

Quality in Good Clinical Practice



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Quality in Good Clinical Practice

The views presented herein do not represent those of the Federal government.

The information provided is only intended to be general summary information. It is not intended to take the place of statute, regulations, or official policy.

What I do at CMS

Department of Health and Human Services (HHS)

HHS Mission - To enhance and protect the health and well-being of all Americans.

Centers for Medicare & Medicaid Services (CMS)

Center for Clinical Standards & Quality

Quality, Safety & Oversight Group

Quality, Safety & Education Division



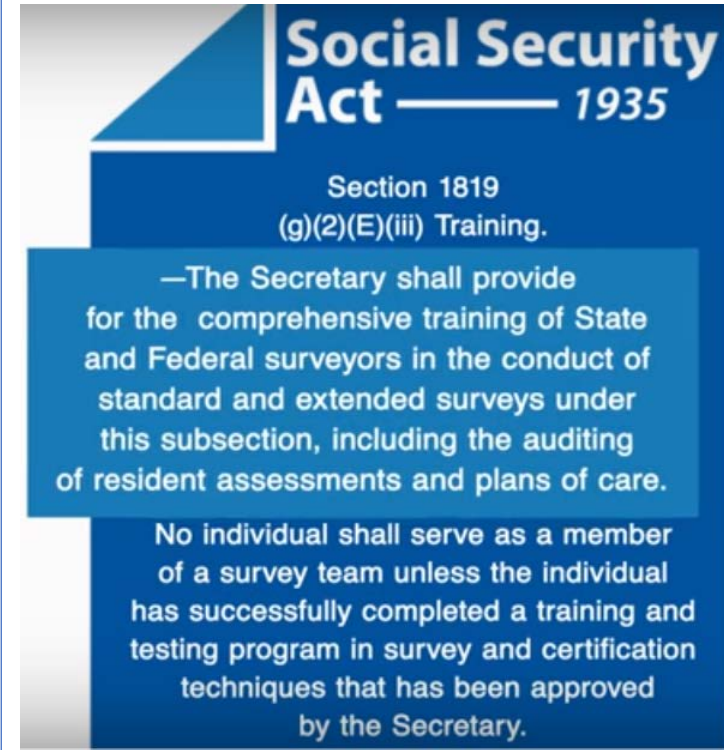
<http://www.hhs.gov/>
<http://intranet.cms.gov/>

What I do at CMS

Quality, Safety & Education Division

Our Mission is to provide the design, development, and delivery of high-quality training to the Surveyors within our country.

The Goal is to empower State Agencies, Regional Offices, and Accrediting Organizations with the knowledge and skills needed to survey a provider or supplier type in accordance with the survey process, conditions, and standards.



What I do at CMS

There are 17 different Provider and Supplier Types.

- Provider types - Hospitals, Home Health Agencies, Hospice, Long Term Care, etc.
- Supplier types - Ambulatory Surgical Centers, End Stage Renal Disease Facilities, Rural Health Clinics, etc.

Survey process, conditions, and standards?

For example –

- Hospitals - 42 CFR Part 482 - CONDITIONS OF PARTICIPATION
- Nursing Homes - 42 CFR Part 483 – CONDITIONS OF PARTICIPATION
- Ambulatory Surgical Centers - 42 CFR Part 416– CONDITIONS FOR COVERAGE

What I do at CMS

Survey process, conditions, and standards?

- Hospitals –
- 42 CFR Part 482
- Regulations
- Legally binding

The screenshot shows the e-CFR website interface. The browser address bar displays the URL: https://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title42/42cfr482_main_02.tpl. The left sidebar contains navigation links: Home, gpo.gov, govinfo.gov, Browse / Search Previous, e-CFR Navigation Aids (Browse, Simple Search, Advanced Search with Boolean and Proximity options, Search History, Search Tips, Corrections, Latest Updates, User Info, FAQs, Agency List, Incorporation By Reference), and the Electronic Code of Federal Regulations e-CFR logo. The main content area is titled 'Electronic Code of Federal Regulations' and states 'e-CFR data is current as of December 26, 2017'. It shows the breadcrumb path: Title 42 → Chapter IV → Subchapter G → Part 482. Below this, it lists: TITLE 42—Public Health, CHAPTER IV—CENTERS FOR MEDICARE & MEDICAID SERVICES, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED), SUBCHAPTER G—STANDARDS AND CERTIFICATION, and PART 482—CONDITIONS OF PARTICIPATION FOR HOSPITALS. A horizontal line separates the title from the subpart details. Subpart A—GENERAL PROVISIONS is listed, with two sections: §482.1 Basis and scope. and §482.2 Provision of emergency services by nonparticipating hospitals. Another horizontal line follows. Subpart B—ADMINISTRATION is partially visible at the bottom.

