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The Fundamentals of Good Clinical Practice

Introduction

Good Clinical Practice (GCP) is a foundation for all clinical research, driven by a desire to ensure everyone who participates in studies is given the protection they deserve. The fundamental principles of GCP have not changed since they were introduced more than 50 years ago. However, as the use of technology in clinical research has evolved to include electronic signatures, records and more, there are new considerations. Recent updates to GCP also put a greater emphasis on risk-based study management and quality-focused thinking.

This whitepaper will review the guiding principles of GCP, address recent updates and discuss how clinical research teams should apply them to ensure compliance.

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Why Good Clinical Practice Is So Important

Good Clinical Practice is an attitude of excellence in research that provides a standard for study design, implementation, conduct and analysis. More than a single document, it is a compilation of many thoughts, ideas and lessons learned throughout the history of clinical research worldwide.

Here's a closer look at some of the major milestones that led to greater concern for good clinical practice and the documentation that followed:

1932-1972

The Tuskegee Syphilis Study

For more than 40 years, African-Americans with syphilis were lied to and misled in the name of science. The U.S. Public Health Service conducted studies on 600 people to explore the effects of untreated syphilis. These patients did not give informed consent and were denied access to Penicillin, a proven treatment for syphilis. Many died as a result, infected others with the disease and passed it on to their children.

1939-1945

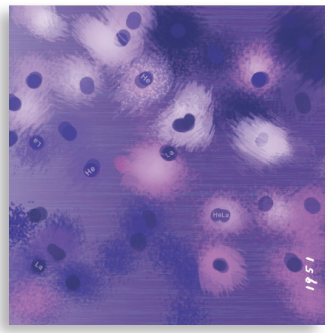
World War II Nazi Experiments

Physicians from the German Nazi Party conducted a series of grotesque medical experiments on unwilling prisoners of concentration camps during the Holocaust. The intent of these experiments was to develop new weapons, help treat German soldiers, and advance eugenic racial ideologies. Many of the experiments resulted in death, disfigurement or permanent disability.

1947

Nuremberg Code

After World War II ended, 23 physicians from the German Nazi Party were tried for crimes against humanity for their roles in wartime experiments on prisoners. In what became known as the 'Doctors' Trial' in Nuremberg, Bavaria, Germany, 16 physicians were found guilty. A set of 10 ethical principles known as the Nuremberg Code was included in the trial verdict, including the essential nature of voluntary consent, and the idea that the risks should never exceed the benefits in human subjects research.



