ICH Good Clinical Practice E6 (R2)

Contents

Course Objectives

Upon completion of this course, you will have an understanding of:

- What Good Clinical Practice (GCP) is
- The basic principles of GCP
- What being 'GCP qualified' means and why conducting a study according to GCP is important
- The responsibilities of the investigator
- How GCP should be adopted in the conduct of clinical research

What is Good Clinical Practice

The World Health Organisation’s (WHO) 2002 Handbook for Good Clinical Research Practice (GCP) states that in order to establish the safety and effectiveness of specific health and medical products and practices, it is necessary to carry out clinical research. Randomized controlled clinical trials (designed to answer important scientific and health care questions) have contributed to much of what we now know regarding the safety and efficacy of specific products

and treatments. However the Handbook emphasises that '*such research can be relied upon only if it is conducted according to principles and standards collectively referred to as "Good Clinical Practice"'* (WHO, 2002).

GCP is defined by the International Conference on Harmonisation's (ICH) 2016 guideline for Good Clinical Practice as 'a *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'.*

What is Good Clinical Practice

The principles of GCP are concerned with the safety, rights and well-being of participants and the validity and quality of the research data. The thirteen principles of the 2016 ICH-GCP guidelines are as follows:

- **Principle 1**: The study must be conducted according to the Declaration of Helsinki and consistent with GCP and all applicable regulatory requirements.
- **Principle 2**: Any foreseeable risks and inconveniences of the subject must be weighed against the anticipated benefits.
- **Principle 3**: The rights, safety and well-being of participants always take precedence over the interests of science and society.
- **Principle 4**: Available non-clinical and clinical information on the investigational medicinal product being used must be adequate to support the study.
- **Principles 5 + 6**: The research should be scientifically sound and described in a clear, detailed protocol that has received approval from the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) and needs to be followed
- **Principle 7**: Medical care must be provided by a qualified physician.
- **Principle 8**: Individuals involved in running studies should be qualified by education, training and experience to perform their tasks.
- **Principle 9**: Informed consent must be freely given by each participant.
- **Principles 10 + 11**: Information must be recorded, handled and stored in a manner that allows accurate reporting, interpretation and verification and which ensures the confidentiality of participants' records. This applies to all records, irrespective of the type of media used.
- **Principle 12**: Investigational products must be used in accordance with the approved protocol.
- **Principle 13**: Systems that assure the quality of all aspects of the trial should be implemented with a focus upon ensuring subject protection and reliability of trial results.

Who is Involved with GCP?

Everyone involved in clinical research should have an understanding of GCP but there are three key roles that need to be defined in order to understand why GCP adherence is so important for clinical research. They are the **Sponsor**, the **Investigator** and the **Sub Investigator**:

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)

Sub Investigator - *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)

Recognition of GCP

In some regions, such as Europe and the USA, the requirements of ICH-GCP 2016 guidelines are embedded in their legislation. However, even though this requirement is limited to specific studies, such as intervention trials with investigational medicinal products, the **sponsor** and many other organisations (e.g. funding agencies, publishers) request that studies are conducted according to GCP principles to ensure a similar 'standard'.

It is important for investigators in low-and middle-income countries to demonstrate clearly that they are, pragmatically, adopting the principles of GCP and are therefore working to this same standard. 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.

Being GCP Qualified

The investigator must be aware of, and comply with, GCP as it applies to their particular study and should be acquainted with all regulatory and ethics requirements, both nationally and locally.

All individuals involved in implementing any aspect of a clinical research study must be suitably qualified to be able to perform their tasks in compliance with GCP requirements. According to GCP, being 'qualified' means that each individual involved in implementing a part of the research study must be capable of doing their job through their:

- education
- training
- experience

It is important to note that whilst there are plenty of GCP training courses offered by different organisations, there is no actual GCP 'qualification'. This course will explain what the GCP responsibilities of an investigator are. It is being aware of these responsibilities that typically defines someone as being 'trained' in GCP. Study investigators and staff should be already appropriately trained in their field and then receive protocol-specific training on study related activities.

Investigators' GCP Responsibilities

GCP guidelines advise that the following aspects of a study are the investigator's responsibility:

1. Gaining informed consent from study participants
2. Randomisation 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

Gaining informed consent from study participants

The investigator must always comply with the ethical and regulatory international and local requirements for the process of **informed consent**.

