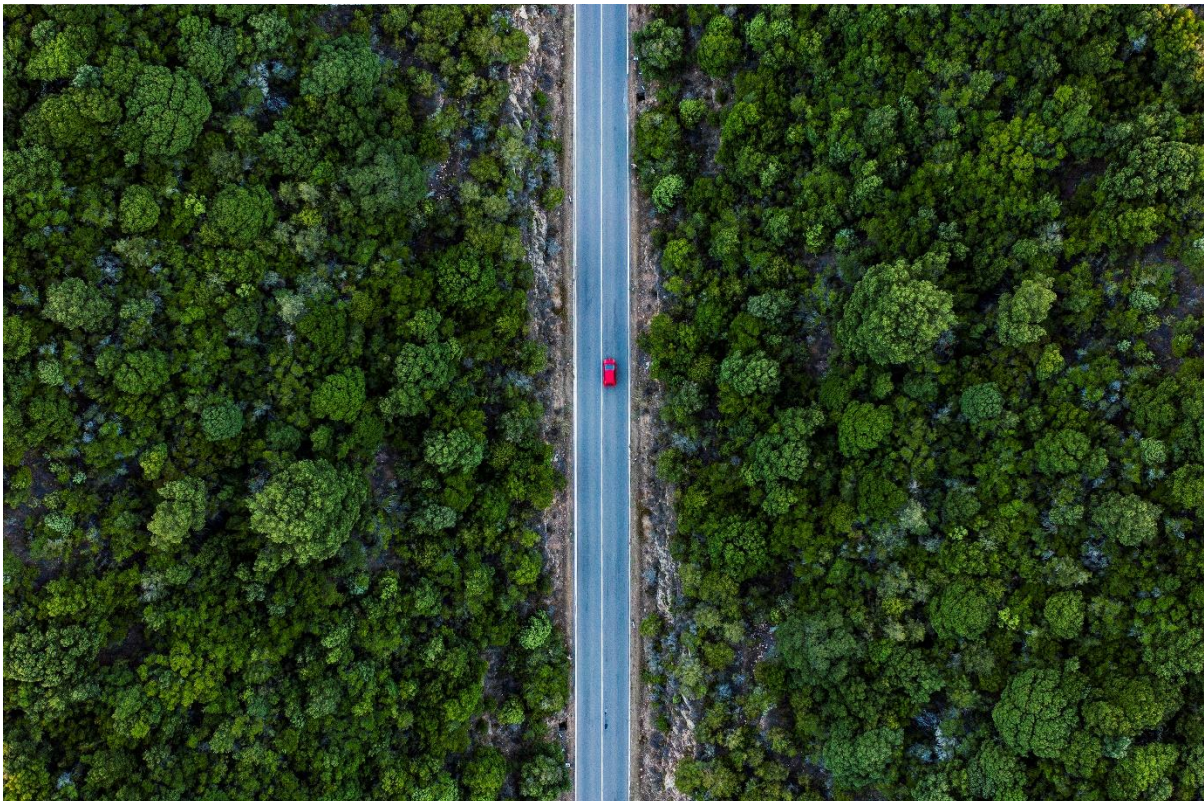


Clinical ResearcherTM

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Rules and Regulations: Staying on the Straight and Narrow

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EXECUTIVE DIRECTOR'S MESSAGE

The Hits Just Keep Coming

Jim Kremidas



As we wait for the giant ball to drop in New York's Times Square, it's only natural to reflect on the year ending in just a few weeks. Here at ACRP, we're excited about what has transpired over the past 12 months, and all that we've accomplished together. I thought this month's column would be a good occasion to review a few of your organization's "greatest hits."

In some ways, I think we're most proud of the [complimentary eLearning and ethics training](#) we released in July. Without a strong ethical foundation, clinical trial practitioners will not fulfill their mission. There are few higher callings than protecting the safety of vulnerable patients and clinical trial participants.