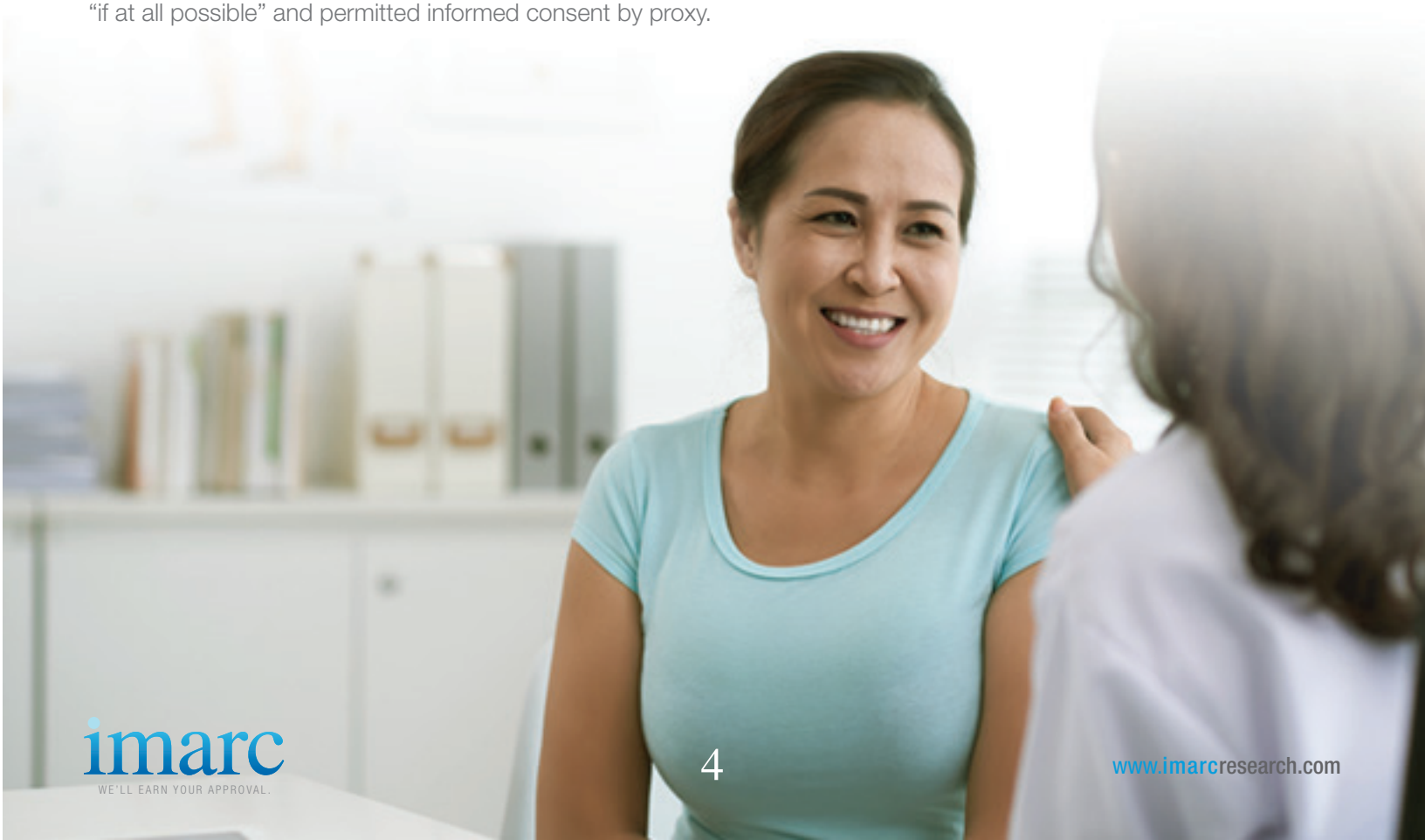
1951
Henrietta Lacks

The story of Henrietta Lacks (1920-1951) demonstrates the importance of informed consent in clinical research. While receiving treatment for cervical cancer in 1951, a researcher took cells from Henrietta's tumor without her knowledge. The cells were particularly proliferative and were cultured for additional research purposes. These cells became part of the HeLa immortal cell line, which have been used to test an early polio vaccine, and conduct AIDS and cancer research. The HeLa cell line has contributed to many other advancements in medicine, been the subject of books and films, and expanded discussions regarding biomedical research and consent.

1964
Declaration of Helsinki

The World Medical Association created the Declaration of Helsinki to address the issue of inadequate ethical regulation in research involving human subjects. It tied the 10 points identified in the Nuremberg Code to the Declaration of Geneva and addressed issues of clinical research in addition to issues of medical practice.

