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WHAT'S NEW IN GCP?

Important Updates in Clinical Research including the ICH E6 R2 Addendum, updated Common Rule, 21st Century Cures Act, Electronic Records and Signatures Guidance, and the Final Rule updates for 21 CFR 812

Introduction

Clinical research professionals need to keep up to date with changes to the industry to ensure their studies remain compliant and human subjects are protected as research becomes more complex. Several important changes have taken place over recent years, including **greater emphasis on risk-based and quality-focused thinking**, as well as the increased use of electronic technologies to accomplish research activities. Paper-based studies are now the exception to studies conducted with electronic case report form (eCRF) systems, electronic medical records (EMR) are nearly ubiquitous, many research systems are moving to the cloud, and patient-centered study designs are more common with the rising use of mobile technology. IMARC Research understands the importance of staying informed as research evolves and has prepared this whitepaper to highlight and summarize changes in key areas, including:

- The Integrated Addendum to the International Council for Harmonisation's Guideline for Good Clinical Practice (GCP) E6(R2), published 9 November 2016.
- Revised Common Rule (45 CFR Part 46), published 19 January 2017, compliance deadline delayed to 19 July 2018.
- The 21st Century Cures Act 21st Century Cures Act, signed into law 13 December 2016.
- Draft Guidance for Industry: "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers," published June 2017.
- Final Rule updates to 21 CFR 812 (concurrent with updates to 21 CFR 807 and 814), published 21 February 2018 and effective 21 February 2019.

Read on to learn about these important changes in the clinical research industry.

1. Integrated Addendum (R2) to ICH GCP E6—What you need to know

Over the past twenty years ICH E6 (R1) has been utilized and interpreted by an entire industry around the world, proving to be one of the most durable international standards in the clinical research industry. It continues to have a presence assuring data integrity and the protection of human subjects and is often referred to as a primary guideline for Good Clinical Practice (GCP). When the original ICH E6 (R1) text was prepared and finalized in May of 1996, clinical trials were performed in a largely paper-based process. Over the years the industry has taken a universal shift–research has modernized and clinical trials have evolved–prompting the need for modernization of the content.

> ***... this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recordings and reporting while continuing to ensure human subject protection and reliability of trial results.***
>
> ***ICH E6 (R2)***

Why revise the guidelines?

The ICH E6 Guideline for GCP (R2) Integrated Addendum, representing the first major changes of the GCP guidelines since 1996, reflects the evolutions in technology like electronic data capture (EDC), electronic medical records, clinical trial management systems, and mobile technologies, as well as the adoption of enhanced risk-based quality management processes by the industry to make clinical trials more efficient.

The R2 Addendum consists of 26 items added to address the gaps and concerns from 398 GCP inspections carried out by the European Medicines Agency (EMA) from 2002-2012. The EMA submitted an inspection report—including details of investigative sites, sponsors, CROs inspections—to the ICH in 2014 summarizing that critical and major findings were mostly in relation to: **Monitoring, Data Management, Clinical Study Reports, and Source Documentation.** The results can be attributed to inadequate Sponsor and Investigator oversight. The changes between R1 and R2 versions focus on strengthening Sponsor and Investigator responsibilities as well as updates to monitoring and electronic systems. The report presented by the EMA noted that the design and conduct of trials needed improvement and that the original framework of GCP needed to be modernized to address these GCP inspections and other trends seen in the industry.

Who does the new guideline affect?

Sponsors, Investigators, Institutional Review Board/Ethics Committee members and administrators, study monitors, clinical research coordinators and other research professionals are all affected by these changes.

A noteworthy aspect about the ICH E6 (R2) addendum is that it does not significantly change what many research professionals already know and do, including using risk-based and quality approaches. It was designed to keep the original structure intact while adding text to specify responsibilities and incorporate today's world of clinical trials. With that said, the addendum affects the industry as a whole and the entire life cycle of a clinical trial. From a Sponsor's perspective the revisions provide instruction for a more proactive approach to trial design, as well as risk-management and monitoring. However, Contract Research Organizations (CROs), often delegated tasks by the sponsor, are not left out and need to take notice of the revisions as well. **Sponsor and CROs need to consider adopting both a quality and risk-based management approach to studies, including monitoring.**

From a clinical research site perspective, Investigators need to be aware of the changes to their responsibilities and obligations relating to delegation and oversight, and collection of essential documents. Sites can also anticipate a shift in how a trial is monitored as CROs and Sponsors continue to use a risk-based monitoring (RBM) approach. In contrast to the regular visit intervals sites are accustomed to, remote monitoring contact will likely increase and on-site visits will occur when merited by the critical data points and items in the RBM plan. The new guidelines have a major impact on Sponsors, CROs, and site staff alike, forcing improved planning and communication, and pushing the industry further towards a proactive risk-based philosophy for managing clinical trials.

