

CRA TRAINING

BASIC I: GCP FOR SITE MONITORS

# GCP ESSENTIALS

WHAT A MONITOR NEEDS TO KNOW ABOUT GCP

DAN SFERA

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## WHAT IS GCP?

- ▶ Good Clinical Practice (GCP) is a set of internationally recognized ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials.
- ▶ Three basic ethical principles of equal importance are respect for persons, beneficence, and justice
- ▶ Approved by ICH members
- ▶ Adopted by National Regulatory Authorities
- ▶ Developed in accordance with existing standards in US, Europe, Japan Australia, Canada, Nordic countries and WHO



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## GCP OBJECTIVES

- ▶ The purpose of having GCP is to
  - ▶ To harmonize the regulations and guidelines for drug development
  - ▶ Assure the quality, safety and efficacy of a clinical trial
  - ▶ Provide standards and guidelines for the conduct of clinical research
- ▶ The developed guidelines are applicable for drugs, biologics and medical devices



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## GCP CONTENTS

- ▶ 1. Glossary
- ▶ 2. The Principles of ICH GCP
- ▶ 3. Institutional Review Board / Independent Ethics Committee
- ▶ 4. Investigator
- ▶ 5. Sponsor
- ▶ 6. Clinical Trial Protocol and Protocol Amendment
- ▶ 7. Investigator's Brochure
- ▶ 8. Essential Documents for the Conduct of Clinical Trial

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# GCP HISTORY



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## MAJOR EVENTS (OVERVIEW)

Year	Event
1938	U.S. Food, Drugs and Cosmetic Act
1947	Nuremberg Code created
1948	Declaration of Human Rights
1962	Thalidomide is denied FDA approval in the USA
1962	USA – Kefauver Harris Amendment or "Drug Efficacy Amendment" passed
1964	The Declaration of Helsinki is established by World Medical Association
1972	Tuskegee syphilis experiment ends
1978	USA – GCP adopted by FDA
1979	The Belmont Report
1982	International Guidelines for Biomedical Research Involving Human Subjects are established
1991	European Community EC GCP Guidelines become operational
1993	WHO issues its set of GCP Guidelines
1996	The ICH Guidelines on GCP Operational
1997	ICH-GCP guidelines becomes law in some countries
2000	Worldwide – The DoH (declaration of Helsinki) Amended
2005	EU – "The GCP Directive"
2005	WHO – Handbook for GCP Guidance for implementation
2016	ICH E6 GCP (R2) addendum was released

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## KEY EVENT: NUREMBERG CODE (1948)

- ▶ Nuremberg code was developed after Nuremberg trials relating to human testing by Nazis during World War II.
- ▶ Some of the guidelines that emerged after the Nuremberg Code are
  - ▶ Voluntary participation
  - ▶ Informed Consent
  - ▶ Minimization of risk



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## KEY EVENT: DECLARATION OF HELSINKI (1964)

- ▶ Declaration of Helsinki is a product of the World Medical Association's 1964 Helsinki Declaration which specified the ethical responsibilities of researchers to trial participants.
- ▶ The Declaration of Helsinki requests that:
  - ▶ Research must conform to scientific principles
  - ▶ Independent ethics committees (such as IRBs) should review protocols
  - ▶ Supervision and conduct of trial is only performed by suitably qualified persons
  - ▶ Objectives and possible benefits should be balanced against risk to subjects
  - ▶ Privacy is respected and minimal physical and mental impact is placed on subjects
  - ▶ Informed consent should be obtained

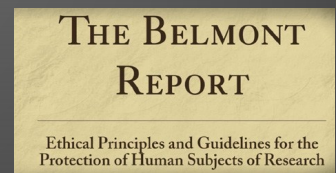


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## KEY EVENT: BELMONT REPORT (1979)

- ▶ The Belmont Report was written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
- ▶ Was never adopted by law or by the HHS but has continues to be influential ethical framework for protecting human subjects.
- ▶ Three main principles for study participants:
  - ▶ Respect for persons – treating people as autonomous and providing protection for those who can't provide adequate consent
  - ▶ Beneficence (nonmaleficence) – assessment of risks and benefits for study participants
  - ▶ Justice – forbids exploitation for vulnerable populations



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## THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH-GCP)

- ▶ GCP is an international quality standard that is provided by the International Conference on Harmonisation (ICH)
- ▶ Goals: Harmonize technical procedures and standards; improve quality; speed time to market
- ▶ In 1997, the FDA endorsed the GCP Guidelines developed by ICH
- ▶ ICH guidelines have been adopted into law in several countries, but used as guidance for the FDA in the form of GCP.