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Electronic Code of Federal Regulations
e-CFR

Electronic Code of Federal Regulations

e-CFR data is current as of **December 26, 2017**

[Title 42](#) → [Chapter IV](#) → [Subchapter G](#) → [Part 482](#)

TITLE 42—Public Health

CHAPTER IV—CENTERS FOR MEDICARE & MEDICAID SERVICES, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

SUBCHAPTER G—STANDARDS AND CERTIFICATION

PART 482—CONDITIONS OF PARTICIPATION FOR HOSPITALS

Subpart A—GENERAL PROVISIONS


§482.1	Basis and scope.
§482.2	Provision of emergency services by nonparticipating hospitals.

Subpart B—ADMINISTRATION

What I do at CMS

Survey process, conditions, and standards?

- Hospitals –
- 42 CFR Part 482
- Appendix A
- Guidance

 Secure | https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_a_hospitals.pdf

State Operations Manual Appendix A - Survey Protocol, Regulations and Interpretive Guidelines for Hospitals

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(Rev. 172, 11-17-17)

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[Task 5 - Exit Conference](#)

What I do at CMS

Survey process, conditions, and standards?

- Hospitals – (provider)
- 42 CFR Part 482 (regs)
- Appendix A (guidance)
- TAG – A-0048 (surveyor)

A-0048

(Rev. 37, Issued: 10-17-08; Effective/Implementation Date: 10-17-08)

[The governing body must:]

§482.12(a)(4) Approve medical staff bylaws and other medical staff rules and regulations;

Interpretive Guidelines §482.12(a)(4)

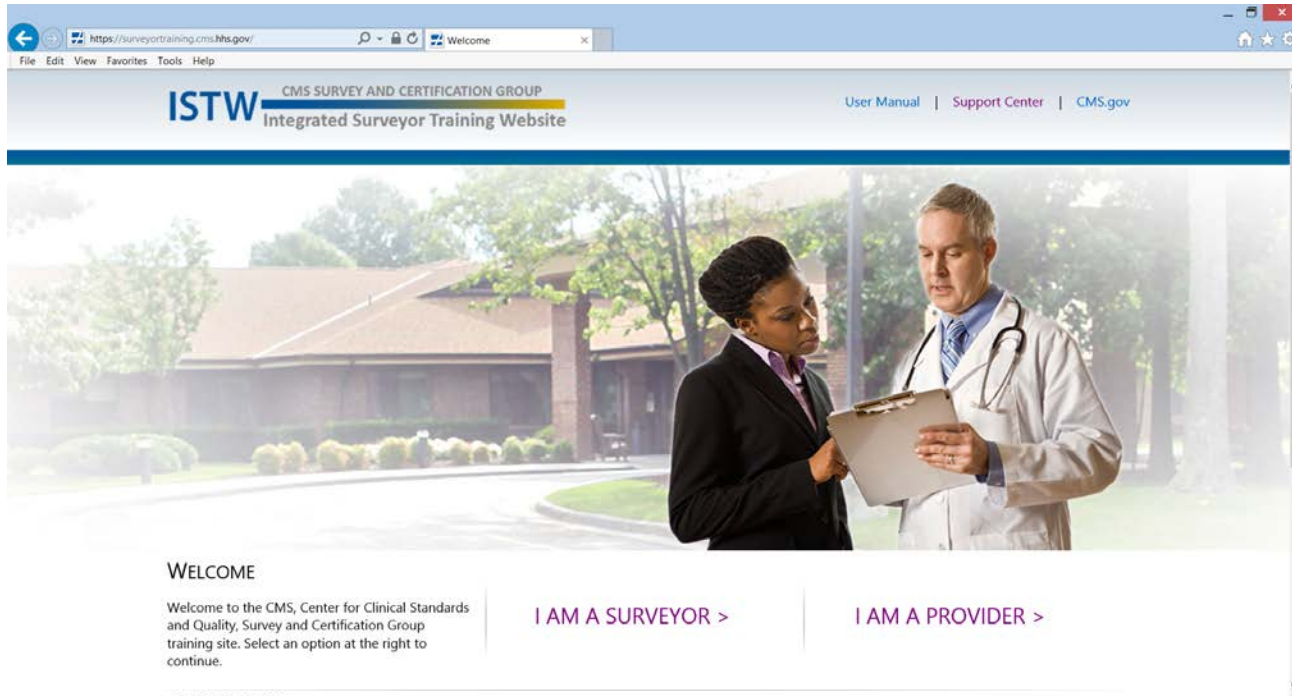
The governing body decides whether or not to approve medical staff bylaws submitted by the medical staff. The medical staff bylaws and any revisions must be approved by the governing body before they are considered effective.