What are the revisions?

The GCP revisions focus on improvement of study design and conduct to increase human subject protection and data integrity. The majority of the changes affect the Sponsor, calling on them to implement new methods to ensure that the safety, rights, and well being of subjects are protected, while balancing efficiency and quality. However, Investigators are included in the changes as well, with updates involving delegation, oversight, and documentation.

Key topics included in the R2 Addendum include:

- Defining responsibilities of Sponsors and Investigators
- Use of a risk management approach to study design
- Implementation of risk-base and centralized monitoring plans
- Improving data integrity, ALCOA-C

Updated Sections in ICH E6 (R2)

ICH E6 Sections	Revisions Made To:	Items Addressed
Introduction	Introduction	Reasons for R2
Glossary	1.63, 1.64, 1.65	New definitions
The Principles of ICH GCP	2.10, 2.13	Added clarifications
Institutional Review Board (IRB)/ Ethics Committee (IEC)	None	N/A
Investigator	4.25, 4.2.6, 4.9.0	Delegation, oversight, and documentation (ALCOA-C)
Sponsor	5.0, 5.2.2, 5.5.3(a), 5.5.3(b), 5.5.3(h), 5.18.3, 5.18.6(e), 5.18.7, 5.20.1	Quality management, oversight, validation of systems, data integrity, RBM, monitoring plans, root cause analyses for noncompliance
Clinical Trial Protocol and Protocol Amendment(s)	None	N/A
Investigator's Brochure	None	N/A
Essential Documents for the Conduct of a Clinical Trial	8.1 (Introduction)	Sponsor and Investigator recordkeeping

Expanded Definitions

The ICH E6 adds three new terms to the glossary:

- **Certified Copy (Section 1.11.1)**

  Not a new term itself, but defined in the new addendum. It defines a certified copy as paper or electronic and that it must be verified by a dated signature or generated via a validation process.

- **Monitoring (Section 1.38)—Monitoring Plan and Monitoring Report**

  Defines what is required to be included in the 'Monitoring Plan': methods, responsibilities and requirements. The addendum requires Sponsors to develop a report for centralized monitoring activities in addition to the required reports for traditional site visits.

- **Validation of Computerized Systems (Section 1.60.1)**

  Sponsors must establish a process to document that the requirements of the system are fulfilled from design through study completion.

Investigator Responsibilities

As noted by the EMA GCP inspection report, lack of Investigator oversight has become a critical issue attributing to study deficiencies. The ICH addendum has added language to emphasize the Principal Investigator's sole responsibility for conduct of a trial at the site, and it reiterates that the Investigator is allowed to delegate trial-related responsibilities. Section 4.2 "Adequate Resources" specifically adds the investigator is responsible for supervision of any persons or party that is delegated any study tasks. Furthermore, it states the PI is responsible for ensuring all parties involved are qualified and trained for the tasks assigned. Procedures should be put in place to ensure integrity of the tasks and data generated. The added text to Section 4.9 "Records and Reports" reminds us of the ALCOA principle introduced by previous FDA guidance's, specifying that "data should be Attributable, Legible, Contemporaneous, Original, and Accurate," with the added "C" for complete: ALCOAC. Overall, these updates emphasize the Investigator's responsibility for oversight and documentation in keeping with industry best practices.

Sponsor Oversight

Quality Management

The most extensive changes come to the Sponsor section of the ICH E6 Guideline. Sponsors are now responsible for implementing a "quality management system" to support studies from trial design to conduct and study completion. The addendum adds that a risk-based approach should be utilized to develop a study protocol and study materials, using the process described in Section 5.0:

Critical Process and Data Identification • Risk Identification • Risk Evaluation
Risk Control • Risk Communication • Risk Review

Although defining the approach is new to GCP, utilizing a risk-based approach is not. The FDA and EMA have provided guidance on risk-based approaches to monitoring (and study management in general) and the ICH is following suit in adopting them as well as adding Quality Management requirements to GCP. The use of Risk-Based and Quality Management processes will ensure that attention is being put into the activities that have the largest impact on clinical trial quality.

Sponsors are also required to demonstrate adequate oversight of CROs and other vendors or subcontractors. Section 5.2.2 states that the "Sponsor should document approval of any subcontracting of trial related duties and functions by a CRO." As stated in the previous version of the guideline, Sponsors are permitted to delegate trial-related responsibilities. The addendum requires the Sponsor to document how this will be assessed and maintained, which again emphasizes the importance of oversight and quality management included in the R2 version of the guideline.