Informed Consent - *A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.* (1.28, ICH GCP 2016)

A key condition is that prior to the study start the investigator must obtain written approval from the IEC/IRB.

During the consent process, the participant (or their legal acceptable representative) must be fully informed of all pertinent aspects of the study, including the approval by the IEC/IRB. All oral and written communication and information that they will be provided with must be in a non-technical and understandable language. Never should any oral or written study information waive a participant's rights or release those involved in running the research from liability for negligence.

If the individual cannot read, an impartial witness must be present. The 2002 Council for International Organisations of Medical Sciences (CIOMS) guidelines emphasize that if the consent taker does not speak or read the language of the participant they are not allowed to consent that person without a witness who does understand the participant's language.

The witness signs the **Informed Consent Form (ICF)** to confirm they observed that the participant had the information sheet explained to them, that they understood the information, that they had their questions answered and that they freely consented. The participant provides their mark/thumbprint and the consent taker writes their name.

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; a copy of a blank form is not acceptable to document the consent. The whole informed consent process including all documentation regarding communication of new information should be documented in the medical records/source file.

Gaining informed consent from study participants

The 2016 ICH GCP guideline specifies what should be included in the information that a potential participant is provided with. This includes:

- information on all applicable parts of the study such as its purpose, duration, how many will be recruited, required procedures (including randomisation, if applicable), the fact that it is research - not individualised medical treatment, and key contacts;
- reassurance that the individual can always ask the research team for additional

information at any time and that, if they change their mind about participation, they can leave the study without obligation to explain why;
- an explanation of the benefits and risks involved in taking part, costs involved and any compensations that may be provided;
- details of what is expected of them, their length of involvement, what action will be taken if they suffer a study related injury and whether there are any alternative treatments/options open to them;
- information on who has the authority to view their personal details and how this information will be handled;
- an explanation that if a better treatment is developed or if it is determined the study is unsafe, the study could be stopped and their participation would be terminated.

For the full ICH-GCP requirements (section 4.8.10) please click here

The consent taker must allow the individual ample time and opportunity to inquire about details of the study and to decide whether or not to participate. All questions about the study should be answered to the person's satisfaction. A potential participant should never be coerced or unduly influenced to consent to participating.

The investigator must obtain the sponsor's approval (if one exists) of any suggested revisions, prior to submission for approval to the IEC/IRB. If important new information becomes available which may be relevant to the participants, any written material that they may receive must be revised to reflect this information. Approval from the IEC/IRB is needed for these amendments. Participants must be informed, in writing, in a timely manner about the new information and this should be documented.

Gaining informed consent from study participants

Vulnerable Subjects - *Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent (1.61, ICH GCP 2016).*

When studies include individuals unable to consent for themselves (e.g. minors, those with mental incapacities) the person should be informed in a manner in which they can understand and if capable, should assent and sign/mark an assent form. The informed consent form will then be signed and dated by their legal representative.

In emergency situations, when prior consent of the participant is not possible, the consent of their legally acceptable representative should be sought. When prior consent of the participant is not possible and the representative is not available, recruitment procedures should be described in the protocol or other IRB/IEC approved documents and will usually involve the use of an impartial witness. The subject or subject's legal representative should be informed as soon as possible and provide consent to continue and other consent as appropriate. This normally applies to studies that might enroll trauma victims.

Further consideration should be taken into account when taking informed consent from a vulnerable person or population. According to **CIOMS** (*Guideline 13, CIOMS International Ethical*

Guidelines for Biomedical Research Involving Human Subjects, 2002.), in the context of research ethics, vulnerable persons are those who are relatively or absolutely incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests. The full ICH-GCP definition of a vulnerable subject is available by clicking here: (*1.61, ICH GCP 2016*)

Special justification is required to invite vulnerable individuals to participate in research. If selected, their rights and welfare must be strictly protected and participation is only justified if the research is responsive to their or their community's needs and priorities.

Randomisation procedures and unblinding

The investigator should follow randomisation and blinding procedures as stated in the study protocol.