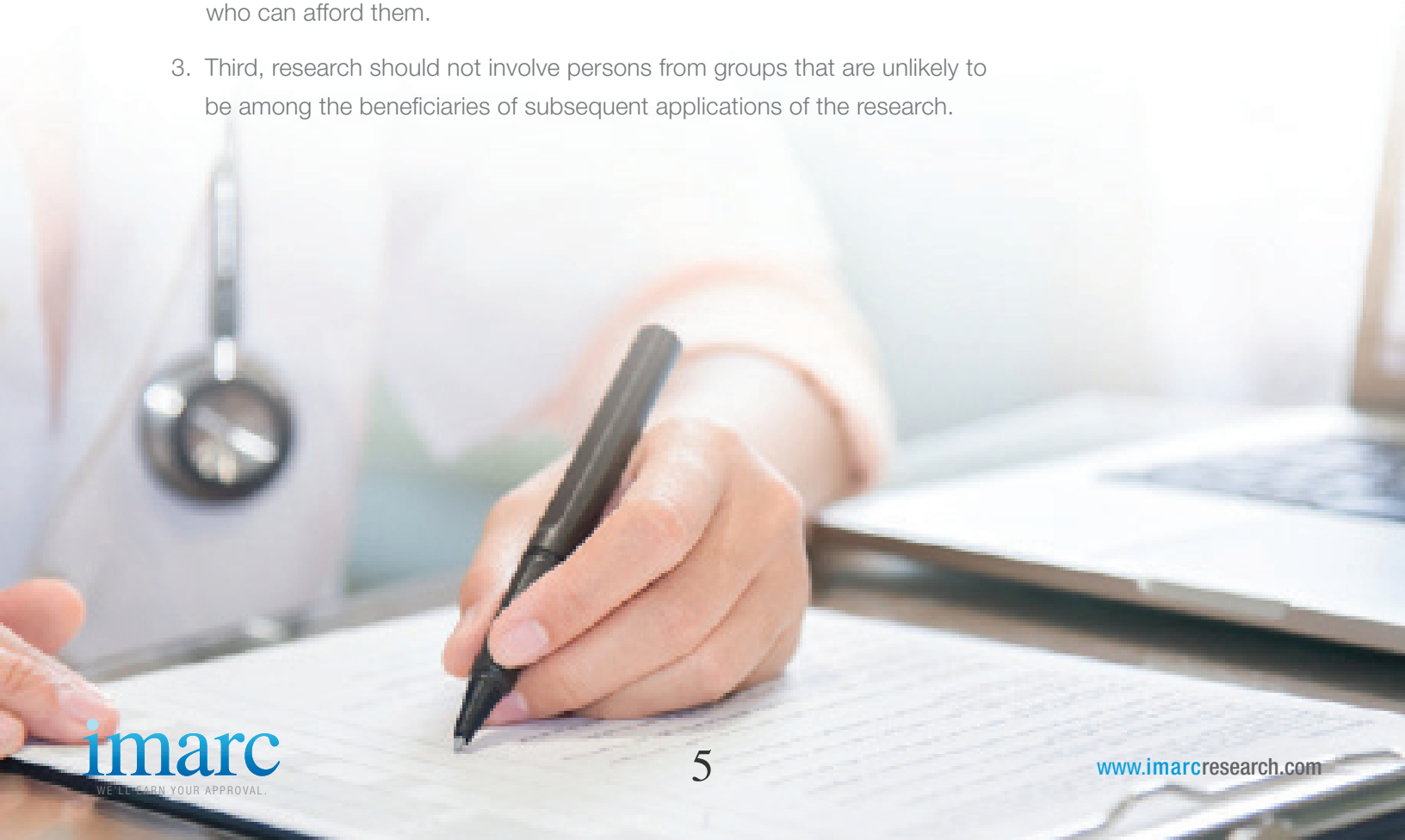
The Declaration of Helsinki outlines principles for ethical research conduct, stressing the importance of human subject protection above all other considerations. While the Nuremberg Code stated informed consent was "essential," the Declaration of Helsinki modified this to say it should be obtained "if at all possible" and permitted informed consent by proxy.



1979
The Belmont Report

Following public awareness of the Tuskegee syphilis study after 1972, Congress passed the National Research Act, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This commission met regularly for nearly four years, culminating in a summit at the Smithsonian Institution's Belmont Conference Center in February 1976. The resulting Belmont Report summarized the three ethical principles the commission concluded should guide human research: **respect for persons, beneficence and justice.**

- The first ethical principle describes the concept of respect for persons. According to the Belmont Report, individuals should be treated as autonomous agents, and persons with diminished autonomy are entitled to protection.
- The second ethical principal describes the concept of beneficence. Individuals should not only be protected from harm, and research professionals must seek to do no harm, but efforts should also be made to secure the well-being of human subjects.
- The third ethical principal describes the concept of justice, which can be broken down into three points.
    1. First, subjects should not be selected because of their easy availability, compromised position, or manipulability.
    2. Second, research that is supported by public funds to develop therapeutic devices and procedures should not provide advantages only to those who can afford them.
    3. Third, research should not involve persons from groups that are unlikely to be among the beneficiaries of subsequent applications of the research.