> ***Sponsors should focus on trial activities essential to ensuring human subject protection and the reliablity of trial results. Quality management includes the efficient design of clinical trial protocols, data collection tools and procedures, and collection of information that is essential to decision making.***
>
> ***ICH E6 (R2)***

Electronic Systems

Section 5.5 changes added that the Sponsor must use a risk assessment in validation of electronic trial systems. The addendum specifies the SOPs required to be maintained by the Sponsor for electronic data systems. The SOPs must include details for setup, install, use, and validation/functionality testing, data backup, recovery, and training for users. It also puts the responsibility for reliable data on the sponsor; section 5.5.3(h) states the Sponsor must "ensure the integrity of the data" including "when making changes to the computerized systems, software upgrades, and data migrations."

> ***"The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials... A combination of onsite and centralized (off-site) monitoring activities may be appropriate. The sponsor should document the rationale for the chosen monitoring strategy."***

The addendum defines and offers specific instructions for centralized monitoring, separating it from on-site monitoring.

Sponsors are responsible for considering the following when choosing a Risk-Based Monitoring (RBM) strategy:

- **Develop a systematic, prioritized, risk-based approach.**
- **Develop a Monitoring Plan tailored to human subject protection and data integrity.**
- **Use varied approaches to improve effectiveness and efficiency.**
- **Document the rationale for the monitoring strategy.**
- **Document results of monitoring activities.**

Furthermore, it discusses the advantages of using centralized monitoring and how it can help to identify missing or inconsistent data, detect data trends, evaluate data integrity, analyze site/investigators, and select sites for on-site monitoring.

Finally, in section 5.18.6(e), both centralized and on-site monitoring reports are now required to be provided to the Sponsor (including appropriate CRO staff). The reports should include sufficient detail of monitoring activities to allow for compliance with the monitoring plan to be verified by the Sponsor. This new requirement in turn adds an additional responsibility to the Sponsor, as detailed in section 5.20, which requires them to follow-up on identified non-compliances. The R2 Addendum adds that the Sponsor should take appropriate action when needed if non-compliance seriously affects or has the potential to affect human subject protection or data integrity.

The ICH addendum encourages Sponsors to utilize RBM, to choose (and document) an approach that is a combination of centralized and on-site monitoring, as appropriate, that allows for optimal oversight of the study.

Essential Documents for the Conduct of a Clinical Trial

The introduction to Section 8 of the revised guideline adds a requirement specifying that both the Sponsor and Investigator/institution should maintain their respective essential documents in a storage system which provides a process for identifying, versioning, searching, locating and retrieving documents. It also states that the Sponsor should ensure that the Investigator/institution has control of their case report form (CRF) data and essential documents before, during and after the trial. It further states that copies of original documents must meet the definition of certified copy as defined in the glossary. The R2 Addendum makes clear that the Sponsor should not have exclusive control over the electronic CRF data. The Sponsor must ensure that the Investigator has “control of and continuous access” to the CRF data reported to the Sponsor throughout the conduct of the trial.

Interpreting and implementing the guidelines—What to Remember

It is not surprising that CROs and Sponsors are often cautious about implementing large changes that will affect their clinical studies. The proposed risk-based and quality-focused approaches should be looked at as opportunities to become more efficient and effective. It is important to review the guidelines and assess the impact the revisions will have on you. How you choose to interpret and implement the guidelines will depend on your organization's structure and culture.

5 STEPS TO CONSIDER AS YOU REVIEW ICH E6 GCP (R2)

Interpret: How do the guidelines apply to you? The biggest challenge you will face is determining how to interpret the guidelines and implement effectively for your organization. Consider your organization's culture and approach the guidelines in a way that will be purposeful to your needs to achieve success. While the guidelines have some flexibility when it comes to how they should be implemented, how you choose to interpret and then implement them must be justifiable.

Evaluate: Analyze your current process and find gaps Examine current practices and processes to determine what is already in place and where the gaps exist. Ensure that your new processes and procedures fit your culture. Things to consider:

- Do you have the right people with the right skills?
- Do you have the proper technologies in place?
- Can the teams you work with embrace change with you?

Prioritize: Make a plan, use a risk-based approach to focus on what is critical Develop plans for assessment and a strategy towards implementation of a quality management system. Consider performing a risk assessment and ensure that the methods for your risk-based approach are proportionate and align with your overall strategy. Focus on critical gaps in current processes that focus on patient safety, data integrity, and regulatory compliance.