Survey Procedures and §482.12(a)(4)

- Verify that the medical staff operates under current bylaws, rules and policies that have been approved by the governing body.
- Verify that any revisions or modifications in the medical staff bylaws, rules and policies have been approved by the medical staff and the governing body, e.g., bylaws are annotated with date of last review and initialed by person(s) responsible.

What I do at CMS

Quality, Safety & Education Division provides Training on the survey process, conditions, and standards - <https://surveyortraining.cms.hhs.gov/>



Research - Code of Federal Regulations (CFR)

HHS 45 CFR 46 – *congruent with FDA 21 CFR 56*

- Regulates protection of human subjects in most federally funded research
- Subpart A
 - Protection of Human Subjects
 - “The Common Rule”

HHS 45 CFR 46 – Vulnerable Subjects Protection

- Subpart B
 - Pregnant women, human fetuses, and neonates
- Subpart C
 - Prisoners
- Subpart D
 - Children

Legally binding

Research - Code of Federal Regulations (CFR)

21 CFR 50 – FDA

- Protection of Human Subjects
- Focuses on the Informed Consent

21 CFR 56 – *congruent with HHS 45 CFR 46*

- Describes roles and functions
 - Institutional Review Boards (IRB)

Legally binding

Research - Guidance Documents

ICH

- **International Conference on Harmonisation**
- **Global Standards for Conduct of Research**
 - Quality Assurance – chemical & pharmaceutical.
 - Safety Guidelines – in vitro and in vivo (preclinical).
 - Efficacy Guidelines – E2 (data management) & **E6 (GCP)**.
 - Multidisciplinary Guidelines – topics that don't fit above.

GCP (E6)

- **Good Clinical Practice**
 - Ethical Principles, IRB, Investigator, Sponsor, Protocol, Amendments, Investigator Brochure, Essential Documents (regulatory binder).

What is good enough?

What percentage of the time would you like to perform your job without any mistakes? Is 99.9% of the time “good enough”?



- 16,000 pieces of mail lost every hour.
- 500 surgical operations performed unsuccessfully each week.
- One unsafe landing at Newark airport each day.
- One hour of unsafe drinking water each week.
- 20,000 checks deducted from the wrong account each hour.
- Over 2 million people sick or dead from food poisoning each year.

Quality in Good Clinical Practice

And, what characterizes “Good Research”?

Quality	<i>“Can I recognize it when I see it?”</i>	<ul style="list-style-type: none">- If it is peer reviewed.- If it speaks to an outcome.- If it provides statistical and clinical significance and defines conclusions.
Extrinsic Factors	<i>“How is research rewarded?”</i>	<ul style="list-style-type: none">- If it gets published.- If it gets funded.- If it earns my Ph.D.
Intrinsic Factors	<i>“How is good research recognized?”</i>	<ul style="list-style-type: none">- If it is compelling.- If it is useful.- If it justifies assumptions.

What is good enough?

How do you know whether the new knowledge reported from a clinical study was based on **valid data** or whether the research was conducted in an **ethical** manner?



The Investigator can be fined, jailed, and/or banned from research

Dr. Robert Fiddes –15 months in Federal Prison.