Allocation of the intervention by random is introduced into controlled research studies with the aim to reduce the chance of selection bias so that the participants in one group are not in some way different from those in another group. Various methods for randomisation are available and usually, the statistician will decide on the appropriate method for the research question and study design. The investigator must strictly follow the randomisation scheme to ensure the unbiased allocation of participants into comparable groups.

Blinding (also called masking) is introduced into controlled research studies to avoid conscious or subconscious observation bias on the parties involved, invalidating the results. The blinding can be single-blinded so that only the participants do not know what they receive, or double-blinded so that neither the participants nor the investigators know the treatment in each group. Another way of blinding is to keep only observers blinded who evaluate certain criteria such as laboratory staff or clinical staff evaluating efficacy or safety endpoints.

There are occasions when it may be necessary to unblind the intervention a participant has received. 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'.*

The protocol should contain the procedure to be followed when unblinding is required and the investigator must be familiar with and follow these procedures. If unblinding is necessary, GCP guideline suggests that the investigator adheres to the following:

- 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. However it is important to remember a pragmatic approach should be taken, for example, it might be impractical to do this in emergency situations, in which case the sponsor should be notified as soon as possible after the unblinding takes place.
- there is full documentation of the unblinding which must include the justification for the action.

Medical care of participants

Principle 7 of the ICH GCP guideline recommends the involvement of a qualified physician in the conduct of a trial. The physician should be an investigator or sub-investigator and is responsible for the medical care given to participants and for all study-related medical decisions.

It is essential to remember that the rights, safety and well-being of the research participants always take precedence over the interests of science and society.

Therefore study participants should be monitored and any suspected adverse events (AE) should be attended to by the study physician.

Adverse Event - *Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.* (1.2, ICH GCP 2016)

GCP recommends that this doctor must ensure that there is adequate care provided in the case of an AE or clinically significant abnormal laboratory values. They should inform the participant if medical care is needed for an illness that occurs between or during study interventions. It is also advisable that they inform the individual's physician (if one exists) of their participation in the study, 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

As Hackshaw (2009) explains '*all proposed trials should be reviewed and approved by an IEC. It examines the trial protocol, and any documentation intended for the trial subject, such as the patient information sheet, consent form and questionnaires'.*

The requirements for the composition and functioning of an **Independent Ethics Committee (IEC)** and **Institutional Research Board (IRB)** are laid down in the ICH and WHO GCP guidelines.

IEC - *An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.* (1.27, ICH GCP 2016)

IRB - *An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.* (1.31, ICH GCP 2016)

IEC/IRB approval must be sought for all procedures which will involve participants. This includes 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. This approval encompasses any planned compensations for time, inconvenience, etc. and any other material or written

information to be provided to participants. Further documents submitted for review include the study protocol, the Investigator's Brochure.

The study cannot begin until IEC/IRB approval has been obtained. Once approval is granted, evidence of it must be kept clearly indicating which documents were submitted for approval. Care should be taken to ensure that the approval clearly mentions and covers all required items.

During the trial, the investigator must ensure that all updates of approved documents are submitted to the IEC/IRB for review. Some IEC/IRB requires an annual renewal of the approval and a summary report after the end of the trial. The investigator must submit an annual progress report on the study to the IEC/IRB.

Investigational product(s) management

An Investigational Product is a pharmaceutical form of an active ingredient or placebo being used in a clinical study including variations of an already approved product. The ICH GCP guideline states that the investigator is responsible for the accountability of the investigational product at the site that is being used in the study. The investigator may, however, assign the duties to a qualified pharmacist.

The investigator is responsible for:

- maintaining the investigational products 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 investigational products are only used as specified by the approved protocol;
- keeping a list of randomisation code numbers assigned to participants;
- explaining the correct use of investigational products to the participants; and
- reconciling all investigational products received.

Study protocol compliance

Generally, the protocol will have been signed by both the investigator and the sponsor to confirm their agreement. It is essential that the investigator does not deviate from the processes and procedures laid out in the protocol or make any changes to the protocol before IEC/IRB and sponsor approval.

Chin and Lee (2008) state that '*ideally a protocol should be so well written, and should anticipate all contingencies so well that there is no need for a protocol amendment or any waivers in the course of the study'. In such a case the interpretability of the study is maximal. However, this is rarely the case'.*

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. With a few exceptions e.g. where urgent safety measures may be required, approval must be obtained before the amendment is implemented.