Working together, we're making clinical trials safer, more efficient, and more effective for the people who need them most. As a member of ACRP, you are helping lead the way to raise the bar for clinical trial performance.

More Greatest Hits

We've also had some other exciting events in 2019, including:

In April, we unveiled the [ACRP Medical Device Professional](#), or ACRP-MDP®, a subspecialty designation which can be earned through successful completion of a 60-question multiple choice

exam designed to validate clinical research professionals who have demonstrated knowledge in medical device trials.

We also enjoyed some great progress with the [Partners in Workforce Advancement](#) initiative (PWA), which provides a unique, high-profile opportunity for organizations to partner with ACRP and support initiatives focused on creating a sustainable workforce for the future—including a flagship initiative to implement an “Awareness of Clinical Research as a Career Option” campaign targeting healthcare professionals and students.

New PWA members in 2019 include the Medical University of South Carolina, Dartmouth-Hitchcock Health, the North Carolina Biotechnology Center, Covance, the George Washington University School of Medicine and Health Sciences’ Department of Clinical Research and Leadership, and Wake Forest Baptist Health/Wake Forest University. They joined existing members FOMAT Medical Research, Javara, Inc., National Institute for Health Research, OhioHealth Research Institute, Roche/Genentech, the University of North Carolina at Chapel Hill, and the U.S. Department of Veterans Affairs.

Further, we secured some exciting partnerships in 2019, including [a program with VIARES](#) to help contract research organizations address global workforce challenges, [with VirTrial](#) to help sites prepare for “hybrid” clinical trials, and [with Forte](#) to advance technology competency in the clinical research workforce.

I wish you a healthy, happy, and prosperous 2020, and I thank you for all you are doing to further improve the worldwide clinical trial enterprise. Here’s to greater things to come!

As always, I welcome your thoughts and input on how we can better serve you and the broader industry. Please feel free to e-mail me directly at jkremidas@acrpnet.org.

Jim Kremidas is Executive Director of ACRP.

CHAIR'S MESSAGE

Together, We are Making History

John P. Neal, CRCP



Historians like to use certain years as shorthand. For example, in American history, citing the years 1776, 1929, and 1945 immediately conjure up important images and turning points regarding independence, economic collapse, and a world war victory, respectively. It's not my intention to be quite so dramatic in my final message as your outgoing ACRP Association Board of Trustees Chair, but I do think 2019 is going to go down as an important and very positive year in the history of ACRP.

In so many ways, your organization has taken the lead and set the pace in the advancement of clinical trial safety and efficacy by advocating new certifications and standards in the clinical trial workforce. Whether it's through the exciting—and expanding—work of the [Partners in Workforce Advancement](#) or the [Workforce Innovation Steering Committee](#), 2019 saw many new individual members and organizations join our shared quest to further professionalize the clinical trial industry.

Most importantly, ACRP has helped employers to recognize the value of certification for clinical trial personnel across the board. ACRP has produced and disseminated data in 2019 that show certification reduces turnover, improves performance, and generally speeds delivery of key drugs and devices to the patients who need them. It's important work, and I know you share my pride in helping the effort.

Further, as Executive Director Jim Kremidas notes in his [recent column](#) looking back at ACRP's productive year, in April we unveiled the [ACRP Medical Device Professional certificate](#), or

ACRP-MDP®. This subspecialty designation can be earned through successful completion of a 60-question multiple choice exam designed to validate clinical research professionals who have demonstrated knowledge in medical device trials. It's another exciting example of how ACRP is addressing the needs of both members and their employers.

Finally, I'd like to take this opportunity to thank each of you for your help as I close out my term. I had the chance to interact with many of you at ACRP events throughout 2019. Each time, I was inspired by your enthusiasm and talent. It is always uplifting to spend time around you, and I look forward to remaining an active ACRP member for years to come.

John P. Neal, CRCP, is Founder and Chairman of PCRS Network, LLC, and the 2019 Chair of the Association Board of Trustees for ACRP.