**Drs. James Wilson, Mark Batshaw, and Steven Raper -
UPenn paid \$517,496, Medical Center paid \$514,622.
Doctors banned for 5 years from research.**

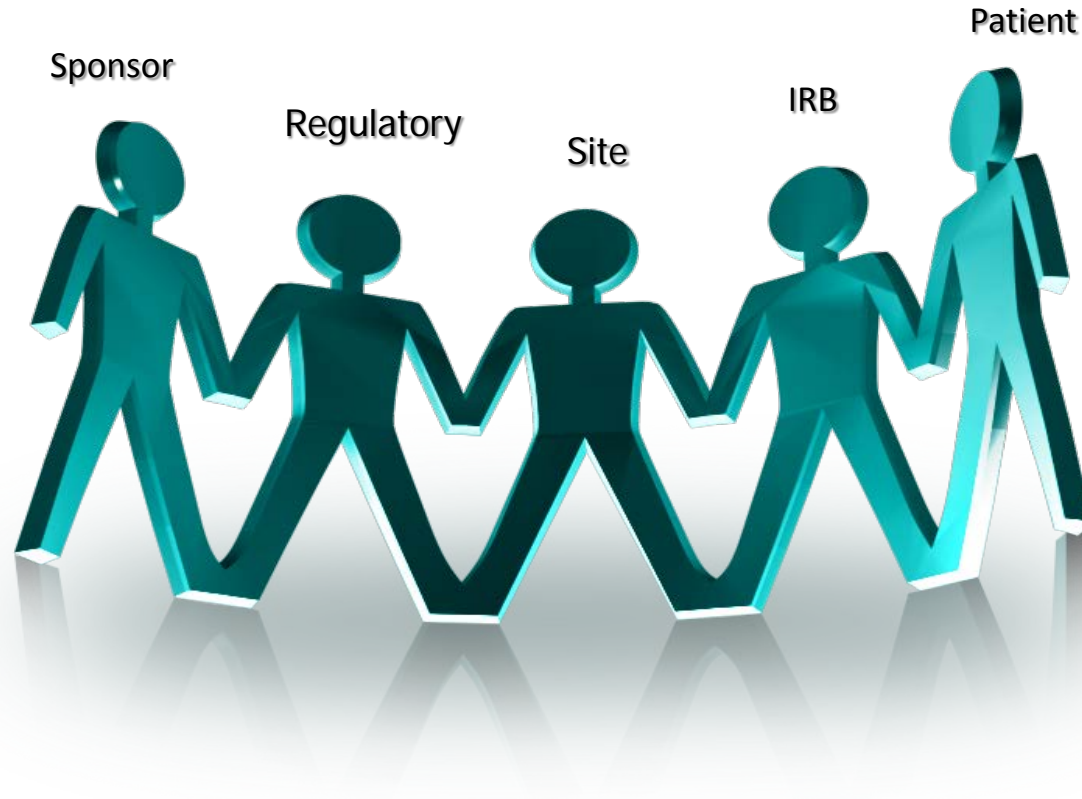
**Eric Poehlman, MD – 12 months in Federal Prison +
\$180,000 fine.**

Maria Palazzo, MD – 100 months in Federal Prison.

**Anne Kirkman-Campbell, MD - 57 months in prison,
fined \$557,251 + \$925,774 in restitution.**

**Scott Reuben, MD – 6 months in prison, 3 years
supervised release + \$5,000 fines, \$361,932 in
restitution + \$50,000 in assets.**

This is where Good Clinical Practice comes in ...



Good Clinical Practice (GCP) in Conducting Research



GCP refers to a standard that ensures ethical and scientific quality in human subject research.

GCP includes internationally recognized standards that must be observed to ensure study quality.

GCP is critical for those involved in clinical research operations.

Background

The overarching objectives of Good Clinical Practice (GCP) -

- To protect study participants' rights, safety, and well-being.
- To ensure that trial data are credible.

The evolution providing these assurances of quality has been guided by two forces -

- **Historical events of scientific misconduct.**
- **Economic globalization.**

Historical Events of Misconduct

The Nuremberg Code (1949) was the first internationally-adopted code of ethics.

Kefauver-Harris Amendments (1962) to the U.S. Food, Drug, and Cosmetic Act began the IND process in the United States.

The World Medical Association (1964) published the first version of the Declaration of Helsinki.

The Belmont Report (1979) established boundaries between practice and research.