1991
The Common Rule

The Common Rule is U.S. federal policy (Code of Federal Regulations Title 45 Part 46) that arose from the Declaration of Helsinki and the Nuremberg Code. In addition to the general ethical treatment of human subjects, it outlines Institutional Review Board (IRB) regulations, safeguards the informed consent process, and includes protections for vulnerable populations including pregnant women, children and prisoners.

2010
Poly Implant Prosthese Breast Implant Scandal

Over a 20-year period, Poly Implant Prosthese produced more than 2 million sets of breast implants using a cheaper, industrial-grade silicone not approved for medical use. The implants ruptured at a rate that was double the industry average, and the silicone caused inflammation, possible scarring and other harmful long-term effects. Public awareness of the scandal resulted in a major overhaul of European device regulations in 2017 under two new regulations (EU 2017/745 and 2017/746), with 2020 and 2022 implementation deadlines (for medical devices and in vitro diagnostics, respectively).

Guiding Principles of Good Clinical Practice

The Nuremberg Code, Declaration of Helsinki and the Belmont Report formed the foundation for many of the informed consent guidelines that are still in place today. There have been several other foundational documents, including:

World Health Organization (WHO) Guidelines

The World Health Organization released its guidelines for Good Clinical Practice as a reference for regulators, sponsors, investigators and ethics committees.

The guidelines address the following topics:

- Justifications for a clinical trial and protocol
- Protection of trial subjects
- Responsibilities of investigators, sponsors and monitors
- Assurance of data integrity and product accountability
- Roles and responsibilities of regulatory authorities

International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice

The International Conference on Harmonization was an international collaboration to unify standards in the European Union, Japan and the United States with additional countries participating, including Australia. The guidelines established 13 guiding principles of good clinical practice.

These guidelines can be grouped into five major concepts:

1. **Conduct clinical trials with an ethical eye.**
   Trials should be conducted in accordance with the ethical principles originating in the Declaration of Helsinki. Freely given informed consent should be obtained from every subject prior to participation.

2. **Subject protection is a paramount priority.**
   Benefits should always outweigh the risks, and the rights, safety and well-being of trial subjects should prevail over the interests of science and society.

3. **Have a well-designed plan, and stick to it.**
   The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) should safeguard the rights, safety and well-being of all trial subjects, paying special attention to vulnerable populations.

4. **Select qualified study staff.**
   The research team should consist of investigators and delegated staff who collectively have the qualifications and experience to conduct the proposed trial.

5. **Documentation is essential.**
   The investigator or institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the trial's subjects. Data should be attributable, legible, contemporaneous, original, accurate and complete.

These guidelines reflect the views of regulatory bodies and should be followed when submitting any clinical trial data to them.

Additionally, the ISO 14155:2011 guideline is the Good Clinical Practice standard specifically focused on medical devices, and is published by the International Organization for Standardization. The concepts and requirements for controlled, ethical research in the guideline closely follow ICH E6 GCP, but are focused on the particulars of device research.

FDA Clinical Research Regulations

The FDA formally adopted ICH E6 GCP guidelines, making it clear that these are the standards they expect. Sponsors, principal investigators and everyone involved in clinical research should understand the regulations and why they are important when submitting data to the FDA.