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 enactment. 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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2. OHRP: <https://www.hhs.gov/ohrp/>
3. FDA guidance on revised Common Rule: <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM623211.pdf>
4. Nuremburg Code: <https://history.nih.gov/research/downloads/nuremberg.pdf>
5. Federalwide Assurance: <https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/fwas/fwa-protection-of-human-subject/index.html>
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8. PRIM&R: <https://www.primr.org/>
9. ACRP: www.acrpnet.org



Joy Jurnack, RN, CCRC, CIP, FACRP, is a patient/subject advocate, Senior Director in Site Engagement with Slope.io, Inc, and a member of the Board of Trustees of the Academy of Clinical Research Professionals, which oversees the ACRP certification programs.

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PEER REVIEWED

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

Mirei Matsukawa, MSN; Takashi Yokota, LLB, CCRP, CReP; Yumi Ikehara, MMS



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

- | |
|--|
| <ul style="list-style-type: none">1. Procedure for clinical trial implementation<ul style="list-style-type: none">1.1 Measures for specific research implementation<ul style="list-style-type: none">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

3. Guidance and supervision by MHLW for violation of implementation standards

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

Obtaining informed consent
Protection of Personal Information
IRB/EC review
Reporting to IRB/EC and MHLW
Monitoring and audits
Compensation and indemnification
Transparency of funding and conflict of interest
Information disclosure
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 inquiries.

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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Leveraging Audit Trails to Monitor Clinical Study Risk

Steve Young



The clinical research industry has gone through an important transformation over the past 15 to 20 years, from a largely paper-based paradigm to one in which electronic systems are regularly—and increasingly—leveraged for all aspects of clinical trial planning, execution, and management. Internet-based electronic data capture (EDC) systems have replaced paper case report forms, manual double-data entry processes, and faxing of paper queries.

Further, the use of direct source data capture methods is steadily increasing and replacing the EDC-based data transcription paradigm. This includes investigator-led and patient self-assessments using laptops or tablet devices, patient diary information using hand-held mobile devices (iPhones, etc.), and wearable sensors that automatically record and transmit various health-related measurements (glucose levels, heart rate, etc.).

The benefits of these eClinical technologies are significant, including more efficient and reliable capture of a broader array of patient data than was previously possible. They also enable much quicker data access to various stakeholders for trial monitoring and oversight activities. Centralized risk monitoring in particular benefits from more timely access to study data, to support the most proactive detection and mitigation of emerging issues in study conduct—issues that may have an impact on patient safety and/or the reliability of trial results.

Centralized statistical monitoring of clinical patient data—as also presented in section 5.18.3 of ICH E6(R2) from the International Council for Harmonization—along with key risk indicators (KRIs) and quality tolerance limits (QTLs), have proven to be very effective at identifying various study conduct–related issues that traditional site monitoring and data management review methods fail to find. Issues discovered range from malfunctioning measurement devices, to site training and/or sloppiness issues, and even to intentional misconduct including fabrication of patient data. These issues—often detected initially as various types of statistically unusual patterns or trends in data—reflect misapplied operational processes that may result in generation of incorrect or otherwise unreliable clinical data.

Following the Evidence

While the statistical monitoring of patient data is very effective, use of the audit trail information and other operational data (e.g., EDC query data, protocol deviations, site issue logs, etc.) from all of these eClinical systems can also be extremely powerful in helping to expose study conduct issues that may be impacting data reliability and integrity. Much of the data collected from these eClinical devices represents critical study data—supporting key efficacy and safety evaluations—and thus their appropriate use and functioning are of critical importance for the operational success of the study.