Economic Globalization

The Global Economy affected the evolution of GCP -

- Costs of running trials began to rise.
- More industry sponsored trials are conducted overseas.
 - Trials are less expensive to conduct.
 - Participants may be more readily recruited.
 - Strict FDA regulations reject foreign study data.

Economic Globalization

This led other countries to review their procedures for trial quality.

- Impact on their economic and intellectual drug development market.
- Streamline drug development.
- Reduce or obviate duplicate testing.

Representative experts from regulatory bodies and the pharmaceutical industry embarked on a process to develop a unified standard.

Economic Globalization

Experts from the European Union (EU), Japan, and the United States embarked on a new process.

Used a process of expert working groups and consensus decision making (1990).

These working groups gave rise to

- **The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).**

ICH GCP

ICH GCP E6 – “GCP Guideline” 1990

ICH GCP E6 (R1) – “GCP Guideline” June 1996

ICH GCP E6 (R2) – “Integrated Addendum to GCP” Dec. 2016 (effective June 2017)

The ICH E6 guidelines that originally provided a standardized framework for harmonization needed to be modernized for the current research landscape and address these GCP inspection findings.

A couple of the main focuses from the **R2** revisions include:

- GCP guidelines should be followed when **generating clinical trial data** that are intended to be submitted to regulatory authorities.
- These principles should be applied to other clinical investigations that may have an **impact on the safety and well-being of human subjects**.

ICH GCP

The ICH defines GCP as

...an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

ICH GCP

The ICH defines GCP as

...an international ethical and scientific **quality standard** for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the **data and reported results are credible and accurate**, and that the rights, integrity, and confidentiality of trial **subjects are protected**.

Investigators and study team members must be fully aware of their obligations and responsibilities required by the -

- Sponsors
- Local oversight bodies
- Applicable Federal Regulatory Agencies

... **PRIOR** to conducting research!!

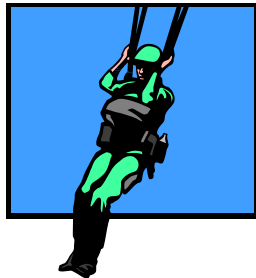
The Key Aspect of GCP

The rights, safety, and well-being of the trial subjects should prevail over the interests of science and society.

The Principles of ICH GCP

The rights, safety, and well-being of the subjects are the most important consideration – and should prevail over interests of science and society.

WWII



The Principles of ICH GCP

Available non-clinical and clinical information on the investigational product should support the proposed clinical trial.

Ellen Roche was a 24-year-old healthy lab technician at JHU asthma and allergy center. In 2001, she enrolled in her boss' **study as a healthy volunteer.**

She inhaled a chemical (hexamethonium) that blocks the nerves the researchers believed were involved in asthma attacks.



After her death, the investigation revealed that the scientist who led the study did not thoroughly research the drug – in 1972, the chemical was no longer approved for use, and earlier papers warned about its toxic effects.

The Principles of ICH GCP

Clinical trials should be conducted in accordance with the ethical principles.

A trial should be initiated and continued only if the anticipated benefits justify the risks.



Study Drug + Suspension

versus



Placebo + Suspension

The Principles of ICH GCP

Medical care given to, and decisions made on behalf of, subjects should always be the responsibility of a **qualified** physician.

- Each involved in conducting a trial should be **qualified by education, training, experience.**

Should be aware of and comply with GCP and the applicable regulatory requirements.

Should have sufficient **time** to properly conduct and complete the trial.

The Principles of ICH GCP

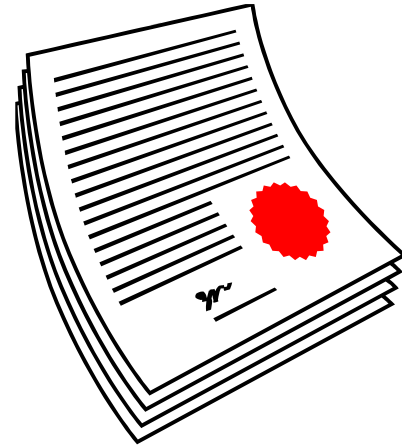
Freely-given informed consent obtained.

- A current and valid informed consent document must be used.
- The participant must fully understand that participation in the research study is voluntary.
- The study staff must ensure that informed consent is obtained in a setting free of coercion and undue influence, and that all questions are answered.
- When the study staff believes the patient understands fully about the study, the participant signs last page of the IRB approved consent form.

