Guidelines for Good Clinical Practice

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Background

The International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines.

Originally founded in 1990

Reformed as a non-profit legal entity under Swiss Law on 23 October 2015

Now include 16 members and 32 observers

ICH Assembly met in Singapore on 17-18 November, 2019.

Mission

- to achieve greater harmonisation worldwide to ensure that safe, effective and high quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting respecting high standards.

Background (Contd:)

The work carried out by ICH under the Efficacy heading, the guidelines for good clinical practice is E6 and was finalized in 1996 describing the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

Background (Contd:)

The Harmonized Guideline has been amended in 2016 with an Integrated Addendum to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting, while continuing to ensure human subject protection and reliability of trial results.

GCP covers aspects of monitoring, reporting and archiving of clinical trials, and incorporates addenda on the Essential Documents and on the Investigator's Brochure.

Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R2)

Current *Step 4* version

dated 9 November 2016

Why do we need an addendum to ICH E6?

Since 1996 adoption of ICH E6 GCP, clinical trials have evolved substantially.

Increases in globalization, study complexity, and technological capabilities.

Approach to Good Clinical Practice (GCP) needs modernization to keep pace with the scale and complexity of clinical trials and to ensure appropriate use of technology.

Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2)

In conjunction with other ICH guidelines relevant to the conduct of clinical trials (e.g., E2A (clinical safety data management), E3 (clinical study reporting), E7 (geriatric populations), E8 (general considerations for clinical trials), E9 (statistical principles), and E11 (pediatric populations)

Provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions.

The E6(R2) addendum text should take priority.

Recognition of GCP

In Europe and the USA, the requirements of ICH-GCP 2016 guidelines are embedded in their legislation but limited to specific studies.

The sponsor and many other organizations (e.g. funding agencies, publishers) request that studies are conducted according to GCP principles to ensure a similar 'standard'.

Investigators from low-and middle-income countries need to demonstrate clearly that they are, practically, adopting the principles of GCP.

This ensures that their studies give assurance that their participants were protected and the results are just as reliable as the results from research conducted in any other GCP compliant studies across the globe.

What is Good Clinical Practice?

An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

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 are credible.

Who is Involved with GCP?

Everyone involved in clinical research

Sponsor – An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. (1.53, ICH GCP 2016)

Investigator - A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. (1.34, ICH GCP 2016)

Subinvestigator - Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). (1.56, ICH GCP 2016)

13 Key Principles of ICH GCP

Principle I (Ethics)

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

Ethical conduct of clinical trials

Principle 2 (Ethics)

Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

Benefits justify risks

Principle 3 (Ethics)

The rights, safety and well-being of participants always take precedence over the interests of science and society.

Right, safety & well-being of subjects privilege

Principle 4 (Protocol & Science)

The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

Non-clinical & clinical information support the trials

Principle 5 (Protocol & Science)

Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

Compliance with a scientifically sound, detailed protocol

Principle 6 (Responsibilities)

A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethic committee (IEC) approval/ favorable opinion.

IRB/IEC approval prior to initiation

Principle 7 (Responsibilities)

The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

Medical care/ decision by qualified physicians

Principle 8 (Responsibilities)

Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

Each individual is qualified (education, training, experience) to perform his/her tasks

Principle 9 (Informed Consent)

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

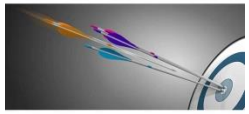
Freely given from every subject prior to participation

Principle 10 (Data Quality & Integrity)

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

This principle applies to all records referenced in this guideline, irrespective of the type of media used.

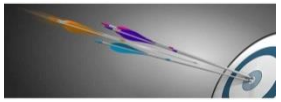
Accurate reporting, interpretation and verification



Principle 11 (Data quality & Integrity)

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Protect confidentially of records



Principle 12 (Investigational Product)

Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

Conform to GMP's & used per protocol

Principle13 (Quality Control/Quality Assurance)

Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such system.

Systems with procedures to ensure quality of every aspect of the trial

Guideline for Good Clinical Practice E6 (R2)

Investigators' GCP Responsibilities

1. Gaining informed consent from study participants
2. Randomization procedures and unblinding, when needed
3. Medical care of study participants
4. Communication with the IEC/IRB
5. Investigational product(s) handling and management at the site
6. Study protocol compliance
7. Qualified staff and agreements
8. Records and reports management
9. Safety reporting
10. Ensuring adequate resources
11. Management of premature termination or suspension of a study
12. Progress reporting and final reports

Guidelines for Good Clinical Practice E6 (R2)

Gaining informed consent from study participants

Must be in a non-technical and understandable language

An impartial witness must be present and sign.

Assent must be taken and sign/mark an assent form.

In emergency situations, the consent of their legally acceptable representative should be sought.

The participant must have signed/marked the consent form before they can take part in the study.

A signed/marked copy of the consent form must be given to the participant.