It is important to understand the difference between a substantial and non-substantial protocol amendment. Substantial amendments are those that could affect the:

- safety or physical or mental integrity of the participants
- scientific value of the study
- conduct or management of the study

- quality or safety of any medicinal product used for clinical trials

Non-substantial amendments are those that do not impact on these factors and are usually things like administrative changes e.g. the member joins or leaves the Steering Committee. The IEC/IRB needs only to be notified in writing of this type of amendment.

It is, according to the 2016 ICH GCP guideline, acceptable to deviate from the protocol when the purpose of the deviation is to eliminate an immediate hazard to the participants. If such a deviation is necessary, the sponsor, IEC/IRB and, if required, the regulatory authority should be informed as soon as possible after the event.

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

Investigator qualifications and agreements

As previously outlined, 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 requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IEC/IRB, and/or the regulatory authorities'* (ICH GCP 2016).

Additionally, the investigator should be thoroughly familiar with the protocol and investigational product as described in the Investigator's Brochure, the product information and any other literature on the product.

In the case of marketed products, the investigator should be familiar with the product information such as the Summary of Product Characteristics and what it is normally used for, any contra-indications, etc.

Investigator qualifications and agreements

The investigator can delegate duties to adequately qualified study staff; for example, a qualified pharmacist can be in charge of the day-to-day storage and delivery of the IMP but the overall responsibility of that duty is the investigators. Any delegated responsibility must be clearly recorded in the study **delegation log**.

The investigator must allow the study to be **Monitored, Audited and Inspected** to enable oversight by the sponsor and regulatory authorities.

Monitoring *- The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).* (1.38, ICH GCP 2016)

Audit *- A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).* (1.6, ICH GCP 2016)

Inspection *- The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed*

appropriate by the regulatory authority(ies). (1.29, ICH GCP 2016)

Records and reports management

It is the investigator's responsibility to ensure that all records are accurately maintained and all reports are completed and submitted on time.

Source Data - *All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).* (1.51, ICH GCP 2016)

Source Documents - *Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).* (1.52, ICH GCP 2016)

The investigator must retain sufficient source data; this should be accurate and outline all relevant observations on each of the trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable and explained, if needed, and the clarity of original data should be maintained.

All the information required for each trial subject as specified in the protocol is recorded in a **Case Report Form (CRF)**; this is usually a printed, optical or electronic document.

Records and reports management

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, initials, and explanation without obscuring the original entry; and
- available for access when required by the appropriate bodies (e.g. auditor, sponsor, IEC/IRB, etc)

Additionally, the investigator must maintain all essential documents and retain them as long as stipulated by the sponsor after the completion of the trial. The study's financial aspects should be documented as agreed upon by the sponsor and the investigator.

Essential documents - *Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced* (1.23, ICH-GCP 2016)

ICH-GCP section 8.1 provides guidance on essential documents for the conduct of clinical trials, to read the full guidance click here.

The clinical monitor, auditor, IRB/IEC and regulatory authority should be granted direct access to all trial-related documents. The investigator should submit summary reports to the IRB/IEC on the progress of the study at least annually. Written reports of significant amendments to the study or increased risk to participants should be promptly reported to the sponsor, IRB/IEC and relevant bodies. Upon completion of the trial, the investigator should provide the sponsor with all the required reports before providing a final summary report of the study and its outcomes to the IRB/IEC, regulatory bodies and the community where the participants were recruited from.

Safety reporting

Adverse Event - *Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (1.2, ICH GCP 2016).*

Adverse Events (AE) and abnormal laboratory results should be documented and reported to the sponsor and all appropriate groups as required by applicable regulations and the protocol. This includes **Adverse Drug Reactions (ADRs)**, **Unexpected ADRs** and **Serious Adverse Events (SAEs)**. An **ADR** is when there is a **reasonable possibility** that an AE has a **causal relationship** to the medicinal product being tested (1.1, ICH-GCP 2016). An **Unexpected ADR** is when an adverse reaction is **inconsistent** with the characteristics of the medicinal product or its applicable product information (1.60, ICH-GCP 2016).