The Principles of ICH GCP

Trials should be scientifically sound and described in a clear, detailed protocol –

... with prior IRB/IEC approval.



Example of a Research Protocol

5.2 On-Study Evaluations

At the stated intervals during the study, efficacy will be examined in each patient by the following evaluations:

- Before each cycle of therapy (window for visits is +/- 2 days):
 - Weight and height measurements.*
 - Vital signs (blood pressure, pulse rate, respiration rate and temperature).*
 - CBC with differential, platelet count (within two working days prior to start of cycle).*
 - Limited medical history and physical examination.*
 - Performance status evaluation.*
 - Blood chemistry and liver function tests (within two working days prior to start of cycle). Blood chemistry tests will be done weekly during treatment.*
 - ECG (on Days 1, 2, 8 and 15 of Cycle 1; and Day 1 only of Cycle 2 and beyond).

*For Cycle 1, these evaluations do not need to be repeated if the baseline evaluation was obtained ≥ 7 days from Cycle 1, Day 1.

- Cycle 1 and Cycle 2, Day 1 only:
 - Pharmacokinetics as per instructions in section 13. (Expansion Cohorts- PKs will be done at the discretion of the PI)
- Continuously during the study:
 - Toxicity rating using the NCI Common Terminology Criteria for Adverse Events version 4.0.
- After completion of every two cycles of therapy
 - CT or other imaging of known disease, if clinically indicated.

Example of Study Schedule

Starting with Cycle 1, Day 1 study visit windows are +/- 2 days



Procedures	Baseline ¹	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2	Cycle 3 and on	Off Study assessment (if patient is able to participate)
Medical History	C	C				C	C	C
Histology/ Cytology	C							C
CXR ²	C							
CT or other imaging of known disease (if indicated)	C						C ⁴	C ⁷
ECG	C	R (ECG 1 hour after first dose of KML001)	R	R	R	R	R	R
Physical Exam	C	C				C	C	C
Height, Weight, Vital signs	C	C				C	C	C ⁸
Performance Status	C	C				C	C	C
CBC with diff, plt ^{3,9}	C	C				C	C	C
Chemistries ^{3,9} (including Na,	C	C		R	R	C ¹⁰	C ¹⁰	C

The protocol should be strictly followed

A protocol **deviation** is non-adherence to protocol-specific study procedures.

Deviations from the investigational plan must be reported to the appropriate oversight bodies (i.e. Sponsor, IRB, DSMB, FDA, OHRP).

Office for Human Research Protections (OHRP) would ask if the deviation is considered **serious or continuing noncompliance** involving risks to subject or others?

(45 CFR 46.103(b)(5))

The protocol should be strictly followed

Sponsors and/or the IRB typically will not grant **exceptions** to protocol-specific entry criteria to allow patients to enter a study.

If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular patient, **prior approval** from sponsor and the responsible IRB/IEC, in accordance with their SOP, is required before the patient will be allowed to enter the study.

The protocol should be strictly followed

An **Unanticipated Problem** is defined as -

- An unexpected event that potentially increases risk to participants or others.
- Adversely affects the rights, safety, or welfare of the participants.
- Adversely affects the integrity of the study.

Unexpected, related to participation in the research, suggests that the research places subjects or others at a greater risk of harm.

The protocol should be strictly followed

A protocol **violation** is any significant divergence from the study protocol as approved by the IRB/IEC.

- A violation is a serious non-compliance with the protocol that can result in the exclusion of a patient or their results in the study.
 - Examples include, non-adherence to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines.
- In some cases the researcher may be charged with misconduct.