Participants must be informed, in writing, in a timely manner about the new information and this should be documented.

Randomization procedures and unblinding

Various methods for randomization are available and usually the statistician will decide on the appropriate method for the research question and study design.

Unblinding is carried out only in accordance with the protocol.

The sponsor should be notified immediately, and, where appropriate, might need to be contacted before the unblinding procedure can be undertaken.

There is full documentation of the unblinding which must include the justification for the action.

Lu and Davis (2010) state '*there are very few appropriate reasons for breaking the study blinding but they include situations in which the course of a participant's treatment depends on knowledge of which study agent was administered*'.

Medical care of participants

Must ensure that there is adequate care provided in the case of an AE or clinically significant abnormal laboratory values.

Should inform the participant if medical care is needed for an illness that occurs between or during study interventions.

Inform the individual's physician if the participant agrees to it.

Any AE, illness or clinically significant abnormal laboratory values, actions taken and treatments provided should be documented.

It should also be recorded if the individual withdraws, and this should include the reason for withdrawal, if the participant is willing to supply one.

IEC/IRB communication and approvals

Approval for the recruitment procedures (including advertisements), any documents that will be given to potential participants before or during the informed consent procedure and for everything given to participants once they are involved in the study.

Any planned compensations for time, inconvenience, etc and any other material or written information to be provided to participants.

During the trial the investigator must ensure that all updates of approved documents are submitted to the IEC/IRB for review.

Investigational product(s) management

The investigator is responsible for:

maintaining the IPs records which include information on amounts delivered, dispensed, and returned/ destroyed;

ensuring proper storage conditions are maintained and documented including details of dates, quantities, batch numbers, expiry dates;

ensuring the IPs are only used as specified by the approved protocol;

keeping a list of randomization code numbers assigned to participants;

explaining the correct use of IPs to the participants;

reconciling all IPs received.

Study protocol compliance

The study must be conducted according to the approved protocol, GCP and applicable regulatory requirements.

Agreement to follow protocol should be documented in a contract, or similar document, and signed by the investigator/institution and sponsor.

If, during the course of the study, it is found that changes need to be made then approval must be sought again from the same IEC/IRB that has approved the first version.

Acceptable deviation from the protocol is to eliminate an immediate hazard to the participants.

Any protocol deviations, whether under the investigator's control or not, and the reasons for them, should be documented in detail.

Records and reports management

All records are accurately maintained and all reports are completed and submitted on time.

The investigator must retain sufficient source data.

Source data should be legible, original, accurate and complete.

Changes to source data should be traceable and explained, if needed, and the clarity of original data should be maintained.

Data in the CRF should be reported accurately, complete, legible and timely; consistent with the source documents; clearly marked where corrections were made, with a date, initial, and explanation without obscuring the original entry; and available for access when required by the appropriate bodies (e.g. auditor, sponsor, IEC/IRB, etc).

The study's financial aspects should be documented as agreed upon by the sponsor and the investigator.

Safety reporting

The investigator should:

- report AEs / laboratory abnormalities that are critical to safety evaluations as laid out in the protocol
- report all SAEs immediately to the sponsor
- send promptly detailed written follow-up reports on SAEs
- supply additional information on reported deaths

SAEs:

- collected on a specially designed form.
- reported to the sponsor within 24 hours.
- needs to be reported to the IEC/IRB usually within seven calendar days

Management of premature termination or suspension of a trial

Once the decision, all relevant bodies should be notified as soon as possible, stating the reasons for the suspension or termination.

Following the decision to terminate or suspend the study the investigator must:

- inform all participants promptly and as appropriate, e.g., by phone, letter, etc
- assess treatment requirements and develop a follow-up schedule for all participants
- arrange to see participants individually, if necessary
- inform the institution, sponsor, IEC/IRB and other relevant bodies involved and provide a detailed written report, as appropriate

Progress reporting and final reports

The investigator should submit summaries of the trial progress annually, or as required, to the IRB/IEC.

All changes that may significantly affect trial proceedings or increase risk to participants should be outlined in a written report and submitted to the sponsor and IRB/IEC.

The investigator should provide the IRB/IEC and regulatory authorities a final summary of the trial outcomes upon completion.

The investigator should also provide the sponsor with all the required reports at the end of the trial.

Practical application of GCP

Researchers must apply GCP pragmatically so that it meets the needs of the community and of the study.

This makes the operational and administrative conduct of the study both ethical and realistic.

The GCP requirements as stated by 2016 ICH are 'guidelines' and not always mandatory if the requirements are not implemented into national laws as they are in the USA and EU.

Key Points to Remember

GCP is defined as an international ethical and 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, safety and well-being of study participants are protected.

The rights, safety and well-being of the study participants always take precedence over all else.

Studies must be scientifically sound guided by a protocol and respect ethical principles.

Individuals involved in running studies should be qualified by education, training and experience to perform their tasks.

