented for the first time since the Rule was originally made into law in 1981. The policy gained its nickname because it is the "common rule" enforced on all agencies conducting human research within the U.S. government.{1}

As is the case during any regulatory update, revisions to the Common Rule took years to finalize, endured public comment, and were long anticipated by those "in the know" about them pending their eventual enaction. However, not everyone in clinical research lives on both the clinical side and the administrative side to the extent of being aware of what was happening with the Common Rule and what the updates mean to the clinical research enterprise today.

**Exploring the Rules**

As both a certified clinical research coordinator (CCRC) and a certified institutional review board professional (CIP), I find knowledge of how to conduct research from a sound scientific perspective as important and interesting as the regulations governing the ethical realm of human subject protections. I can assure you, not everyone shares my passion, which is exactly why, after reviewing the details about the research team's responsibility in the Common Rule revisions, I felt some further clarity could be helpful to those of us affected by this revision.

When involved in federally funded studies, all research within the institution must adhere to the Office for Human Research Protections' (OHRP's) Common Rule. Research involving drugs and devices are federally regulated by the U.S. Food and Drug Administration (FDA), and while FDA and OHRP are both under the U.S. Department of Health and Human Services, their individual regulations are similar but not exact. Keeping the regulations straight can lead to confusion, and this is where your IRB, the committees operating on a local (site) or central (for-profit) level to which research teams submit all required paperwork for review before the trial can launch, becomes your lifeline. Embedded within the IRB's procedures are all the necessary questions to ensure you have met the requirements for having the conduct of your research approved, regardless of funding or region.

In addition, any pharmaceutical-sponsored research ideally follows the guidance of the International Council for Harmonization (ICH) E6(R2) guideline for Good Clinical Practice (GCP) and the tenets of the Nuremberg Code,{4} both of which are widely incorporated into research conducted internationally. As a clinical research professional, your knowledge of these documents and the application of their contents can weigh heavy when trying to write or implement a protocol. Again, this is where the IRB of record offers directions and will be the only way for you to craft informed consent documents that will be approved, not to mention actually conduct your study.

Let's imagine for a moment that your team focuses on sponsored studies of potential new drugs and/or devices at an academic medical center following the OHRP's Common Rule. This agreement with the federal government allows it to hold a Federalwide Assurance (FWA),{5}

which is a number given to IRBs and commits them to follow OHRP in order to accept federal funds or grants, as in a National Institutes of Health (NIH) award. An institution can have its FWA taken away, thus losing all its federal money, including NIH funding, unless the entire institution follows all the rules of OHRP. The IRB stands as the gatekeepers, whether centrally or locally, minding all research on human subjects (and animals, but that's a topic for a different author to tackle).

**What's New for the Research Team**

The change I want to summarize here for my fellow research professionals is the impact the revisions to the Common Rule have on the informed consent document. But to be clear, when working with either investigational drugs or devices with financial support from any kind of sponsor organization, the research team is advised to comply with the Common Rule (OHRP), FDA regulations, ICH GCP, and Nuremburg Code.

As a research nurse, I have done extensive training and research on language and understanding the document of informed consent. I have been one who has advocated for informed consents to have "information that is given to the subject or representative (that) shall be in a language understandable to the subject or the representative" (21 CFR 50.20 in the *Code of Federal Regulations*).{6} This has been a part of the FDA regulations for years, but implementation of it has remained unclear to research teams and largely unfollowed in terms of the consent document presented to the subject.

The Common Rule updates many items, and the informed consent is the focus here. The Rule says that it establishes "new requirements regarding the information that must be given to prospective research subjects as part of the informed consent process." It looks like OHRP is requiring what has already been required, but not enforced, in FDA regulations. In broad strokes, the following are changes to the general requirements for informed consent (for all the details, see *Federal Register* Vol. 82, No. 12 from January 19, 2017, pages 7210 to 7231){7}:

1. The content, organization, and presentation of the informed consent form are designed such that the subject can decide to participate or not participate in the research.
2. Additions have been made to the elements/sections of the consent.