Here's a short summary of each one and why it's important in GCP:

- Investigational Device Exemptions (21 CFR Part 812)
- Investigational New Drug Application (21 CFR Part 312)
- Protection of Human Subjects - Informed Consent (21 CFR Part 50)
- Institutional Review Boards (21 CFR Part 56)
- Financial Disclosure by Clinical Investigators (21 CFR Part 54)
- Electronic Records and Electronic Signatures (21 CFR Part 11)

(For more detail, visit the Electronic Code of Federal Regulations)

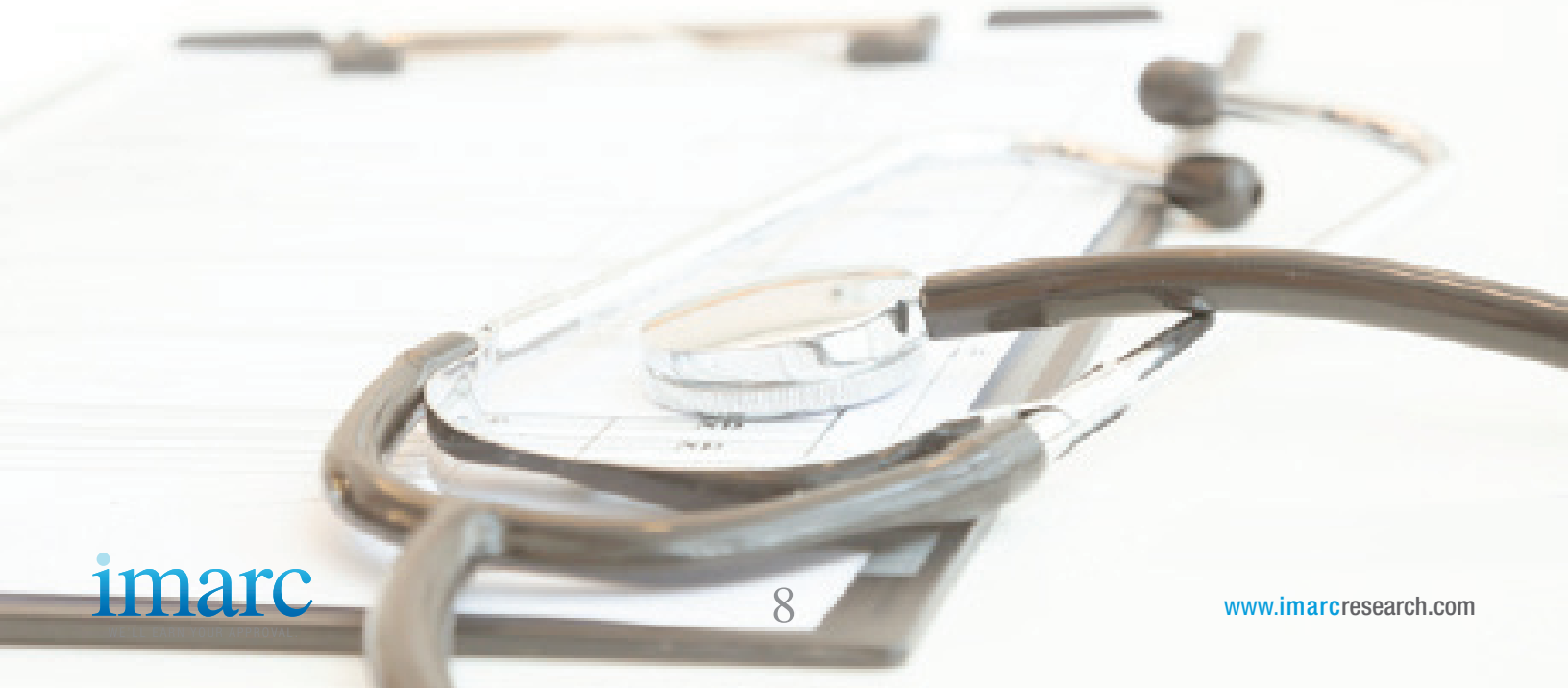
Investigational Device Exemptions (21 CFR Part 812)

This regulation details the FDA's process for accepting investigational device exemptions, which are required for new medical devices that pose a significant risk. The sponsor of the clinical trial is responsible for submitting the IDE application to the FDA and obtaining Institutional Review Board (IRB) approval before the study can begin.

