

Ensuring Clinical Trial Compliance

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2021

UNC SYMPOSIUM

for
RESEARCH ADMINISTRATORS

Objectives

- Define compliance as it relates to clinical trials
- Review compliance standards
- Define protocol compliance
- Discuss why protocol compliance is important
- Discuss methods of demonstrating compliance



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What is compliance?



Compliance

Adhering to a rule - this rule can be in the form of a policy, standard, specification or law.

A research protocol is a document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of the research project

Protocol Compliance – adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements



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Regulations

The regulations define:

- Human subjects
- Interactions/interventions
- Sensitive information or materials

- AND provide standards for how all of the above must be treated, enacted, or protected



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Subjects

- **FDA Drug study: (IND regs)**
 - ...a human who participates in an investigation either as a recipient of the investigational new drug or as a control. *21 CFR 312.3 (b)*
- **FDA Device Study: Subject (IDE regs)**
 - ...a human who participated in an investigation either as a individual on whom or on whose specimen an investigational device is used or as a control. *21 CFR 812.3 (p)*
- **Human Subject (45 CFR 46.102 (e)(1))**
- ...a living individual about whom an investigator conducting research obtains:
- **Information or biospecimens through intervention or interaction** with the individual and uses, studies, or analyzes those information or biospecimens
- Or obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens**

OHRP

- Applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research
- When research is conducted or supported (\$\$\$) by the HHS you must adhere to these guidelines
- [45 CFR 46](#) PROTECTION OF HUMAN SUBJECTS



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HHS/OHRP 45 CFR 46

- 1948 - Nuremberg Code
- 1964 – Declaration of Helsinki
- 1932-1972 – Tuskegee Syphilis Study
- 1974 – Basic Regulations on Protection of Human Subjects
- 1979 – Belmont Report
- 1981 – Protection of Human Subjects (Subpart A)
- 1991 – Common Rule
- 2019 – New Final Rule



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OHRP

The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare, and wellbeing of human subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP is part of the Office of the Assistant Secretary for Health in the Office of the Secretary of HHS.

OHRP provides clarification and guidance, develops educational programs and materials, maintains regulatory oversight, and provides advice on ethical and regulatory issues in biomedical and behavioral research. OHRP also supports the Secretary's Advisory Committee on Human Research Protections (SACHRP), which advises the HHS Secretary on issues related to protecting human subjects in research.

[OHRP](#)



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- Covers any experiment that involves a test article and one or more human subjects where the results are intended to be submitted to the FDA as part of an application for a research or marketing permit
- When testing FDA regulated products (drug, device, or biologic) you must adhere to FDA guidelines
- [21 CFR 312, 812, 50, 54, 56 - Regulations: Good Clinical Practice and Clinical Trials](#)

21 CFR 11

- Details the criteria under which electronic records and signatures are considered trustworthy and equivalent to paper records thereby ensuring authenticity, integrity and confidentiality of electronic raw data.
- [CFR - Code of Federal Regulations Title 21](#)

Which records are in scope?

- The FDA has documented what is in scope for 21 CFR Part 11 for electronic records:
 - Generated as part of Current Good Manufacturing Practice (cGMP) for human and animal drugs and biologics
 - Maintained as part of the statutory requirements for submitting information to the FDA in an electronic format, even if they have not been specifically identified in the regulations
 - Maintained or submitted as part of predicate rules



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Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) is a federal law that required the creation of national standards to protect sensitive patient health information from being disclosed without the patient's consent or knowledge. The US Department of Health and Human Services (HHS) issued the HIPAA Privacy Rule to implement the requirements of HIPAA. The HIPAA Security Rule protects a subset of information covered by the Privacy Rule.

[Health Insurance Portability and Accountability Act of 1996](#)



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HIPAA Privacy Rule

The Privacy Rule standards address the use and disclosure of individuals' health information (known as "protected health information") by entities subject to the Privacy Rule. These individuals and organizations are called "covered entities." The Privacy Rule also contains standards for individuals' rights to understand and control how their health information is used. A major goal of the Privacy Rule is to ensure that individuals' health information is properly protected while allowing the flow of health information needed to provide and promote high quality health care and to protect the public's health and well-being. The Privacy Rule strikes a balance that permits important uses of information while protecting the privacy of people who seek care and healing.

[HIPAA Privacy Rule](#)



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ICH GCP

- Good Clinical Practice (GCP): international ethical and scientific standard
- Established in 1990
- Maintained by the International Council for Harmonisation (ICH)
- Founding Members: European Union, Japan, USA

Good Clinical Practice

- The first version of ICH E6 Good Clinical Practice (GCP) Guidelines was finalized in 1996
- Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data is credible.

Good Clinical Practice (GCP)

- The guideline was amended in 2016 to encourage the implementation of improved and more efficient approaches to clinical trial design, conduct, oversight and recording.
- Updated the standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency

The Principles of ICH GCP: E6



Clinical trials should be conducted in accordance with the ethical principles that have their origin on the Declaration of Helsinki



Before initiating a clinical trial, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. Anticipated benefits must justify the risks



Rights, safety, and well-being of subjects prevail over the interests of science and society

The Principles of ICH GCP: E6 (cont)

- **Protocol and Science**
 - Nonclinical and clinical information supports the proposed trial
 - Trials should be scientifically sound and described in a clear detailed master protocol document

The Principles of ICH GCP: E6 (cont)

- **Responsibilities**

- IRB approval prior to initiation
- Medical care/decisions on behalf of subject made a qualified physician/dentist
- Each individual is qualified by education, training and experience to perform his/her tasks.