Serious Adverse Events (SAEs) or **Serious Adverse Drug Reactions (Serious ADRs)** - *Any untoward medical occurrence that at any dose:*

- *results in death,*
- *is life-threatening,*
- *requires inpatient hospitalization or prolongation of existing hospitalization,*
- *results in persistent or significant disability/incapacity, or*
- *is a congenital anomaly/birth defect* (1.50, ICH-GCP 2016)

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

Individual safety reports should not identify the individual but bear the subject code numbers for identification.

The investigator must ensure that relevant site staff are aware of safety recording and reporting requirements.

The WHO's 2005 Draft Guidelines for 'Adverse Event Reporting and Learning Systems' advises that non-serious adverse events are recorded in the study's case report forms alongside with the other data.

SAEs are usually collected on a specially designed form. SAEs should normally be reported to

the sponsor within 24 hours. If a Data Monitoring Committee (DMC)/Data Safety Monitoring Board (DSMB) is established, the investigator should inform them, typically within a week (Hackshaw, 2009). However, this will depend on the study and will be indicated by the committee/board accordingly.

SAEs that are life-threatening or resulted in death, and which are unexpected and possibly related to the study intervention needs to be reported to the IEC/IRB usually within seven calendar days, other SAEs within 15 calendar days.The protocol defines for the purpose of the study which SAEs needs not to be reported immediately and what constitutes unexpected ADRs.

Ensuring adequate resources

To conduct a sound and valid study the investigator must be able to demonstrate that there is:

- reasonable potential for recruiting the required number of individuals to the study. As Jekel (2007) points out, recruitment of an adequate number of participants is crucial if the study is to answer the question that it has set
- the appropriate amount of time scheduled to carry out and complete the study effectively
- an adequate supply of suitably qualified staff and appropriate facilities for the duration of the study to see it to a successful and safe conclusion. Toto and McPhaul (2011) state that *'the investigator must invest in building a research team that consists of individuals (e.g., study coordinator, co-investigators, biostatistician, research and laboratory technicians, and administrative support) that have the level of expertise required to navigate through the various study challenges*'
- appropriate training on the study protocol, about any investigational product and about their duties to allow the staff to carry out their tasks safely and effectively
- appropriate supervision of any individual or group to whom the investigator assigns trial-related duties at the trial site
- assurance that any person or party retained to perform trial-related duties is suitably qualified to perform those duties. Systems should be implemented to ensure the integrity of trial-related duties performed and any data generated.

Management of premature termination or suspension of a trial

Mihajlovic-Madzarevic (2010) stresses that '*termination or suspension of a study has many implications, especially to a patient's safety'*.

Once the decision is taken to terminate or suspend a study, 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.

It is important to remember that 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. For example, 'on-site monitoring' is not compulsory, section 5.18.3 of the ICH GCP guideline state that *'central monitoring in conjunction with procedures such as investigators' training and meetings and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP.'*

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 in all of their aspects.
- 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.
- 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 a few appropriate reasons for unblinding and one is where the participant's medical management depends on knowing what intervention they received.
- A qualified doctor must be present in any interventional studies, 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.
- A protocol amendment which might have an impact upon the participants' safety or the conduct of the study requires IEC/IRB approval. Administrative changes do not require approval, but the IEC/IRB should be informed of it.
- All SAEs must be reported to the sponsor as defined in the protocol 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, taking into account the needs and requirements of the community within which the research is being carried out.

References and Resources

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6. Mihajlovic-Madzarevic V. Clinical Trials Audit Preparation: A Guide for Good Clinical Practice (GCP) Inspections 2010. Wiley, New Jersey.
7. Toto RD and McPhaul MJ. Clinical Research: From Proposal to Implementation 2011, Lippincott Williams & Wilkins, Philadelphia.
8. WHO 2005 Draft Guidelines for Adverse Event Reporting and Learning Systems
9. WHO 2002 Handbook for GCP: Guide to Implementation

Resources

1. Declaration of Helsinki 2013
2. 2016 ICH GCP Guidelines
3. List GCP Resources

Quiz

Please ensure you have answered all questions before clicking the 'submit' button