3. Broad consent may be given for storage, maintenance, or secondary research use if using identifiable biospecimens.
4. Changes have been made to how any waivers and later alterations of consent are handled.
5. If certain conditions are met, the IRB may approve research where the investigator collects biospecimens without the subjects' consent for purposes of determining the eligibility of subjects.
6. The IRB-approved consent is available on a federal website for review.

IRBs were left to interpret and implement these changes. An institution receiving federal funds, as mentioned above, is expected to incorporate the changes within a concise summary (not defined in the regulations) on the front page on the informed consent—before any of the medical jargon included in the first few pages of a "greater than minimal risk" study. Since individual IRBs are left to their own resources to craft this additional information, you likely will see a revised informed consent form laid out differently depending upon the IRB. In essence, an IRB wants potential subjects to know:

- Why should I be in this study?
- Why shouldn't I be in this study?
- What is the research question and why am I a candidate for the research?
- What types of activities are considered research?
- How much personal, identifiable information will be collected?
- If biosamples are taken from me, how will they be identified, stored, and used, and will any information either be connected to me or returned to me after completion of the study?

What runs consistently through the request for key information is the call for simplicity in language, including a clear description of why one might (or might not) want to participate in the study. For all studies, regardless of their funding source, such important information should be right up front in the document for the subject to read and understand; they shouldn't have to sift through endless scientific jargon and medical lingo to tease out the essence of what the research study is all about.

To date, OHRP has not offered guidance on the revisions. IRBs want to honor the revisions and will assist the research team, but it is up to the team to complete whatever template the IRB supplies with the details required to comply with the Common Rule. IRBs will assist and edit, but the initial work is on the research team. Research staff should be ready and willing to compile this information initially; having an educated potential subject to deal with makes the job of either explaining a study or obtaining consent easier.

**Conclusion**

The complexities inherent in any regulatory revisions to key human subject protections–related documents are exactly, in my humble opinion, why having a working knowledge of the responsibilities of the IRB and appreciating the impact of its functions on the research team are necessary for fostering collective collaboration and a collegial working relationship between these two arms of the clinical research enterprise. Toward this end, I suggest it's time for the Public Responsibility in Medicine and Research (PRIM&R){8} and Association of Clinical Research Professionals (ACRP){9} organizations to form an alliance, working together through education and annual conferences to update research professionals on all aspects of research—both administratively and clinically. Upholding the tenets of human subject protection is our shared goal.

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4. Nuremburg Code: https://history.nih.gov/research/downloads/nuremberg.pdf
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8. PRIM&R: https://www.primr.org/
9. ACRP: www.acrpnet.org

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PEER REVIEWED

# The Importance of Japan's Clinical Trials Act to Research Sites, Staff, and Training Opportunities

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In April 2017, the Clinical Trials Act was established in Japan as a result of several research misconduct issues related to studies that had been initiated by investigators or sponsored by industry. One of the issues included data manipulation in "a post-marketing trial of Diovan (valsartan) conducted by a team at Kyoto Prefectural University of Medicine [and led] by a former professor whose published papers on valsartan were withdrawn from medical journals after questions were raised over the validity of the findings."{1}

The Clinical Trials Act encourages investigators and industries to follow appropriate processes and procedures, and to be transparent in the conduct and reporting of their studies by imposing penalties for violation of the law. It applies specifically to research involving interventional studies with unapproved or off-label medical products use, or on-label medical products use sponsored by industries.