(Serious) Adverse Events

Adverse Event (AE)

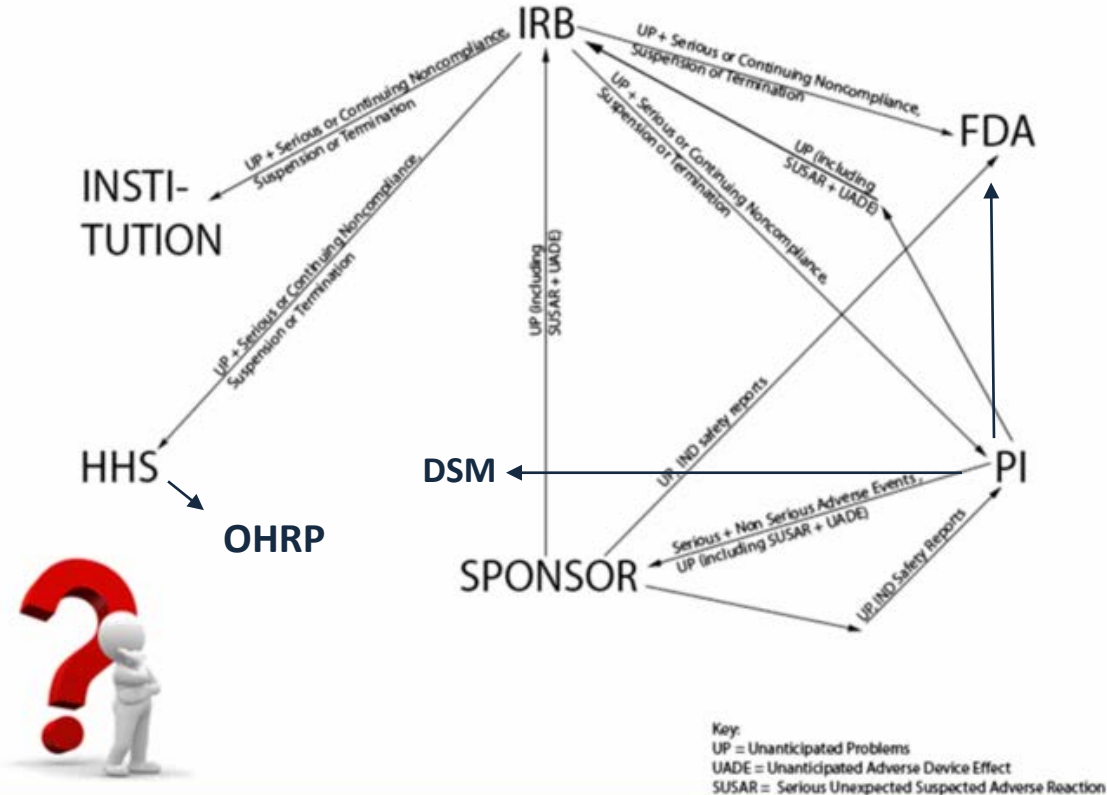
Any undesirable, unfavorable, or unintended sign, symptom, side effect, toxicity, or disease that is experienced by a patient.

Serious Adverse Event (SAE)

- 1) Results in death.
- 2) Is life-threatening.
- 3) Results in hospitalization (or prolongation of existing stay).
- 4) Results in a persistent or significant disability/incapacity.
- 5) Results in a congenital abnormality/defect.
- 6) May jeopardize subject health, and requires surgery/medical intervention to prevent other 5 criteria.

What happens if there is an adverse event or if the protocol is not followed exactly??

REPORTING OBLIGATIONS



The Principles of ICH GCP

All clinical trial information should be recorded, handled, and stored in a way to allow accurate reporting, interpretation, and verification.

The confidentiality of records should be protected.



After the trial ...

After completion or termination of the trial -

- Investigational Product(s) accountability at the site.
- Completed subject identification code list and treatment allocation document.
- Audit certificate, final close-out monitoring report, and/or a clinical study report.
- Final report by the investigator to IRB/IEC (where required) and to the regulatory authority(ies) (where applicable).
- Ensure that the investigator has continuous access to the Case Report Form (CRF) data reported to the sponsor.

Quality in Research

GCP requirements for auditing and monitoring research -

- Setting up a quality-control system for the study.
- Ensuring trial quality by organizing regular inspections.
- Examining the relevant activities and documents to evaluate whether the trial is being carried out according to the IRB approved trial proposal, the regulations, and guidance.
- Checking that data has been recorded in a timely, truthful, accurate, and complete manner – and that reporting requirements are being met.

Quality in Research

Monitoring –

- Responsibility of the research department to regularly inspect throughout the study.

Auditing – (regular or event-driven)

- Inspecting various trials by those not directly involved in the research (i.e. Sponsor, CRO, IRB, OHRP, FDA, etc.)
- Evaluating whether the conduct, data recording, and analysis of the trial are in accordance with the IRB-approved trial proposal, the regulations, and guidance.
- Systematically inspecting during and/or after the research.