Summary

1. Which of the following is NOT a principle of GCP:
   (Please select all that apply)

   - ☐ Any foreseeable risks and inconveniences must be weighed up against any benefits
   - ☐ Information must be recorded, handled and stored in a manner that allows accurate reporting, interpretation and verification and which ensures the confidentiality of participants' records.
   - ☐ Publication of results is not required if the study results were not as expected.
   - ☐ The study protocol must provide inclusion and exclusion criteria, monitoring details and a publication policy.
   - ☐ Available non-clinical and clinical information on the investigational medicinal product being used must be adequate to support the study.
   - ☐ The study must be conducted according to the Nuremberg Code of 1947

2. ICH-GCP guidelines are a legal requirement and studies found not following it will be terminated.

   - ○ True
   - ○ False

3. It is important for investigators in low-and middle-income countries to adopt good clinical practice guidelines because their studies will consequently be recognised as being of the same standard as other GCP compliant studies across the globe.

   - ○ True
   - ○ False

4. Which of the following is NOT true about the informed consent process:
(Please select all that apply)

   - ☐ IEC/IRB approval must be gained for all participant related materials and documents.
   - ☐ Details of any alternative treatments/options must be given to participants after they have given consent
   - ☐ Consent must be given freely without coercion or undue influence.
   - ☐ A participant can withdraw from the study at any time without providing a reason.
   - ☐ If the participant cannot read or write the consent form can be marked/signed at any time during participation as long as the participant has agreed to join the study.

5. As long as you document the entire process, you can unblind a participant at the request of a site investigator who wants to enter the participant into another study.

   - ○ True
   - ○ False

6. Participants in a study with an investigational medicinal product should only contact the study physician if feeling unwell if their own physician is unavailable.

   - ○ True
   - ○ False

7. Approval from the IEC/IRB is not required for which of the following:

   - ○ Study management plan
   - ○ Study protocol
   - ○ Compensation plans

8. The IMP temperature was not recorded for 3 days, according to protocol this should have been monitored daily; who will you hold responsible?

   - ○ Laboratory technician
   - ○ Sponsor
   - ○ Investigator
   - ○ Nurse

9. The protocol is replaced by which of the following:

   - ○ GCP guidelines
   - ○ Standard operating procedures
   - ○ Statistical analysis plan
   - ○ Study management plan
   - ○ None of the above
   - ○ All of the above

10. AEs and SAEs, as defined by the protocol, are:

    - ○ Only recorded in the case of severe injury or death
    - ○ Carefully and systematically recorded
    - ○ A routine part of all studies and should be ignored

11. Suspension or termination of the study by the investigator should be reported to which of the following groups:

    - ○ Sponsor
    - ○ DSMB

- IEC/IRB
- Collaborators
- All of the above

12. The investigator involved in running a study should be qualified by:
(Please select all that apply)

- Training
- Education
- The World Health Organisation
- Experience
- An academic institution

13. Which of the following are GCP responsibilities of the investigator:
(Please select all that apply)
- Ensuring all study staff are sufficiently qualified
- Communication with participants family members
- Compliance with study protocol
- Compensation of study participants
- Reporting Serious Adverse Events

14. What does IEC Stand for?

- Investigational Ethics Committee
- International Ethics Committee
- Institutional Ethics Committee
- Independent Ethics Committee

15. Which of the following are key principles of GCP
(Please select all that apply)

- The rights, safety and well-being of participants always take precedence over the interests of science and society.
- Individuals involved in running studies should be qualified by training to perform their tasks.
- The research protocol must receive approval from the IEC/ IRB and needs to be followed
- Investigational products must be used in accordance with the standard operating procedure.

16. When conducting a clinical trial in accordance with GCP, what is the most important consideration above all else?

- Protection of participants
- Protocol adherence
- Accuracy of data
- Quality checks

17. In accordance with GCP the investigator must ensure which of the following:
(Please select all that apply)

- Recruitment of an adequate number of participants
- An appropriate amount of time is scheduled to carry out and complete the study effectively
- Appropriate facilities for the duration of the study
- All staff receive appropriate training on the study protocol, the investigational product and their duties

18. Clinical studies should be run applying GCP principles because:

- Applying the principles means that the investigator does not have to follow the study protocol
- It means that the study will be run to a standard which assures the credibility and accuracy of the data and reported results
- Demonstrating that GCP principles are being followed means the study does not need to be audited

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