Following these updates, sponsors seeking IDEs, premarket notifications 510 (k), premarket approvals, requests for De Novo classification, product development protocols, and humanitarian device exemptions are now required to include statements and information about how the studies conform to GCP.

Investigational New Drug Application (21 CFR Part 312)

This regulation governs when and how investigational new drug studies must be submitted to the FDA, as well as when these requirements may be waived.



Protection of Human Subjects - Informed Consent (21 CFR Part 50)

This regulation defines what constitutes informed consent, identifies minimum required elements to include, and details the procedures that must be followed to obtain and document informed consent in clinical trials. It also specifies when exceptions to these procedures apply, such as during emergency research, and includes additional safeguards for vulnerable populations in clinical investigations.

Institutional Review Boards (21 CFR Part 56)

This part defines the role of the IRB in safeguarding the rights, safety, and welfare of human subjects in research, and explains when IRB review is required. It also details how IRB members are to be chosen, procedure requirements, and how boards review research.

Financial Disclosure by Clinical Investigators (21 CFR Part 54)

This regulation requires applicants who submit a marketing application for a drug or medical device to submit certain information related to compensation and financial interests of any investigator conducting clinical studies in the United States. The purpose of this is to ensure any potential bias was properly mitigated to ensure data integrity and human subject protections were not compromised.

Electronic Records and Electronic Signatures (21 CFR Part 11)

This regulation was introduced in 1997, updated in 2003, and further clarified in 2017 and 2019 to account for the growing use of electronic technology in clinical research. To ensure the validity of electronic records and signatures (a fundamental component of informed consent), the systems storing such data must meet specific criteria, including:

- Limiting access to authorized individuals
- Having written policies that hold individuals accountable for actions initiated under their electronic signatures
- Maintaining audit trails and appropriate controls over systems documentation

Recent Changes in Good Clinical Practices

Regulatory agencies have made several important changes in guidelines for Good Clinical Practice to reflect a greater emphasis on risk-based and quality-focused thinking, as well as the increased use of electronic technologies in clinical research.

To ensure that they continue to observe the fundamental principles of GCP as the field evolves, research teams must understand these changes and how to apply them.

Here is a summary of the most recent updates in Good Clinical Practice:

- Integrated Addendum to the ICH Guidelines, E6 (R2), published November 2016
- Revised Common Rule (45 CFR Part 46), published January 2017
- Final Rule updates to 21 CFR 812 (concurrent with updates to 21 CFR 807 and 814), published February 2018 and effective February 2019
- New EU Regulations for Medical Devices and In Vitro Diagnostics (EU 2017/745 and 2017/746)

In addition, a revision to the good clinical practice standard for medical devices, ISO 14155:2011, is expected in 2019 or 2020.

Integrated Addendum (R2) to ICH GCP E6

The R2 addendum introduced the first major changes to the GCP guidelines since 1996. Its purpose was to address new technologies like electronic data capture, electronic medical records, clinical trial management systems, and mobile technologies, as well as the adoption of enhanced risk-based quality management processes.

This addendum consists of 26 items added to address the gaps and concerns identified during nearly 400 GCP inspections conducted by the European Medicines Agency between 2002 and 2012.

Key changes address topics including:

- Specific responsibilities of sponsors and investigators
- Use of a risk management approach to study design
- Implementation of risk-based and centralized monitoring plans
- Improving data integrity

The Role of Principal Investigators

Lack of adequate investigator oversight has been a critical issue resulting in study deficiencies and regulatory inspection findings over the years. The addendum added language emphasizing the principal investigator's sole responsibility for conduct of a trial at the site.

The principal investigator (PI) is responsible for supervising any persons or party delegated to perform study-related tasks. The PI is responsible for ensuring that all parties involved are qualified and trained for the tasks assigned. The PI is also responsible for ensuring all data meets the standards of ALCOA-C (attributable, legible, contemporaneous, original, accurate, and complete).

The Role of Sponsors

Under the new R2 guidelines, sponsors are responsible for implementing a quality management system to support studies from trial design to conduct and study completion. The most extensive changes come to the Sponsor section of the ICH E6 Guideline. 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

Sponsors should also use a risk-based approach to develop protocol & study materials.