Implement: Be consistent, but evolve Once systems have been put into place for adopting the new guidelines, execute and stick with them. Don't deviate from your overall approach, but make sure to continue to reevaluate your processes and systems regularly to ensure they remain effective and relevant. Ensure you have risk assessment and mitigation plans in place and maintain them throughout the entire trial. Update your approach and processes as you gain experience and a better understanding. If you must deviate from your approach be sure it is justifiable and documented to show that you are following a consistent process.

Document! Document! Document! The revised guidelines mention the word 'document' approximately 217 times, indicating that however you interpret and implement the guidelines, the entire process must be documented. Once you have interpreted the revised ICH GCP E6 (R2) guideline, clearly defend and demonstrate how you implement it through continued documentation. For Sponsors and CROs this will mean documenting risk-based approach across the study from developing a quality management system and monitoring plan. Investigators will need to document how they are managing staff and parties involved in clinical trial activities and ensure high quality documentation practices.

Summary

The ICH GCP E6 guideline has been essential to the conduct of clinical research over the years, and after 20 years it was showing its age. The many changes to our industry and new technologies have quickly shifted the process, making it evident that an update was needed. The new risk-based and quality focus in the GCP guideline will lead to better oversight of research by Sponsors and Investigators, modernized approaches for electronic systems will support data integrity, and risk-based trial design will improve compliance and efficiency. All of these GCP updates are intended to support the goals shared by clinical researchers worldwide: protecting human subjects and ensuring data integrity.

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2. Revisions to the Common Rule (45 CFR Part 46)

A recent revision to 45 CFR Part 46, Subpart A, also known as the Common Rule, was issued on January 19th, 2017 and was planned to become effective on January 19th, 2018. Recent notice extended the deadline for compliance to July 19th, 2018. The Common Rule was implemented in 1991 to promote uniformity, understanding and compliance with human subject protections. The recent revisions are intended to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay and ambiguity for investigators.

The revised Common Rule requires all institutions in the U.S. participating in federally funded, multi-site research studies to transition to a single IRB. The rearrangement of IRB oversight and IRB responsibilities must be documented by a written agreement, institutional policy or the research protocol. Exceptions can be made for conflicting laws that state that more than a single IRB reviews the study or if federal agency deems the study is not appropriate for the use of a single IRB. The single IRB will be selected by the federal agency funding the research; however, selection criteria are not specified by the Common Rule. An IRB may also be proposed by the lead research institution but is contingent on the approval of the federal agency.
Let's take a look at how the new Common Rule compares to the NIH Policy for single IRB use:

	New Common Rule	NIH Policy
Scope	Domestic multi-site research (federally funded)	Domestic multi-site research (NIH funded)
Exceptions	If more than a single IRB review is required by law	If use of a single IRB is prohibited by law or government policy
Selection of IRB	If a federal department or agency funding the research determines use of single IRB is 'not appropriate for particular context' Federal agency funder or proposed by lead institution (contingent on agency acceptance).	If there is compelling justification for a requested exception, in the discretion of the NIH Proposed by lead institution (contingent on NIH acceptance).
Compliance Date	January 20th, 2020	January 25th, 2018

The Common Rule also eliminates the need for continuing review for minimal risk research. These types of studies include research meeting the criteria for expedited review or any research where the only remaining activities includes data analysis of identifiable data/biospecimens or accessing follow-up clinical data. Of course, the IRB may conduct continuing review under certain circumstances but the justification must be documented. As a result, it is likely that FDA human subject regulations will be revised in concurrence with the Common Rule in the future.

Human subject protection is a key part to what researchers do on a daily basis and the Common Rule has added additional requirements to the informed consent forms to ensure this. Informed Consent forms must now contain information to allow the patient to have a better understanding of the study's scope, including risks and benefits, allowing the patient to make a more informed decision. Consents must begin with a concise and focused presentation of the key information of the study that is structured to ensure patient comprehension