GCP is a legal requirement in Europe and the USA for specific types of studies; however the principles should be adopted by all types of clinical studies to ensure that all research is conducted to a similar standard.

Key Points to Remember

The investigator must always comply with the ethical requirements and national and local expectations for the process of informed consent.

Informed consent must be given freely by the participant, without undue influence, after receiving all information about the study pertinent to their participation.

There are only few appropriate reasons for unblinding and one is where the participant's medical management depends on knowing what intervention they received.

In any interventional studies must be a qualified doctor who makes all of the study related medical decisions.

IEC/IRB approvals must be obtained after review of all relevant documentation and materials that are intended to be given to study participants.

Key Points to Remember

A protocol amendment which might have an impact upon the participants' safety or the conduct of the study requires IEC/IRB approval.

All SAEs must be reported to the sponsor and to the IEC/IRB according to their requirements.

The investigator must be able to show that the study is valid and sound by demonstrating that the required number of individuals can be recruited, ample time has been scheduled, appropriately qualified staff and suitable facilities are available and that adequate training has been provided to allow staff to undertake their tasks safely and efficiently.

If a study is suspended or terminated the investigator must notify all relevant bodies and all participants as soon as possible.

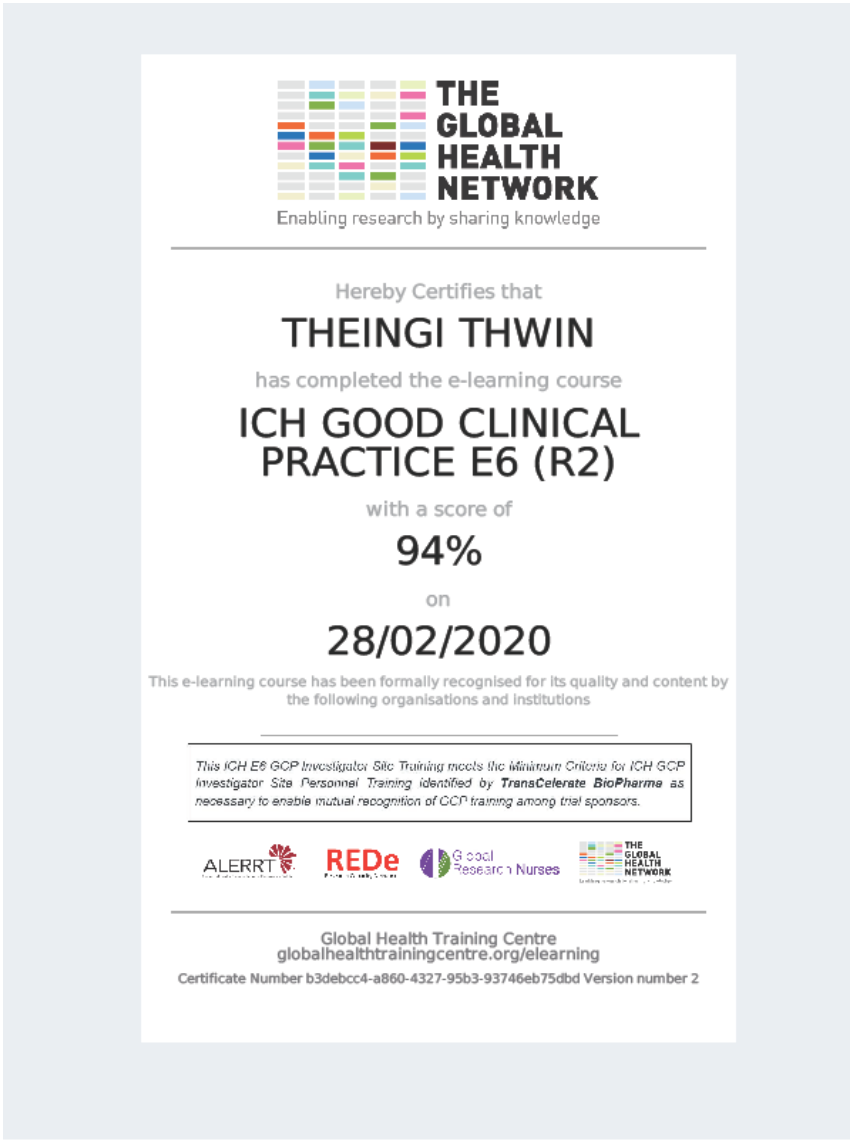
GCP should be applied in a pragmatic manner.

ICH official link and ICH GCP E6(R2) : Guidelines for GCP document

- https://ich.org/page/efficacy-guidelines>

ICH GCP online training,.

- https://globalhealthtrainingcentre.tghn.org/ich-good-clinical-practice/>



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94%

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*This ICH E6 GCP Investigator Site Training meets the Minimum Criteria for ICH GCP Investigator Site Personnel Training identified by **TransCelerate BioPharma** as necessary to enable mutual recognition of GCP training among trial sponsors.*

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