Audit trail data in particular offers us greater insight into the who, how, and when of clinical data generation and processing. When assessed effectively via KRIs, QTL parameters, or other statistical monitoring, these data can alert us to patterns of usage and behavior that are not expected and may represent a problem. The following examples represent just a handful of the KRIs implemented by study teams to leverage audit trail data to successfully identify risks and issues:

- **Visit-to-eCRF Entry Cycle Time**—One of the most common “standard” KRIs leveraged across studies, this monitors the timeliness of sites in transcribing relevant patient data into the EDC system for the study. Long delays may have significant negative implications for the reliability of the EDC data, as well as for the study team to proactively monitor the site risks.

- **Mean Duration of Assessments**—The increasing use of tablet devices for direct entry of patient assessments at the site (i.e., electronic clinical outcomes assessment [eCOA]) is enabling use of audit trail time stamps to assess behaviors such as the average time to complete each assessment. An investigator/assessor or a patient that is taking unusually long or is too quick to complete required assessments may indicate improper application of the assessment or even problems with the eCOA technology. Such a KRI was recently used in a dermatology study to help uncover significant misconduct at one of the investigative sites. In particular, the average duration of a key patient efficacy assessment was around three minutes for this site, while the average across all other sites in the study was closer to 15 minutes. The very short average duration at this site was assessed to be clinically unreasonable and highly suspect.
- **Assessment Time-of-Day**—eCOA and electronic patient-reported outcomes (ePRO) audit time stamps can also be used to reveal unusual and suspicious patterns in time-of-day usage by patients or sites. One real example involves a case of ePRO fraud, in which a site failed to provision the required ePRO devices to its 15 patients. To cover up the mistake, the site coordinator fabricated daily diary entries for each of the patients. The misconduct was first detected by a centralized statistical monitoring test, which discovered that more than 70% of this site’s daily diary entries were being logged in the 6 p.m. hour locally, while the time-of-day distribution of diary entries was much broader at all other sites in the study.
- **Rater Change Rate**—The reliability of many patient assessments relies to some extent on having a single, consistent person or “rater” conducting the assessment across patient visits for each patient. A site that is presenting a high incidence of rater changes may be raising concerns regarding the interpretability of the assessment results. While the names/identification of raters might be captured as part of the clinical data entry, it is also possible to implement this KRI using the user ID data stored with the assessment audit trails.

Conclusion

These examples reinforce a clear additional benefit in the use of mobile technologies and direct-source data capture in enabling more effective operational risk monitoring and quality oversight. Combined with an effective risk planning process which considers the risks associated with these technologies, we should anticipate and look forward to better quality outcomes in this new risk-based quality management paradigm.



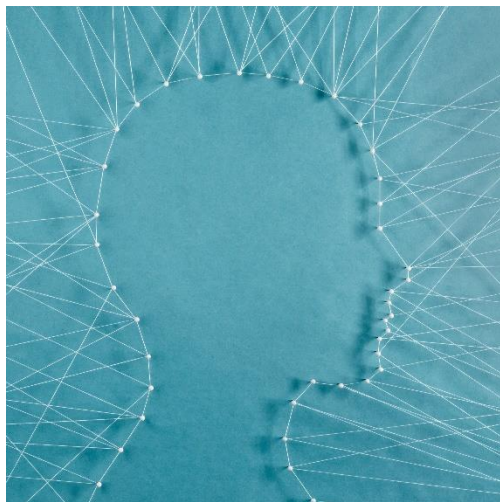
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SCIENCE & SOCIETY

Clinical Standards are Vital to Improving Care, Facilitating Innovation

Al O. Pacino

Clinical research leaders are calling for improvements to the current system. Standardized clinical practices may be answer.



Across the globe, collaboration between healthcare and research organizations is coming head-to-head with rapidly changing regulations. As the need for collaboration increases, independent and institutional members are struggling to streamline their delivery, distribution, and implementation of initiatives across diverse locations.

At the same time, changing regulations are complicating the process of ensuring that these initiatives meet the necessary requirements, especially in developing countries. These issues often strain clinical trial sites' limited resources and prolong the market entry of valuable new drugs and medical devices.