Sponsors must demonstrate adequate oversight of contract research organizations and any vendors or subcontractors.

Although the use of risk-based and quality-focused approaches is not new, the R2 addendum provides more instruction and detail for the clinical research community. For example, the R2 addendum states that sponsors must use a risk assessment to validate electronic data systems and have standard operating procedures that include details for setup, installation, validation, data backup and recovery, and training for users. The sponsor must ensure the integrity of data during changes to the computerized system, software upgrades, and data migrations.

Risk-Based Monitoring

The addendum offers detailed descriptions for centralized monitoring approach, and considerations for developing risk-based monitoring plans. In order to implement a risk-based strategy, a sponsor should:

- Develop a systematic, prioritized, risk-based approach
- Develop a monitoring plan tailored to the specific human subject protection and data integrity risks of the trial
- Use varied approaches to improve effectiveness and efficiency
- Document the rationale for the monitoring strategy
- Document results of monitoring activities in sufficient detail to assess compliance with the monitoring plan

Improving Documentation and Data Integrity

The new R2 addendum specifies that both the sponsor and investigator should maintain their respective essential documents in a storage system that provides a process for identifying, versioning, searching, locating, and retrieving documents.

The sponsor should ensure that the PI/institution has control of their case report form data and essential documents before, during and after the trial. The sponsor must ensure the investigator has "control of and continuous access to" the data reported to the sponsor throughout the trial.

The Takeaway

Sponsors should consider conducting a gap analysis and making changes to Standard Operating Procedures to ensure they are complying with these updates.

Revised Common Rule (45 CFR Part 46)

Several revisions to The Common Rule took effect in July 2018, including:

- The requirement for consent forms to provide potential research subjects with a better understanding of a project's scope, including its risks and benefits, so they can make a more fully informed decision about whether to participate.
- Requirements, in many cases, to use a single IRB for multi-institutional research studies.
- For studies using stored identifiable data or identifiable biospecimens, researchers will have the option of relying on broad consent obtained for future research as an alternative to seeking IRB approval to waive the consent requirement. As under the current rule, researchers will still not have to obtain consent for studies on non-identified stored data or biospecimens.
- The establishment of new exempt categories of research based on the level of risk they pose to participants.
  For example, to reduce unnecessary regulatory burden and allow IRBs to focus their attention on higher risk studies, there is a new exemption for secondary research involving identifiable private information if the research is regulated by and participants are protected under the HIPAA rules.
- Removal of the requirement to conduct continuing review of ongoing research studies in certain instances where such review does little to protect subjects.
- The requirement that consent forms for certain federally funded clinical trials must be posted on a publicly available federal website, such as ClinicalTrials.gov.

The Takeaway

Sponsors AND investigators need to defer to how reviewing IRBs are going to interpret the revised Common Rule. Each IRB will have its own interpretation of the Common Rule, which has implications for what they expect in the informed consent document. An IRB may revise their informed consent template, and the sponsor needs to make sure such revisions follow the updated guidelines. Sites doing any government-sponsored research will also need to know and follow these requirements closely.

Final Rule updates to 21 CFR 812

The FDA issued a final rule on "Human Subject Protection: Acceptance of Data from Clinical Investigations for Medical Devices," which went into effect in February 2019 along with updates to 21 CFR 807 and 814.

This rule updates the FDA's standards for accepting clinical data from investigations conducted both inside and outside the United States to help ensure the protection of human participants. It also helps ensure the quality and integrity of data obtained from these investigations.

This update means sponsors are now required to include statements and information about how studies conform to GCP when data is collected in or outside the United States. They must include this information with their applications in support of:

- Investigational device exemptions
- Premarket notifications (510(k))
- Requests for De Novo classification
- Premarket approvals (PMA)
- Product development protocols (PDP)
- Humanitarian device exemptions (HDE)

If the investigation was not conducted according to GCP, the sponsor must include a waiver request or a statement explaining the reasons for noncompliance. The sponsor must also include 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.