The Act applies only to interventional studies, and not to prospective or retrospective observational studies. As a result, investigators and institutional review board/ethics committee (IRB/EC) staff need to take time to discuss and conclude if a proposed research project falls into this category, because the classification of observational or interventional studies defined by the Japanese Ministry of Health, Labor, and Welfare (MHLW) is complicated. The MHLW "is in charge of the improvement and promotion of social welfare, social security and public health … and [is] in charge of pharmaceutical regulatory affairs in Japan."{2}

Further, the Act is very specific in regard to on-label or off-label usage as recognized by package inserts under the revised Pharmaceutical Affairs Law. It is a very time-consuming process to define on-label or off-label use following the highly detailed rules under the Act, and sometimes investigators need to inquire to MHLW to conclude if a particular usage is on-label or off-label. Even healthcare professionals may misunderstand off-label use as on-label use because some off-label uses are reimbursed by the national healthcare insurance by the notice of MHLW.

In the past, research was conducted under "ethical guidelines for medical and health research involving human subjects for other clinical research,"{3} but that has now been replaced with the Clinical Trials Act. The Act has newly established rules which were not included in previous guidelines, such as reinforcing the functions and managing the transparency of IRBs/ECs (now called certified IRBs), clarifying principal investigators' responsibilities, and enriching the arenas of education and training, monitoring and auditing for data fabrication prevention, maintaining record archives, and handling conflict of interest (see Figure 1).

**Figure 1: The Main Changes in the Clinical Trials Act**

1. Procedure for clinical trial implementation

  1.1 Measures for specific research implementation

    1.1.1 Requirements for the quality of research (e.g., the obligation of monitoring and auditing, record archives)

    1.1.2 Transparency between research sites and pharmaceutical industries (e.g., compliance with the management of conflict of interest)

    1.1.3 Compliance with standards for the conduct of clinical trials

    1.1.4 Patient advocates (e.g., protecting personal information and obtaining informed consent)

    1.1.5 Submission of research plan reviewed by certified IRB

2. Reporting to MHLW and certified IRB about suspected unexpected serious adverse reactions

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|---|
| 3. Guidance and supervision by MHLW for violation of implementation standards<br><br>4. Contracts between sponsor industries and the study sites and disclosure of provided funding |

*Source*: Japan MHLW. The Summary of the Clinical Trials Act.

The Clinical Trials Act advocates direct communication between principal investigators and the MHLW by written notifications regarding clinical research plans, suspected unexpected serious adverse events, or serious noncompliance, which used to be via the investigator's site director and IRB/EC in the previous guideline.

There also are laws, regulations, and guidelines with regard to clinical research in Japan other than the Clinical Trials Act, such as the revised Pharmaceutical Affairs Law, the tenets of Good Clinical Practice (GCP), ethical guidelines for medical and health research involving human subjects for other types of clinical research, and several others. Clinical research for Investigational New Drugs or Biologics License Applications for manufacturing and marketing approval must adhere to the International Council for Harmonization (ICH) GCP guideline or a Japan-specific GCP (J-GCP) guideline, and other clinical research adheres to the Clinical Trials Act or other guidelines.

There are similarities between ICH-GCP or J-GCP and the Clinical Trials Act (see Figure 2), whereas one difference is evident in the submission of adverse event reports, because the Act obligates submission only of reports on serious related adverse events with timelines and contacts that differ depending on whether the product in question is being studied on-label or off-label and whether the reaction is suspected or unsuspected, expected or unexpected, and serious or non-serious.

**Figure 2: Similarities Between ICH-GCP or J-GCP and the Clinical Trials Act**

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|---|
| Obtaining informed consent<br><br>Protection of Personal Information<br><br>IRB/EC review<br><br>Reporting to IRB/EC and MHLW<br><br>Monitoring and audits<br><br>Compensation and indemnification<br><br>Transparency of funding and conflict of interest |

| |
|---|
| Information disclosure<br><br>Record archives |

*Source:* European Medicines Agency. Guideline for Good Clinical Practice E6(R2).