Many organizations have found that the standardization of education, certification, and other processes can increase efficiency, reduce time to market, and improve patient outcomes. When combined with real-time connectivity, moreover, access to standardized information can improve the quality of care.

Standardizing Education to Improve Diagnosis

Hospital La Paz Institute for Health Research (IdiPAZ) in Madrid, Spain and its 48 research groups promote high-quality translational research at basic, clinical, epidemiological, and health services levels. In 2017, IdiPAZ determined there was an international need for paramedics and ER staff to quickly and correctly diagnose the severity of stroke in patients sent to stroke care facilities, to avoid overloading staff and to improve care.

In response, IdiPAZ (in close collaboration with the Madrid Stroke network) created the Madrid-DIRECT scale—a standardized pre-hospital scale for measuring of the probability of mechanical thrombectomy. This scale allows emergency services to refer a patient directly to the corresponding Stroke Center based on clinical examination.

Based on an observational study coordinated by IdiPAZ and the Madrid Stroke Network, the Madrid-DIRECT scale provides valuable guidance about patients' suitability for endovascular treatment based on their pre-hospital evaluations. The organization plans to distribute this standardized scale and others in more than 167 countries to ensure site quality assurance and transparent management of professional competencies, particularly in underdeveloped countries.

Standardization to Improve Regulatory Outcomes

Site managers and staff are finding standardization helps streamline the approval process when facing regulatory roadblocks and limited testing time. They also realize that investing in standards creation improves accountability between sites and the sponsors or contract research organizations (CROs) with which they work.

Many sites in Africa are intriguing to sponsors and CROs, but regulatory hurdles make them hesitant to work with sites in the region. Standardization of well-known requirements, such as medical scales of assessments, can help prove competency to regulators. For African research sites, standardized assessments also improve their candidacy for grants and university and government initiatives by demonstrating research feasibility and transparency.

Centralized and standardized clinical education can advance the goal of reducing educational inequalities throughout the world while improving transparency and human subject protections.

Ultimately, industry-accepted guidelines, best practices, and standards of care for providers and investigative sites can streamline the clinical trials process, potentially bringing more facilities into the industry ready to “hit the ground running” with research. Working closely with accreditation organizations could make meeting regulatory requirements become more manageable.

Conclusion

A global infrastructure that equips investigative sites and healthcare organizations with guidelines, best practices, and globally accepted standards will bring developed and undeveloped nations alike into a global healthcare and clinical research ecosystem. It’s a vital first step toward a world in which no patients, regardless of where they live or their social status, are left behind. Using standardization as a tool, research professionals can gain more time to deliver excellent patient care while contributing to the global effort to accelerate life-changing innovation.



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PI CORNER

An Overview of Oversight

Elizabeth Weeks-Rowe, LVN, CCRA



In the ever-shifting environment of priorities and processes in today's complex clinical research landscape, one constant is the need for investigator oversight of studies. The unshakable commitment to patient safety and credible data practices held by responsible, involved principal investigators (PIs) perpetuates ethical study conduct.

Though consistency is critical in clinical research models, the diversity of investigational sites prohibits standardization of investigator oversight. Oversight practices differ according to the investigational site model, team dynamics, and the delegation required to manage the study at that site. No algorithm exists to define appropriate oversight in terms of levels of different activities (number of patient visits attended, number of adverse events [AEs] attributed per patient, etc.).

Appropriate oversight is driven by active—not passive—investigator involvement, frequent communication with trusted delegates, engagement with study patients, and real-time appraisal of study/team status. Whether the PI is a single practitioner with a small research practice or leads a large study team with contributing sub-investigators and support staff, his or her strengths in leadership and collaboration impact the results.

Focusing in On Commitments

Among other commitments found in Section 9 of Form FDA 1572 from the U.S. Food and Drug Administration, which must be correctly applied to the unique infrastructure of each investigational site, are the following:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

In signing the 1572, the investigator officially indicates his/her commitment to the serious business of study oversight to the regulatory authorities. The mantle of oversight is heavy, but manageable with delegated staff functioning in collaboration with those commitments.