New EU Device Regulations

The European Union has regulated the safety and performance of medical devices since the late 1990s. To reflect progress over the last 20 years, the EU introduced two new regulations in May 2017: one on medical devices and the other on in vitro diagnostic devices (EU 2017/745 and 2017/746, respectively). The new regulations include:

- Stricter ex-ante control for high-risk devices via a new pre-market scrutiny mechanism with the involvement of a pool of experts at EU level
- Reinforcement of the criteria for designation and processes for oversight of notified bodies
- Inclusion of certain aesthetic devices that present the same characteristics and risk profile as analogous medical devices under the scope of the regulations
- New risk classification system for in vitro diagnostic medical devices in line with international guidance
- Improved transparency through a comprehensive EU database on medical devices and a device traceability system based on Unique Device Identification
- Introduction of an 'implant card' for patients containing information about implanted medical devices
- Reinforcement of the rules on clinical evidence, including an EU-wide coordinated procedure for authorizing multi-center clinical investigations
- Stronger post-market surveillance requirements for manufacturers
- Improved coordination mechanisms between EU countries in the fields of vigilance and market surveillance

All parties involved will have to comply with the new regulations by May 2020 for medical devices, and by May 2022 for in vitro diagnostic devices.

Taking Clinical Trials from Good to Great

Clinical researchers have a tremendous responsibility to uphold the principles of Good Clinical Practice and protect human subjects. Their responsibilities and influence have become far more complicated along with the increasing complexities of research, and with the introduction of new technologies, tools, and requirements.

Good Clinical Practice is more than a series of documents, regulations, and standards; GCP is a philosophy of ethical research that has evolved over decades. It starts with a strong working knowledge of current regulations, establishing the right procedures, and training your team to apply them.

Here are a few final recommendations to ensure you are following Good Clinical Practices.

- ## Review Standard Operating Procedures

  Take the time to assess your procedures for clinical trials from start to finish. What are your processes for gathering informed consent? Do you have a risk-based monitoring plan? Are your documents up to date?

- ## Train Your Team

  Under the new GCP regulations and guidelines, sponsors bear greater responsibility for ensuring everyone involved in running a clinical trial follows guidelines for informed consent, electronic signatures and records, data storage, and more. Make sure your team understands not only what they need to do, but why it's so important.

- ## Enlist Third-Party Oversight

  Having the support of a compliance-minded contract research organization like IMARC can help ensure your team follows Good Clinical Practice at every stage in your trial. Our team has experience in applying the principles of GCP since 1999 and can assist clinical researchers in a variety of ways, including:

  - Reviewing standard operating procedures and recommending updates
  - Managing compliant studies from beginning to end
  - Implementing risk-based processes and plans
  - Conducting audits and preparing sites and sponsors for successful regulatory inspections
  - Monitoring sites and securing compliance
  - Providing tailored training for all stakeholders in clinical research

- Document Thoroughly

  Clinical research professionals use “ALCOA-C” as the standard for ensuring all research information is documented properly. ALCOA-C is rooted in 21 CFR 58.130 and now a specific element in the ICH E6 (R2) GCP guideline. Here’s a closer look at how to apply it to all documentation in research, from subject source and reported data, to other essential documents like product accountability records.

ALCOA-C

Attributable
It should be obvious who created a record and when it was created

Legible
The research record should be easy to read

Contemporaneous
Results should be recorded as they are observed, and all signatures should be attached to a date indicating when the signature was added

Original
Records should not be photocopies, or should be certified copies.

Accurate
Records should have a high level of integrity and honesty to what was truly observed; they should be thorough, correct and free of errors

Complete
Investigators and institutions should maintain adequate, accurate and complete source documents

Rachel Silver-Kessler, MS, CCRA

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, consultant, and manager for data monitoring committees. 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 is a Certified Clinical Research Associate through the Association of Clinical Research Professionals, and 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.

To learn more about how we can help you comply with the latest GCP guidelines, contact us today.

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