The other difference is that study protocols should be reviewed by a certified IRB approved by MHLW and, typically, the Act requires central review for multisite studies, not multiple local ones, by a certified IRB to prevent deviation or differentiation in the quality of the review. Healthcare supplied specifically due to research conducted under the Act cannot use Japan's medical care coverage system, which reimburses concomitant drug fees and examination fees during a test drug dosing period, whereas studies conducted only under ICH-GCP or J-GCP are covered, so one of the burdens for investigators under the Act is establishing operating research budgets and finding sponsors.

**Educational Requirements for Becoming an Investigator**

In the present circumstances, principal investigators in Japan usually work full-time in medical practice; they may have experience with a few sponsored studies following ICH-GCP or J-GCP, but little or no experience with investigator-driven, interventional studies.

The education of principal investigators offers few credit hours for research basics during college, so investigators typically learn how to conduct research after becoming physicians through on-the-job trainings. Therefore, when trying to start a study under the Act, less experienced investigators need to learn the expectations of the new regulation at the same time as basic clinical research practices in collaboration with the full clinical team. Governmental resources are limited for aiding investigators in their research, so the requirements of the Act may end up hobbling some proposed studies experiencing insufficient management and ineffective implementation systems.

The educational curriculum for physicians in clinical research depends on what resources are available through the universities or hospitals to which an investigator belongs, and the Act requires site directors to regularly provide opportunities for trainings and education. In Japan, training through external, membership-based, education and networking organizations such as the Association of Clinical Research Professionals is not yet recognized as foundational training for principal investigators. Rather, many sites require their investigators to undergo internal training within their organizations.

Even in order to follow the same protocol as an investigator for a multisite study, the minimum requirements for training to be an investigator for a single-site study can be different. The guideline for

the Act says, “A principal investigator needs enough education and trainings for the research,”{4} but it does not mention specific qualitative and quantitative requirements. The new law needs to define what and how much education and trainings are enough. The training departments for employees at universities or hospitals develop the curricula for educational requirements, but do not often have interactive workshops for new kinds of research projects or coaching through onsite trainings for specific studies.

Investigators need interprofessional education of the sort with “activities [that] are perceived as more successful by learners when faculty have the ability to work creatively with small groups and have a legitimate knowledge base of the profession, enabling them to conduct exercises like shared storytelling.”{5} New principal investigators need to be provided interactive orientation and continuing education in order to ascertain their comprehension of research practices.

Obviously, interactive faculty development workshops take time to plan and require competent management to ensure their effectiveness for learners, and investigators need motivation for learning. Personnel from an organization’s protocol writing department and/or research operations unit often are adequate for introducing new investigators to the inner workings of clinical trials, and this education can progress to interactive workshops as a study continues along its life cycle.

**Qualifications for a Certified IRB Administrator**

Because the Act obligates review by certified IRBs approved by the MHLW for individual studies, certified IRB members and administrators have requirements in terms of training and experience. Particularly, for reinforcing a board’s functions and transparency management, the ordinance of the Clinical Trials Act requires certified IRB members to take training more than once a year to remain active in their positions. The enforcement notification of the Clinical Trials Act further requires that a board should have more than four administrators, including two dedicated administrators with at least a year of related experience, such as research administration of ICH-GCP, J-GCP, or ethical guidelines for medical and health research involving human subjects, plus taking trainings during their duties.

Although certified IRB management is important under the Act, Japan does not have a system of certified IRB/EC professionals (CIPs) such as is common in the U.S. A system of Certified Research Ethics Committee Professionals (CRePs) recently started in Japan,{6} and this is a similar certification as the CIP, which is available through PRIM&R (Public Responsibility in Medicine & Research).

Certified IRB administrators in Japan are usually university faculty staff who may or may not have medical licenses. Ideally, the new law should define how much and what kind of training and experience

is adequate for a certified IRB administrator, because investigators and personnel in related departments often rely on their experience and special knowledge.

There are a variety of inquiries from other departments that the administrator may face, such as how to manage the formatting requirements for IRB/EC submissions, budgeting for IRB/EC fees, handling of test medical products, applying for indemnification, determining national insurance system coverage of research, creating and comprehending reports, and managing the archives of test medical products and records. The organization that established the certified IRB further needs to maintain an appropriate number of board members to adequately review studies and an appropriate level of staff for administrative duties.