The Principles of ICH GCP: E6 (cont)

- **Informed Consent**
 - Voluntary and is freely given from every subject prior to participation
- **Data Quality and Integrity**
 - All trial data should be recorded, handled, stored in a way that allows for accurate reporting, interpretation and verification
 - Confidentiality is protected

The Principles of ICH GCP: E6 (cont)

- **Investigational Products**
 - Manufacturing, handling, storage should conform to Good Manufacturing Practice (GMPs) and used per the master protocol document
- **Quality Control/Quality Assurance**
 - Implementation of systems with procedures to ensure quality of every aspect of the trial

So many regulations/standards ...

- Seems like a lot!
- Can be overwhelming.
- Who can assist?

UNC Office of Human Research Ethics Institutional Review Board

- Responsible for ethical and regulatory oversight of research at UNC-Chapel Hill that involves human subjects.
- Any research involving human subjects proposed by faculty, staff, or students must be reviewed and approved by an IRB before research may begin, and before related grants may be funded.

UNC-Chapel Hill Human Research Protections Program

At UNC-Chapel Hill, human subjects research is a privilege, but not a right. Consistent with that philosophy, it is the mission of the UNC-Chapel Hill Human Research Protection Program to ensure that

- 1. the rights and welfare of human subjects are paramount in the research process;*
- 2. the highest standards of ethical conduct are employed in all research involving human subjects;*
- 3. research investigators are properly trained in the ethical and regulatory aspects of research with human subjects;*
- 4. research investigators deal honestly and fairly with human subjects, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and*
- 5. research using human subjects at UNC-Chapel Hill conforms with all applicable local, state, and federal laws and regulations and the policies of the university.*

Scientific Review Committee

- The mission of the Scientific Review Committee (SRC) is to improve clinical research at the University of North Carolina at Chapel Hill. This is facilitated by providing review of the proposed research for scientific merit (e.g., how the new information will advance understanding in a particular line of scientific inquiry); and scientific integrity (e.g., alignment between study design, target sample size, specific aims, recruitment method, outcome measures, study procedures, data collection/quality assurance, safety monitoring, and aim-specific statistical analysis plan).



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What is the difference between the UNC SRC and the UNC IRB?

- The missions of the UNC IRB and UNC SRC complement each other and do intersect at times, but each have very different duties. It's important to understand the difference between them.
 - The SRC reviews study protocols and evaluates the scientific merit and importance of the study, study design, feasibility, statistical analysis plan and data management plan.
 - The SRC also makes sure that the study has clearly stated aims and measurable outcomes. In addition, the SRC keeps GCP, FDA and UNC Research regulatory and policy requirements in mind during the protocol evaluation process.

Clinical Trial Quality Assurance Program

The Clinical Trials Quality Assurance (CTQA) Program is designed to support investigators in ensuring their trials are conducted in accordance with federal, state, and institutional regulations.

- The CTQA staff can assist with setting up systems and processes at the beginning of a trial to validate all the regulatory requirements and essential documents are in place (i.e., documentation of investigators qualifications, confirming Delegation logs are accurately completed, assisting with training documentation).
- During the study, CTQA staff can work with the study team in doing a “friendly review” to check for compliance. Once completed, any findings are reviewed with the study team. Suggestions or assistance is offered (if needed) to help the team ensure continuing compliance.
- The CTQA Program will also conduct post approval reviews for a percentage of clinical research involving human subjects at the University of North Carolina at Chapel Hill (UNC-CH). These reviews are intended to assist investigators in evaluating compliance with all applicable laws and regulations as well as institutional policies for their studies.



Research Billing Compliance

- **Billing Coverage Analysis**
- In order to comply with federal, state, and institutional regulations and standards for clinical research billing, the University is responsible for establishing effective processes to ensure that all services for a study are billed properly. These processes can be complex because clinical research often involves multiple entities that are responsible for costs incurred during the course of a trial. During a single visit a research participant may receive routine medical care in addition to services or procedures conducted for research purposes.
- UNC adheres to the Centers for Medicare and Medicaid (CMS) regulations for billing to the patient (or a third party on the patient's behalf) in the context of a research protocol. These regulations require that a study be qualifying and that the costs billed to the patient meet specific criteria. You can NEVER bill for items or services that are paid for by the sponsor, promised free in the informed consent, or are part of a non-qualifying protocol.

Importance of Protocol Compliance

- Ensures participant safety
 - Risks to subjects are minimized
- Integrity of the science
 - Consistency of data collection
 - Ensuring staff are educated and trained for their roles

Demonstrating Compliance

If you comply with your protocol, but you do not document it, did it really happen?

- Documentation is a requirement of numerous regulations
 - 45 CFR – OHRP Common Rule
 - 21 CFR 312.62 (b) - FDA
 - ICH GCP E6, part 8

Demonstrating Compliance

- Document Participant Eligibility
- Document Consent
- Document data
- Document Contacts (calls, study visits, etc.)
- Document protocol changes
- Document staff training

What if the protocol wasn't followed?

- Deviations
 - Any change implemented without first receiving IRB approval
- Reporting
 - Follow OHRE SOPs
 - CAPA
 - Follow up

Quality Nightmares

by MasterControl



**"That's how the clinical team decides
which regulations they will follow."**

Questions?





THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL