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STUDIEN-MONITORING.

ICH GCP E6 (R2) Guidance and Compliance

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What are GCPs?

GCPs are defined as standards for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of research studies

IT IS:

- More than rules on a piece of paper
- An attitude of credibility and excellence in research
- Mindset of dedication for quality
- A way to provide a standard for research
- A collection of practices to assure subject safety/protection of rights and data integrity

Why Do We Need GCPs?

- Prevent research misconduct
- Protect the rights, safety and welfare of humans participating in research
- Assurance of the quality, reliability and integrity of data collected
- Provide standards and guidance for the conduct of research

Who is Responsible for GCP Compliance?

- Clinical Investigators
- Sponsors
- Independent Ethics Committees/Institutional Review Boards Contract Research Organizations
- Research Clinical Coordinators
- Clinical Research Associates
- Medical monitors
- Data entry personnel
- Subjects
- Others study team members

Being In Compliance =

Must Adhere to:

- Regulations/Guidance:
  - Federal
  - State / Local
  - Institutional
  - Departmental
- *ICH GCP E6 (R2) guidance*
- IRB policies
- CRO/Sponsor polices/procedures

ICH GCP E6 (R2)

An international quality standard that is provided by the International Conference on Harmonisation

Universally recognized as a critical requirement to the conduct of research involving human subjects

ICH GCP E6 (R2)

- Purpose:
  - harmonize technical procedures and standards;
  - improve quality and speed time to market
  - In 1997, the FDA endorsed the GCP Guidelines developed
  - used as guidance for the FDA/NIH

13 Principles of ICH GCPs

- Ethical conduct of clinical trials
- Benefits justify risks
- Rights, safety, and well-being of subjects prevail
- Nonclinical and clinical information supports the trial
- Compliance with a scientifically sound, detailed protocol
- IRB/IEC approval prior to initiation
- Medical care/decisions by qualified physician

13 Principles of ICH GCPs cont'd

- Each individual is qualified (education, training, experience) to perform his/her tasks
- Freely given ICF from every subject prior to participation
- Accurate reporting, interpretation, and verification
- Protects confidentiality of records
- Conform to GMP's and used per protocol
- Systems with procedures to ensure quality of every aspect of the trial

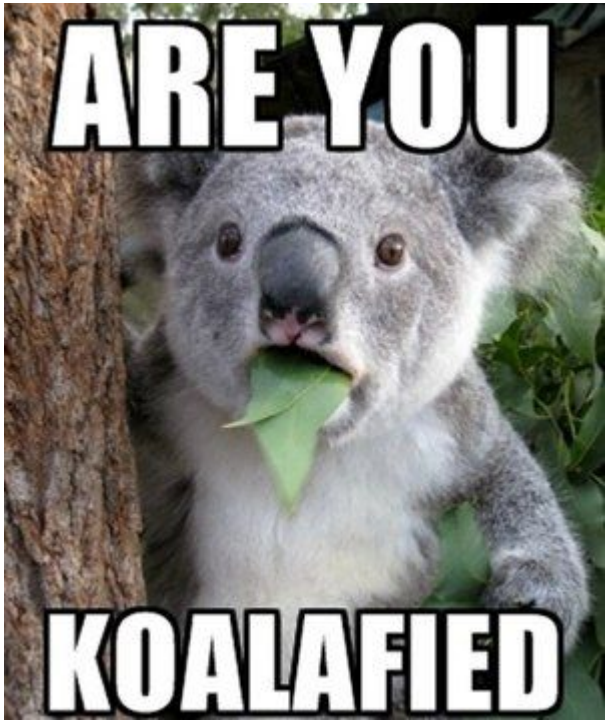
ICH GCP Guidelines Includes the Following Topics

- Glossary
- Principles of ICH GCP
- Institutional Review Board/Independent Ethics Committee
- ***Investigator***
- Sponsor
- Clinical Trial Protocol and Protocol Amendment(s)
- Investigator Brochure
- Essential Documents for the Conduct of a Clinical Trial

ICH GCP E6 (R2) Sections

- Section 1 of ICH GCP Guideline –Glossary
- Section 2 of ICH GCP Guideline –Principles
- Section 3 of ICH GCP Guideline -IRB/IEC
- **Section 4 of ICH GCP Guideline -Investigator**
- Section 5 of ICH GCP Guideline –Sponsor
- Section 6 of ICH GCP Guideline –Clinical Trial Protocol/Amendments
- Section 7 of ICH GCP Guideline –Investigator's Brochure
- **Section 8 of ICH GCP Guideline -Essential Documents**

4.1 Investigator's Qualifications and Agreements



Guideline	Description	How is this documented? Listings as applicable to the study
4.1.1	The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirements and should provide evidence of such qualifications through up to date curriculum vitae and/or other relevant documentation requested by the sponsor/the IRB/IEC, and/or the regulatory authorities	**Credentials:** • **CV/resume, current** • **Medical license** • **Certification** • **Training Log/documentation** • **Protocol Training documentation** • **GCP Training/CITI training**
4.1.2	The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.	**Training Log/Documentation:** • **Protocol** • **IB/drug insert/device manual/pharmacy manual**
4.1.3	The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.	**Training Log/Documentation:** • **Regulations/ICH GCP Guidelines**
4.1.4	The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority.	**Monitoring Log** **Signed CTA with Monitoring Plan**
4.1.5	The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.	**Delegation of Authority Log** **CV/Resume for study staff, licenses/certifications (as applicable)**

4.2 Adequate Resources

Guideline	Description	How is this documented?
4.2.1	The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.	Study Feasibility Meeting/Questionnaire
4.2.2	The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.	Study Feasibility Meeting/Questionnaire Documentation of current studies being conducted
4.2.3	The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.	Study Feasibility Meeting/Questionnaire
4.2.4	The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.	Training Log
4.2.5	The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.	Training log DOAL Documentation of oversight
4.2.6	If the investigator/institution retains the services of any individual or party to perform trial related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.	Credentials Certifications Documentation of oversight of results

4.3 Medical Care of Trial Subjects

Guideline	Description	How is this documented?
4.3.1	A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.	Delegation of Authority Inclusion/Exclusion Worksheets signed by PI PI oversight-review of labs, test results, progress notes
4.3.2	During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.	AE/SAE Log and Documentation Reports of diagnostic tests/labs, per protocol Progress notes Medical Records, if applicable
4.3.3	It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.	PCP letter, if subject agrees
4.3.4	Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights	Contact subject via phone/mail, document accordingly

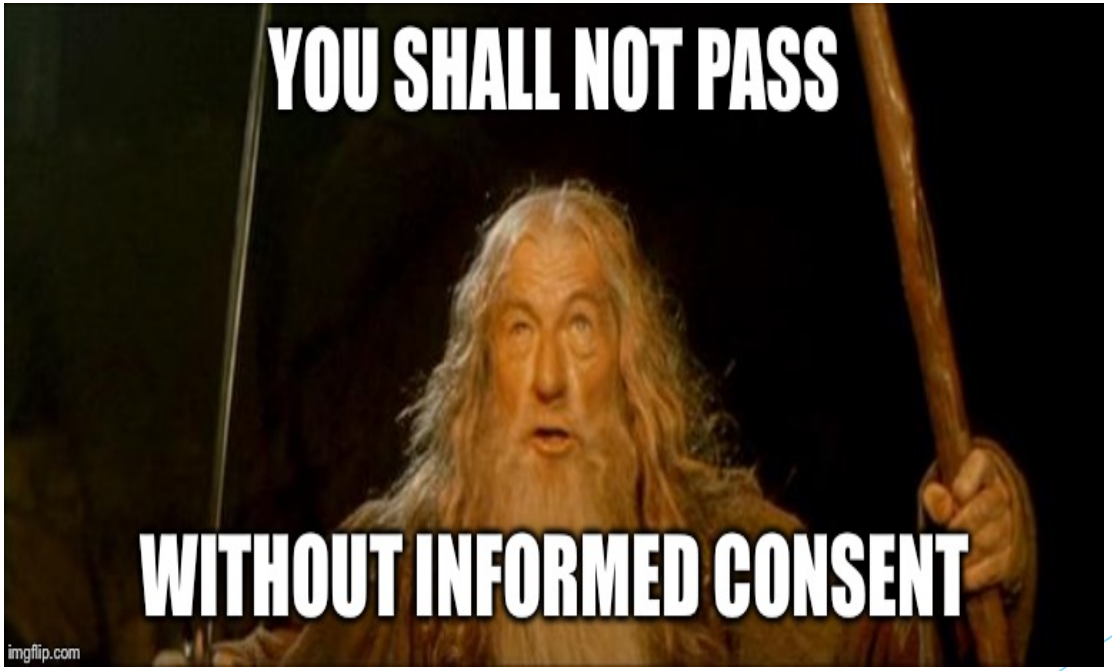
4.4 Communication with the IRB/IEC

Guidance	Description	How is this documented?
4.4.1	Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.	Outcome Letter stating study is approved, approved consent forms, letter stating necessary protocol and forms are approved
4.4.2	As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.	Application to IRB, including necessary documents needing approval
4.4.3	During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.	Amendments, progress reports, deviations, etc

4.5 Compliance with Protocol

Guidance	Description	How is this documented?
4.5.1	The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.	Signed protocol signature page Clinical Trial Agreement (CTA) Source Documentation on all trial subjects, ALCOA-C Appointment calendars
4.5.2	The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).	Deviation Log
4.5.3	The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.	Deviation Log

4.8 Informed Consent of Trial Subjects



Guidance	Description	How is this documented?
4.8.1	In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.	ICF Log/Version Log
4.8.2	The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.	Version, date on site source documents
4.8.3	Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.	Site Source Documentation/Informed Consent Documentation

4.8.4	None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.	Site Source Documentation/Informed Consent Documentation
4.8.5	The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favorable opinion by the IRB/IEC.	Site Source Documentation/Informed Consent Documentation
4.8.6	The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.	Site Source Documentation/Informed Consent Documentation

4.8.7	Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.	Site Source Documentation/Informed Consent Documentation
4.8.8	Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.	Site Source Documentation/Informed Consent Documentation

4.8.11	Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.	Site Source Documentation/Informed Consent Documentation
4.8.12	When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.	Site Source Documentation/Informed Consent Documentation
4.8.13	Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.	Site Source Documentation/Informed Consent Documentation

4.9 Records and Reports

4.9.1	**The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.**	**Source Documentation on all subjects, ALCOA-C CRF documentation**
4.9.2	Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.	Source Documentation on all subjects, ALCOA-C Notes to File Progress notes

4.9.3	**Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.**	**Source Documentation on all subjects, ALCOA-C** **Notes to File** **Progress notes**
4.9.4	The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.	Regulatory Binder, up to date with all essential documents

4.9 Records and Reports

To ensure data integrity, it is essential to have control over the people, processes, systems, and environment in which records are generated/managed and a strong understanding of the data flow.

Data integrity is an essential element of GxP compliance, and in recent years, several regulatory agencies around the world have published draft guidance related to this topic:

FDA - Data Integrity and Compliance with CGMP - Guidance for Industry (April 2016)

MHRA - GXP Data Integrity Definitions and Guidance for Industry (March 2018)

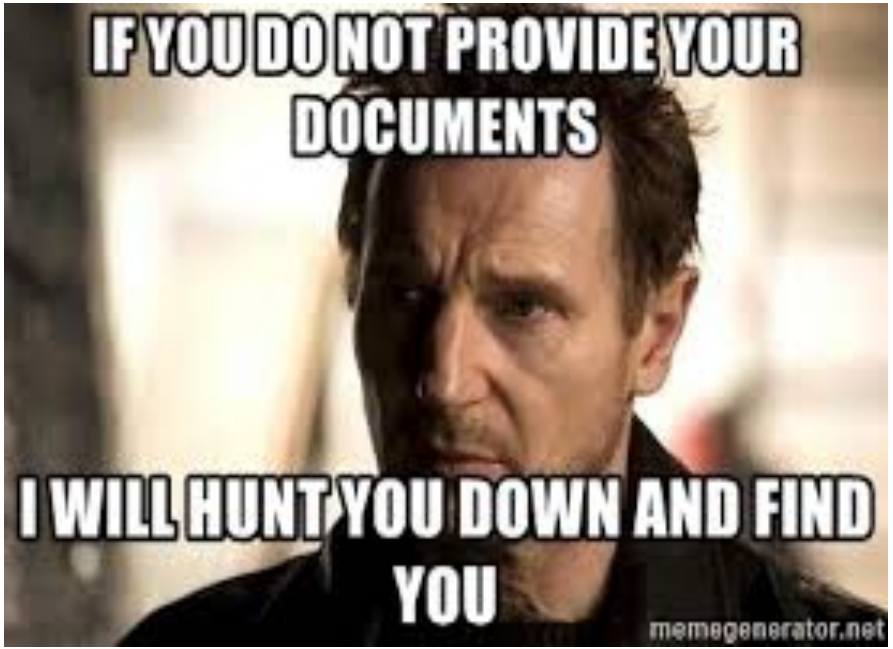
WHO - Guidance on Good Data and Record Management Practices (May 2016)

PIC/S (PI 041-1): Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments (Draft3 – November 2018)

4.13 Final Report(s) by Investigator

4.13	Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.	Close-out form submitted to the IRB Storage of the essential Documents for the appropriate time outlined in the regulations/guidance/CTA Notify the sponsor/IRB (if applicable) of a change in storage location as necessary

ICH GCP Section 8



8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

- The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents.
- The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.
- Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation), based on the importance and relevance of the specific documents to the trial.
- The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor.
- The sponsor should not have exclusive control of those data. When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.
- The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

What Can We Do To Help Ensure Compliance?

- **Be proactive**
- Become familiar with the GCPs/Regs
- Participate in initial and ongoing training
- Attend research meetings/conferences/trainings
- Develop/Follow SOP/Policies/Procedures

Summary

- ***#1 job*- Protect the rights, safety, and well-being of subjects**
- Clean, accurate, complete data
- Follow regulations, SOPs and guidelines
- Get organized and keep up to date
- Follow the protocol

- Keep PI, IRB, Institution, study team, and sponsor updated
- Continuing education / training
- Document, Document, Document to demonstrate compliance!!!
- Report, Report, Report as required!!!


END OF THE PRESENTATION?
FALSE. IT IS NEVER OVER
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thank you . . .


Any Questions


NEVER-ENDING
TRAINING!