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## **GCP PRINCIPLES**

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2. The Principles of ICH GCP  
ICH E6 GCP (R2)



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## **PRINCIPLES OF ICH-GCP**

- ▶ ICH-GCP is based on 13 principles which are consistent with the Declaration of Helsinki.
- ▶ Ethics:
  - 1) Ethical conduct of clinical trials
  - 2) Benefits justify risks
  - 3) Rights, safety, and well-being of subjects prevail
- ▶ Protocol and science:
  - 4) Nonclinical and clinical information supports the trial
  - 5) Compliance with a scientifically sound, detailed protocol



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## PRINCIPLES OF ICH-GCP

### ► Responsibilities:

- 6) IRB/IEC approval prior to initiation
- 7) Medical care/decisions by qualified physician
- 8) Each individual is qualified (education, training, experience) to perform his/her tasks

### ► Informed Consent:

- 9) Freely given from every subject prior to participation

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## PRINCIPLES OF ICH-GCP

### ► Data Quality and Integrity:

- 10) Accurate reporting, interpretation, and verification
- 11) Protects confidentiality of records

### ► Investigational Products:

- 12) Conform to GMP's and used per protocol

### ► Quality Control / Quality Assurance:

- 13) Systems with procedures to ensure quality of every aspect of the trial



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## MONITORING UNDER GCP

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5.18 MONITORING  
ICH E6 GCP (R2)



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## MONITOR EXPECTATIONS

- ❑ Everyone is responsible for following GCP guidelines, including monitors.
- ❑ Monitors have a big role in making sure that sites are producing quality data and recording it appropriately, as required by GCP guidelines.
- ▶ Section 5.18.1 Purpose states that the purposes of trial monitoring are to verify that:
  - ❑ (a) The rights and well-being of human subjects are protected.
  - ❑ (b) The reported trial data are accurate, complete, and verifiable from source documents.
  - ❑ (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

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## MONITOR EXPECTATIONS

### - 5.18.4 MONITOR'S RESPONSIBILITIES

- ❑ The monitor, in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site :
  - ❑ (a) Acting as the main line of communication between the sponsor and the investigator.
  - ❑ (b) Verifying that the investigator has adequate qualifications and resources and these remain adequate throughout the trial period, that facilities including laboratories and equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.



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## MONITOR EXPECTATIONS

### - 5.18.4 MONITOR'S RESPONSIBILITIES

- ❑ (c) Verifying for the investigational product (IP)
  - ✓ (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
  - ✓ (ii) That the IPs are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
  - ✓ (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the IPs.
  - ✓ (iv) That the receipt, use, and return of the IPs at the trial sites are controlled and documented adequately.
  - ✓ (v) That the disposition of unused IPs at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.
- ❑ (d) Verifying that the investigator follows the approved protocol and all approved amendments

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## MONITOR EXPECTATIONS

### - 5.18.4 MONITOR'S RESPONSIBILITIES

- ❑ (e) Verifying that written informed consent was obtained before each subject's participation in the trial.
- ❑ (f) Ensuring that the investigator receives the current IB, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirements.
- ❑ (g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.
- ❑ (h) Verifying that the investigator and staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

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## MONITOR EXPECTATIONS

### - 5.18.4 MONITOR'S RESPONSIBILITIES

- ❑ (i) Verifying that the investigator is enrolling only eligible subjects.
- ❑ (j) Reporting the subject recruitment rate.
- ❑ (k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date, and maintained.
- ❑ (l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.



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## MONITOR EXPECTATIONS

### - 5.18.4 MONITOR'S RESPONSIBILITIES

- ❑ (m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other.
  - ✓ (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
  - ✓ (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.
  - ✓ (iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
  - ✓ (iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
  - ✓ (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

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## MONITOR EXPECTATIONS

### - 5.18.4 MONITOR'S RESPONSIBILITIES

- ❑ (n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained, and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.
- ❑ (o) Determining whether all AEs are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirements.
- ❑ (p) Determining whether the investigator is maintaining the essential documents.
- ❑ (q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

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**CRA Training:**

- ❑ **Basic I: GCP for Site Monitors**
- ❑ **Basic II: Site Selection**
- ❑ **Basic III: Site Initiation**
- ❑ **Basic IV: Site Monitoring**
- ❑ **Basic V: Site Close-out**
- ❑ **Advanced: I: Source Documents**
- ❑ **Advanced II: Site Regulatory**
- ❑ **Advanced III: Protocol Deviations, IP Accountability, Miscellaneous**

*THANK YOU*