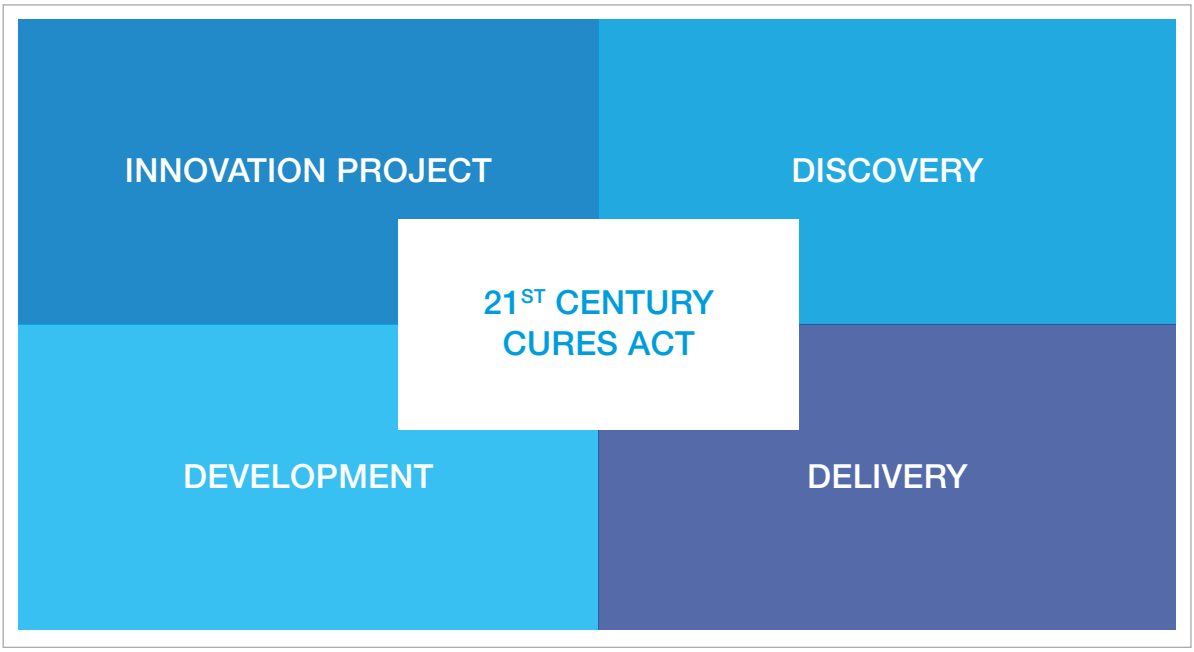
For studies that involve the collection of identifiable private information or identifiable biospecimens, new requirements are outlined in the Common Rule revision. A statement must be included in the consent form stating: (a) identifiers may be removed from identifiable private information/biospecimens and the resulting information/biospecimens could be used for future research studies or distributed to another investigator for future research or (b) patient's information/biospecimens will not be used or distributed for future research activities.

In addition, when applicable, the following additional elements will be included in the consent:

- **The patient's biospecimens will be used for commercial profit and if the patient will receive any royalties.**
- **Whether clinically relevant research activities will be disclosed to patients and the conditions when this is applicable.**
- **If the research will or might include whole genome sequence for research involving biospecimens.**

The US government continually works to keep up with the dynamic industry of clinical trials and to ensure that regulations across Federal departments are current and consistent. The updated Common Rule will help reduce burdens, delays, and uncertainties for Investigators while working towards the continued effort to protect the human subjects that are enrolled in trials.

3. The 21st Century Cures Act



Innovation Project: FDA to hold public meetings to issue guidance that would assist sponsors to incorporate adaptive designs and statistical models in new drug applications

Discovery: "Real world evidence" will be used in the evaluation of drugs and devices

Development: Sponsors can request an accelerated approval development plan

Delivery: FDA to ease their requirements put on companies looking for approval of a "breakthrough" drug or device

This Act, signed into law in December 2016, will have many implications to members of the research community. Regulations related to federal research requirements, such as reporting policies for financial disclosure of conflict of interest, will be reviewed by a newly established "Research Policy Board" in order to reduce the administrative burdens for researchers. Additional guidance will be issued by the Department of Health and Human Services to clarify that researchers may remotely access personal health information (PHI) if both the security and privacy safeguards of the HIPAA Privacy Rule are followed. The Act also gives the NIH the ability to require that grant recipients share their scientific data from the funded research; however, it is not yet clear how this collected data will be shared. While data is being shared, there must be a focus on the privacy protection for human research subjects. Current law states that data collected may not disclose any identifiable, sensitive information about the research subject (except when required to by law, necessary to treat the individual, when the subject gives consent or when disclosure is for the purpose or research). This Act extends these privacy protections to identifiable biomedical research data, where the NIH can withhold biomedical information about individuals that could be used to re-identify them through requests for records filed under the Freedom of Information Act.

The 21st Century Cures Act also affects the future of study design and data collection. Public meetings will be held by the FDA to issue guidance to assist sponsors in incorporating adaptive designs and novel statistical models into their studies. In order to expedite the approval process, the FDA will also evaluate real world evidence of new indications of previously approved drugs or devices. This is a way to apply valuable and timely information from observations studies, feedback from patients and previous research. Additional guidance will be issued to clarify how to collect patient experience data and how to prepare the submission of such data to the FDA and well as how the FDA will utilize and analyze this data.