Quality in Research

Ensuring quality in research?

Adhere to the Policies, Regulations and Guidelines.

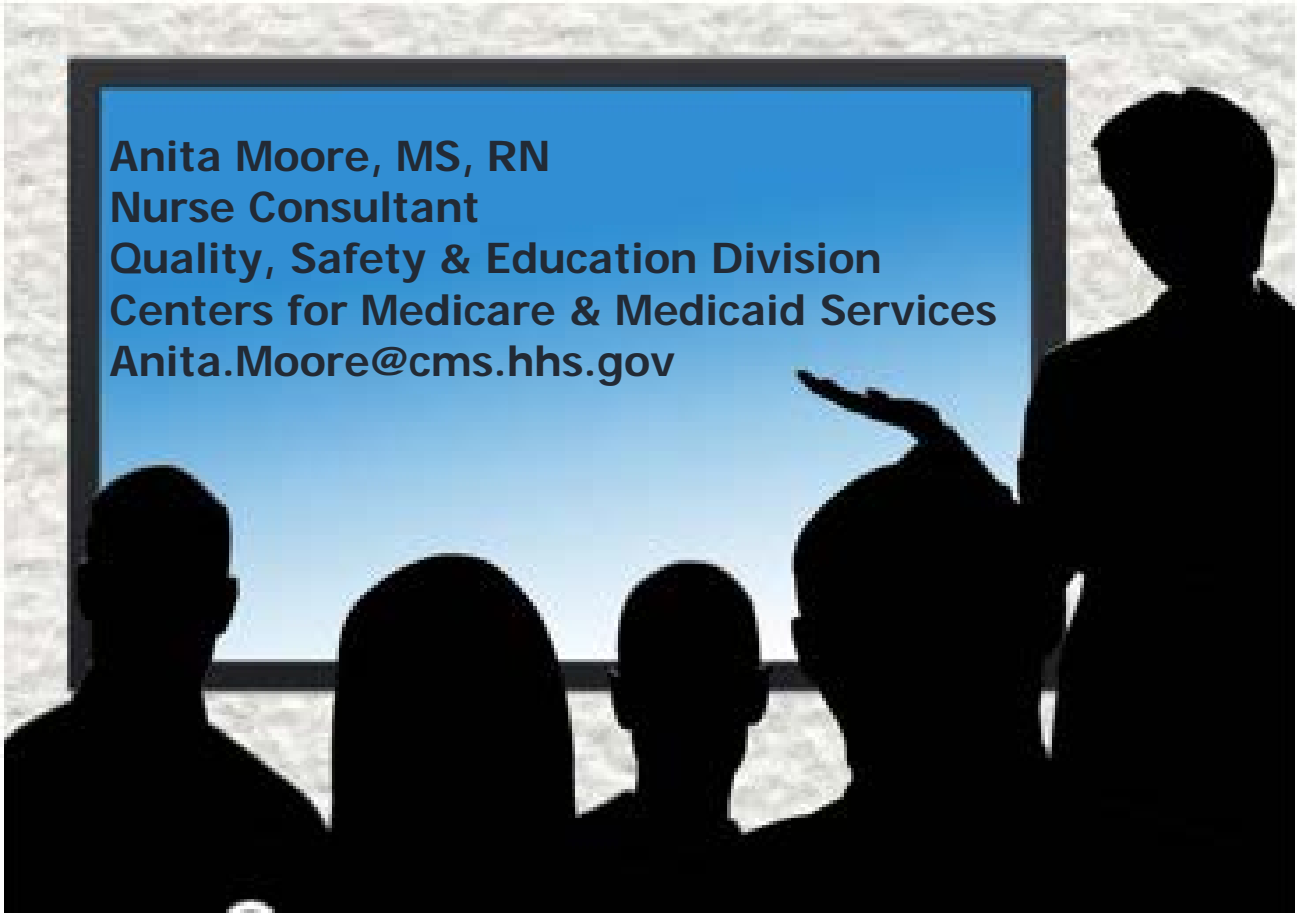
And remember ...

The rights, safety, and well-being of the trial subjects should prevail over the interests of science and society.



Questions and Answers

Q&A



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