Currently, some administrators have medical licenses and clinical research experience. The administrators need good interpersonal skills, the ability to detect possible regulatory issues such as poor documentation procedures, and research know-how based on their medical knowledge and experiences interacting with investigators.

Although the Act does not require certified administrators, the role requires a certain level of competency, and the qualifications of the administrator are critical to their ability to satisfy compliance. The administrator will be the compliance gatekeeper for explaining to investigators about ethical requirements of the Act and increasing investigators' awareness. As the investigators interact with the administrator on a daily basis, the research administrator should be a certified professional with ample medical background and experience so that he or she can provide adequate responses to any inquires.

There are about 100 certified IRBs in Japan now, with probable variations in the quality of reviewing, though MHLW aims for there to be standardized, transparent, and efficient functioning of these boards. In the future, CRePs for about 100 certified IRBs could exchange information, mutually confirm and cooperate on operability issues, and verify their functions with each other to meet the aims of the Act.

**Final Thoughts**

Although we have our concerns about the complicated definition of the scope of research it covers, the Clinical Trials Act enables proper conduct of clinical trials when followed appropriately. The Act should be more specific about what kind of education is required for principal investigators and how to implement trainings. Furthermore, for proper certified IRB management, we should be aware of the importance of the CIP certification and cross-validation of the practices of certified IRBs.

Overall, and considering the past research misconduct issues it is intended to address through improvements in research transparency and ethics, the Act appears to be having a positive impact on clinical trials in Japan. However, no single law will resolve all the issues we face in the clinical research enterprise. Two challenges that we have experienced under the new law are what kind of and how to implement education for investigators and certified IRB administrators, and what qualifications certified IRB administrators should have in order to be more effective.

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## CLINICAL RESEARCHER—DECEMBER 2019 (Volume 33, Issue 10)

## HOME STUDY

## *Rules and Regulations: Staying on the Straight and Narrow*

**Opinion: Shedding Light on the Impact of the Revised Common Rule on the Informed Consent Document**

LEARNING OBJECTIVE

After reading this article, the participant will be able to describe the impact on research teams of recent changes to the Common Rule regarding the informed consent document.

DISCLOSURE

Joy Jurnack, RN, CCRC, CIP, FACRP: *Nothing to disclose*

**1. What is the informal name of the policy enforced on all agencies conducting human research within the U.S. government?**

A. The Belmont Report
B. The Nuremberg Code
C. The Code of Federal Regulations
D. The Common Rule

**2. What part of the U.S. government enforces the Federal Policy for the Protection of Human Subjects?**

A. The U.S. Food and Drug Administration
B. The Office for Human Research Protections
C. The Institutional Review Board
D. The Office of Inspector General

**3. Researchers involved in studies sponsored by pharmaceutical companies should also follow the expectations of which of the following sources?**

A. The Nuremberg Code and ICH GCP E6(R2)
B. The PhRMA Guide to SOPs and Six Sigma
C. The Declaration of Helsinki and The ACRP Bylaws
D. The CRC Field Manual and The U.S. Pharmacopeia

**4. An institution that fails to follow the rules of the OHRP can lose which of the following?**

A. New Drug Approval
B. CMS Coverage Determination
C. Federalwide Assurance
D. Investigators Brochure

**5. Changes to the general requirements for informed consent reflected in the Common Rule updates include those made in which of the following areas?**

1. Availability of consent on federal website
2. Further use of identifiable biospecimens
3. Availability of legal counsel regarding consent
4. Handling of waivers and later alterations of consent

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

**6. Where should the changes in the Common Rule be reflected in the informed consent document?**

A. In an appendix at the close of the document.
B. In a summary on the document's front page.
C. On a web-only version maintained by the study site.
D. On a specialized flier inserted into the document.