4. Draft Guidance for Industry: "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11– Questions and Answers"

In the draft guidance entitled "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers," released in June 2017, the FDA continues to encourage the risk-based approach in validation of electronic systems, implementation of audit trails, and archiving of electronic records by providing twenty eight questions and answers to ensure compliance with regulations. The new guidance expands upon and clarifies recommendations issued in the August 2003 Guidance for Industry "Part 11, Electronic Records; Electronic Signatures – Scope and Application."

The scope of the guidance document applies to electronic records and signatures, addressing the applicability of Part 11 requirements for the following electronic systems:

Electronic systems owned or managed by sponsors and other regulated entities

Electronic services outsourced by the sponsor

Electronic systems primarily used in the provision of medical care

Mobile technology

Telecommunications systems

Electronic systems owned or managed by sponsors include commercial off-the-shelf (COTS) office utilities software, electronic case report forms (eCRFs), electronic data capture (EDC) systems, electronic trial master files (eTMFs), and electronic Clinical Data Management System (eCDMS). When using a risk-based approach for validating electronic systems, research personnel should consider the purpose of the record and the attributes and intended use of the system used to produce the record. In general, sponsors should have an electronic system validated if that system processes critical records. For COTS systems that perform functions beyond office utilities, such as an EDC system, validation should include documentation from the vendor with results of their validation to establish that the electronic system functions in the manner intended. The guidance also addresses FDA inspections of electronic systems, vendor audits, security safeguards, and electronic storage for archiving study related records.

Sponsors are increasingly outsourcing electronic services, including data management services such as cloud computing. The sponsor should ensure that the outsourced electronic service provides data security safeguards including validation documentation, ability to generate accurate and complete copies of records, retention of records, archiving capabilities, access controls and electronic signature controls.

Electronic systems primarily used in the delivery of medical care, for example electronic health records (EHRs), are systems that are designed for patients not involved in research and that are managed by the institution providing the care. These systems produce data that may be useful in clinical research. The FDA does not intend to assess compliance of these systems with 21 CFR 11. This is described in the draft guidance for industry “Electronic Source Data in Clinical Investigations.”

Mobile Technology may be used to capture, record or transmit data directly from research subjects. This section applies to mobile technology that the sponsor owns as well as research involving participants using their own devices. These can include mobile platforms, applications and wearable sensors. The guidance advises that sponsors should ensure that basic user access controls are implemented, specifically for mobile apps, to verify that entries come from the study participant. In cases where controls are impractical, such as a device intended for a single study participant to wear, sponsors should consider obtaining a signed declaration that the study device will only be used by the participant. The guidance also advises that for each electronic data element, there should be an associated authorized data originator. This may be a person, computer system or device that is authorized to enter, change, or submit data into the sponsor’s EDC system. If data is automatically transferred from the device into the EDC system without human intervention, then a data element identifier should be created that identifies the particular mobile technology as the originator of the data element. What does the FDA consider to be the source data when mobile technology is used? FDA considers source data as the data that is first recorded in a permanent manner. Many times the first permanent record in using mobile technology is the sponsor’s EDC system, and not the mobile technology. In this case, an audit trail should begin with the EDC system.

Telecommunication Systems used to communicate with participants throughout the study including telephones, email, live chat or video conferencing systems can be used to record source data. Adequate controls should be in place to ensure that the source data cannot be altered and that the reliability, confidentiality and privacy of records are preserved.

The draft guidance also discusses methods to create and use electronic signatures. To be considered equivalent to full handwritten signatures executed on paper, electronic signatures must comply with all applicable requirements under Part 11. Part 11 permits a variety of methods to create electronic signatures, including computer-readable ID cards, biometrics, digital signatures, and username and password combinations. The FDA does not specify the method to identify an individual providing an electronic signature. Many methods are accepted including providing an official document or the use of security questions to confirm an identity. Electronic signatures based on biometrics are accepted if the requirements in 21 CFR 11 are met. In addition, biometrics should meet the standards set forth by various government agencies that develop biometric standards.

Here is a sampling of questions answered by the FDA's guidance document:

What will be the FDA's focus during inspections for electronic systems that fall under the scope of 21 CFR 11?

- Implementation of the electronic system
- Source data that is transferred to another data format to ensure checks are in place
- Review of standard operating procedures (SOPs), training, technical support and auditing to ensure that the system is functioning and being used as intended

What access controls should sponsors implement for mobile technology accessed by study participants for use in clinical investigations?

- Basic user access controls including identification code, username and password, or electronic thumbprints and other biometrics are implemented as appropriate
- Signed declaration from the study participant for electronic devices intended for a single study participant to wear or use
- Basic user access controls are not necessary when using ingestible sensors and implantable electronic devices

How should sponsors and regulated entities verify the identity of the individual who will be electronically signing the records?