Different Models, Same Mission

The most common investigational site models are the academic medical center, the single or multispecialty private medical practice with a research department, and the dedicated research site/site group.

The practices may differ in size and scope, but the intentions concerning study quality are clear: To ensure investigator involvement.

A PI/professor at an academic medical center, like in the following example, may lead a team of trained investigators working in unison to fulfill oversight responsibilities.

Joel M. Gelfand, MD, MSCE, is professor of dermatology and of epidemiology, vice chair of clinical research, medical director of the Dermatology Clinical Studies Unit, and director of the Psoriasis and Phototherapy Treatment Center at the University of Pennsylvania Perelman School

of Medicine. A renowned PI, he describes oversight practices relative to trial complexity and specialty by noting, “To some degree it depends on the complexity of the trial and who the sub-investigator is. For lower risk trials when my sub-investigator is a board-certified dermatologist with experience in research, I review the source docs for all the visits (made simple, as we are on EMR), and we have a standing weekly meeting where trial subjects are discussed. Of course, I am otherwise available 24-7 via cell phone if an urgent issue needs to be addressed.”

Dr. Gelfland describes additional involvement in these terms: “For a more complex trial, I typically see the patient with the sub-investigator at screening and baseline, and then as needed if there are AEs occurring. Of course, if the protocol requires a single investigator for all visits, then I see [the patients] at all visits.”

Meanwhile, the dedicated research site model is structured for 100% trial conduct, as opposed to trials being a “side business,” the way they are in a fee-for-practice physician’s office. The oversight process can be as simple as a sole practitioner (PI) seeing the majority of study patients, or the larger center contracting with several physician investigators (PIs and sub-investigators) who share patient care. The successful research site follows an oversight process that prioritizes communication frequency and transparency between the PI and staff.

Daniel A. Perez, BS, CCRP, director of clinical research operations at MACRO trials in Los Angeles, Calif., addresses PI oversight practices that require a commitment of all team members to succeed, saying, “For our team, this means that the PI and study coordinator have regularly scheduled 1:1 meetings (weekly or biweekly). The frequency of these 1:1 meetings is set considering the trial’s complexity, volume of enrolled patients, or anticipated volume of adverse events.”

Perez explains that wider, team-wide meetings are held on monthly intervals after the PI and study coordinator have had a chance to assess and vet the information that needs to be disseminated, or after opportunities for improvement have been identified for broader discussion. “We take this a step further by preparing meeting slides [and] agendas, [and by] maintaining detailed attendance records of our study team meetings.”

Perez further describes appropriate delegation practices that support PI oversight. “We designate what we call a “super sub-investigator” who is our go-to for coverage if the PI has a slammed clinic schedule or is unavailable. At the beginning of the trial, we then facilitate a meeting between the PI and sub-investigator where a few things get ironed out. Those items include:

- Seeking alignment on any assessments that may not be very straightforward (i.e., non-standardized assessments left to the investigator’s individual call);
- Establishing lines of communications and preferences (cell phone calls/texts, e-mail, face-to-face, etc.);
- Developing a plan for co-managing any potential AEs, with final say coming from the PI, but the sub-investigator being empowered to act in the PI’s absence; and
- Ensuring that sub-investigators are present at team-wide meetings either in person or via video conferencing.

Further Considerations

An FDA guidance for industry on “Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects” describes the framework for ethical oversight in terms of the appropriate supervisory, delegation, and communication/training responsibilities the investigator should fulfill. Section III of the guidance covers Clarification of Certain Investigator Responsibilities, and its first subsection focuses on Supervision of the Conduct of a Clinical Investigation. According to that subsection, “The investigator should develop a plan for the supervision and oversight of the clinical trial at the site. Supervision and oversight should be provided even for individuals who are highly qualified and experienced.”

The ongoing goal of a successful investigational site is for all its personnel to work in concert to achieve ethical oversight practices.



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