**7. Which of the following is listed as something "an IRB wants potential subjects to know" from reading an informed consent document?**

A. What types of activities are considered research.
B. How many times biosamples will be taken for the study.
C. An estimate of the therapy's likelihood of success.
D. Who are the major investors in the investigational product.

**8. Which of the following does the author say is behind the request for key information in informed consent language?**

A. A call for transparency.
B. A call for responsibility.
C. A call for simplicity.
D. A call for neutrality.

**9. As of publication of this article, what is the status of OHRP guidance on the Common Rule revisions?**

A. OHRP announced it will have no guidance.
B. OHRP plans to publish guidance in 2021.
C. OHRP published guidance in late 2019.
D. OHRP has not yet offered guidance.

**10. The author suggests an alliance between which two organizations to foster collaboration between IRBs and research teams?**

A. ACRP and PRIM&R
B. ACRP and FDA
C. ACRP and OHRP
D. ACRP and NIH

**The Importance of Japan's Clinical Trials Act to Research Sites, Staff, and Training Opportunities**

LEARNING OBJECTIVE

After reading this article, the participant should be able to describe the genesis of the Japanese Clinical Trials Act of 2017, how it differs from earlier legislation and ICH-GCP/J-GCP, and its expectations for the education/qualifications of investigators and certified IRB administrators.

DISCLOSURE

Mirei Matsukawa, MSN; Takashi Yokota, LLB, CCRP, CReP; Yumi Ikehara, MMS: *Nothing to disclose*

**11. Japan's Clinical Trials Act applies to which kind of clinical study?**

A. Placebo controlled
B. Retrospective
C. Observational
D. Interventional

**12. What legislation in Japan recognizes on-label and off-label drug usage through package inserts?**

A. ICH GCP and J-GCP guidelines
B. Pharmaceutical Affairs Law
C. Certified Research Ethics Committee Professionals Act
D. Nuremberg Code

**13. New rules in the Clinical Trials Act include a focus on clarifying which of the following areas?**

A. Conflict of interest when publishing results
B. The ethics of profitable research sites
C. Principal investigators' responsibilities
D. Oversight of vendors used for study management

**14. The Clinical Trials Act advocates direct communication between which two parties?**

A. Principal investigators and the Ministry of Health, Labor, and Welfare
B. Study sponsors and the International Council for Harmonization
C. Clinical research coordinators and institutional review boards
D. Patient advocacy groups and the Certified Research Ethics Committee

**15. Which of the following reflect areas of difference between ICH-GCP/J-GCP and the Clinical Trials Act?**

1. Tracking of research staff competencies
2. Submission of adverse event reports
3. IRB review of study protocols
4. Reporting of conflicts of interest

A. 1 and 2 only
B. 1 and 4 only
C. 2 and 3 only
D. 3 and 4 only

**16. How do Japanese investigators typically learn how to conduct research?**

A. Through classes mandated by the MHLW.
B. Through on-the-job trainings.
C. Through attendance of conferences.
D. Through for-profit universities.

**17. What do the authors say about training of investigators by organizations such as ACRP?**

A. It is considered illegal and subject to penalties.
B. It is broadly encouraged by the Clinical Trials Act.
C. It is not recognized as foundational in Japan.
D. It will soon be mandated by the MHLW.

**18. The authors cite personnel from which areas as often being adequate for introducing new investigators to clinical trial topics?**

A. Patient recruitment and research billing
B. Site management and human resources
C. Laboratory units and data management
D. Research operations and protocol writing

**19. How many administrators does the Clinical Trials Act require for certified IRBs?**

A. More than four.
B. Less than five.
C. Exactly seven.
D. From six to nine.

**20. The authors cite which of the following as examples of inquiries from other departments that a certified IRB administrator may face?**

1. Formatting IRB/EC submissions.
2. Responding to media coverage.
3. Handling test medical products.
4. Managing various archives.

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only