- Verify the identity of the individual before establishing or assigning an electronic signature
- Safeguards to confirm the identity of the individual and prevent alteration of the signature
- Identification may include official identification and use of security questions to confirm an identity

10 Key Takeaways from the Electronic Records and Signatures Draft Guidance Document

1. FDA reminds sponsors that records must still be maintained in accordance with the underlying predicate rules.

2. FDA recommends sponsors use a **risk-based approach** when deciding to validate electronic systems, implement audit trails, or archive required records for clinical investigations.

3. FDA regards the validation of electronic systems, the ability to generate complete and accurate records, archive records, and the use of audit trails as tools to ensure the quality of electronic records.

4. Sponsors should have electronic systems validated if they process critical records that are submitted to the FDA. For electronic software that processes non-critical records (i.e. spreadsheets, word processing, PDFs) the extent of validation should be guided by the organization's internal procedures.

5. Sponsors should ensure that processes are in place to **control changes** and evaluate the need for revalidation after changes occur to an electronic system using a risk-based approach.

6. During inspections, FDA will focus on any source data that are transferred to another data format or system to ensure that critical data is not altered during the process and that checks are in place by the sponsor. **The FDA will also review standard operating procedures and support mechanisms such as training records.**

7. Sponsors can retain electronic copies of source documents in place of the original source paper document. In this case, Part 11 regulations would apply to the system used to create the copy and a process should be in place to ensure that the electronic copy is an accurate representation of the original paper document.

8. In cases where electronic records are modifiable, the sponsor should have **audit trails** in place to ensure the reliability of the electronic copy.

9. If a sponsor uses an electronic service vendor, a service agreement, specified requirements of the outsourced service, and a procedure to notify the sponsor of any changes and incidents with the service should be available to the FDA upon request. It is ultimately the **responsibility of the sponsor** to ensure that outsourced electronic services are validated appropriately by reviewing standard operating procedures and results of system validation.

10. An electronically signed record must contain the printed name of the person signing, the date and time the signature was executed, and the meaning associated with the signature. Electronic signatures and handwritten signatures attached to electronic records must be linked to the electronic record to show that signatures cannot be transferred or copied and **the identity of the individual should be verified** before establishing an electronic signature.

Through publication of this draft guidance, the FDA provides important insight for consideration by Sponsors, institutional review boards (IRBs), Investigators, contract research organizations (CROs) and other research personnel for applying these recommendations in order to ensure the quality, authenticity, and reliability of electronic records and signatures.

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5. Final Rule updates to 21 CFR 812 (concurrent with updates to Parts 807 and 814)

The FDA issued a final rule on "Human Subject Protection: Acceptance of Data from Clinical Investigations for Medical Devices" on 21 February 2018, with a compliance deadline of 21 February 2019. According to the FDA, the rule **"updates the FDA's standards for accepting clinical data from clinical investigations conducted both inside and outside the United States to help ensure the protection of human participants, and to help ensure the quality and integrity of data obtained from these clinical investigations…"** and "to reflect the increasing globalization of clinical trials and the evolution of clinical trial standards for protecting human subjects."

Sponsors will now be required to include statements and information about the conformance to GCP of the study/studies (when data was collected outside of the US) included in applications for support of investigational device exemptions (IDE), premarket notifications (510(k)), requests for De Novo classification, premarket approvals (PMA), product development protocols (PDP), and humanitarian device exemptions (HDE). If the investigation was not conducted according to GCP, a waiver request or a statement explaining the reasons for noncompliance and a "description of steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of the subjects have been adequately protected" must be included.

Similarly, a **statement regarding compliance** with FDA regulations for human subject protection, institutional review boards, and IDEs will be required for studies conducted in the US. If the investigation was not conducted in compliance with these requirements or regulations, a statement must be included describing the reasons for noncompliance.

These changes are intended to allow flexibility for global studies and provide consistency across different submission or application types. Regulations in 21 CFR Parts 807, 812, and 814 were changed to apply these updates consistently. The FDA also published a guidance document at the same time the final rule was published, to aid researchers in understanding these new requirements.

The Supporting Information required by 21 CFR 812.28 is summarized below for an IDE or a device marketing application or submission that includes data from a clinical investigation conducted outside the United States:

1. Names of investigators and names and addresses of the research facilities and sites where records relating to the investigation are maintained (Section 812.28(b)(1))
2. Investigator qualifications (Section 812.28(b)(2))
3. Description of the research facilities (Section 812.28(b)(3))
4. Detailed summary of the protocol and results of the investigation, and if requested, case records or additional background data (Section 812.28(b)(4))
5. Information regarding the device (Section 812.28(b)(5))
6. Discussion demonstrating that the data and information constitute valid scientific evidence (Section 812.28(b)(6))
7. The name and address of the IEC that reviewed the investigation and a statement that the IEC meets the definition in section 812.3(t) (Section 812.28(b)(7))
8. Summary of the IEC's decision to approve, or provide a favorable opinion of, the investigation (Section 812.28(b)(8))
9. Description of how informed consent was obtained (Section 812.28(b)(9))
10. Description of incentives provided to subjects to participate (Section 812.28(b)(10))
11. Description of how the sponsor monitored the investigation and ensured that the investigation was carried out consistently with the protocol (Section 812.28(b)(11))
12. Description of how investigators were trained to comply with GCP and to conduct the investigation in accordance with the protocol (Section 812.28(b)(12))
13. Significant/non-significant risk determination for OUS clinical investigations (Section 812.28(a)(2))

Waivers, records, and implementation are also discussed in the FDA's guidance document. Researchers are encouraged to review the updated regulations and guidance document in detail to determine what steps should be taken within their organizations to ensure compliance.

Conclusion

While the regulations and principles involved in conducting ethical clinical research do not change often, when there are updates to important guidelines and regulations, clinical research professionals must stay informed. **The ICH E6 GCP (R2) Addendum, Common Rule revisions, additional investigational device regulations, 21st Century Cures Act, and draft guidance for electronic records and signatures in research, collectively represent important updates in the industry.** Professionals at Sponsors, CROs, IRBs, and research sites should take note of the changes that apply to their daily responsibilities and implement changes where needed to stay compliant. That way clinical research studies will continue to provide protections for participating subjects, robust results, and the evidence needed to bring new treatments to patients that need them.

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Ryan Begun

Ryan joined IMARC in February 2015 as an internal Clinical Research Associate. His work ethic and critical thinking led to his advancement as a field-based Clinical Research Associate (CRA) and Lead CRA. His knowledge and application of the regulations has made Ryan a great asset during site BIMO audit preparations resulting in no FDA findings. Additionally, he has been involved with IMARC's internal training efforts. Before his time at IMARC, Ryan worked as a Research Assistant conducting emergency department based research studies, working across a variety of therapeutic areas. He holds a Bachelor of Science degree in Biomedical Engineering from the University of Pittsburgh.

Lauren Luzar

Lauren joined IMARC in 2015 as a Clinical Research Associate and has monitored In Vitro Diagnostic (IVD) device studies investigating Alzheimer's disease, vitamin D, and acute myocardial infarction diagnosis as well as studies for thoracic and abdominal aortic aneurysm treatment. Prior to joining IMARC, Lauren worked in various roles in clinical laboratories as a certified Medical Laboratory Scientist (MLS) for 9 years. Lauren received her Bachelor degree in Biology from the Ohio State University and her Master of Business Administration degree from the University of Akron.

Melanie Miller

Using her experience as a research assistant in both academic and clinical research environments, Melanie brings a diverse viewpoint to clinical research. Melanie joined IMARC in March 2017 as a Clinical Support Services Associate. She serves as the Administrator for Data Safety Monitoring Boards (DSMBs), Clinical Events Committee's (CECs), and Medical Monitors, supporting safety oversight activities. She also assists with client training and site support services as well as internal training for IMARC staff.

Prior to joining IMARC she was a Clinical Research Coordinator at a private practice, coordinating adult and pediatric studies investigating psychiatric and mental health related diseases. Her experience also includes over five years of experience as a Research Assistant in an academic research laboratory environment, developing and validating novel assays related to HIV-1 and SIV. She is a member of the Association of Clinical Research Professionals and became a Certified Clinical Research Coordinator (CCRC) in 2015. Melanie received her Bachelor of Arts degree in Neuroscience from Hiram College.

Rachel Silver-Kessler

Utilizing her background as a biomedical engineer, Rachel brings a unique perspective and valuable tool set to clinical research. Her critical thinking skills allow her to apply the regulations across various roles including as a monitor, auditor, trainer, and manager for DSMBs, CECs, and medical monitors. These skills and experiences have influenced her advancement to her current position as Director of Clinical Support Services at IMARC.

In October 2015, Rachel helped IMARC launch its Safety Management services, and she oversees the administration of independent safety oversight for studies. Rachel was also part of the core team that launched IMARC University, a series of affordable online training and continuing education courses designed to prepare clinical research professionals for compliance. Rachel also assisted IMARC in achieving ISO 9001 certification with the implementation of a robust quality management system. She became a Certified Clinical Research Associate through the Association of Clinical Research Professionals in 2013. Rachel holds a Bachelor of Science degree in Biomedical Engineering from Case Western Reserve University and Master of Science degree in Clinical Research Administration from The George Washington University.

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