Good Clinical Practice (GCP) is a global quality process that is applied to the conduct of all clinical trials on new medicinal products. Study investigators – including physicians and other healthcare professionals at all levels of experience – have GCP responsibilities, but most researchers do not fully understand what this involves. Investigators who do not work in accordance with GCP will be unable to perform trials on new products in the future.

This easy-to-read guide covers the most important GCP responsibilities of the study investigator and his/her team. By following the 12 golden rules described within these pages, the investigator will have fulfilled most of the important GCP requirements as specified in the latest guideline ICH E6(R2).

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12 Golden GCP Rules for Investigators

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Preface

The globally accepted Good Clinical Practice (GCP) responsibilities of the investigator described in this book are applicable to all therapeutic trials in humans on new medicines. They may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

The complex requirements are simplified here into 12 'rules' – not in any order of priority – where GCP compliance is most important. An investigator who is able to implement, in each trial, all of the recommendations made in this book will gain the respect of both the regulatory authority GCP inspectors and study sponsors. Investigators who do not comply with GCP may not be invited to undertake trials on new medicines.

The requirements presented here are based on the GCP guidelines of the International Council for Harmonisation (ICH). These standards have been adopted by the regulatory authorities and pharmaceutical industries in Europe, the USA, Japan and other countries worldwide. GCP implementation is often tedious and some actions may be perceived as pointless and bureaucratic. However, subject protection and the collection of reliable data are important in all trials. Strict adherence to GCP ensures that the quality processes are in place to meet these goals every time.

Investigators should be aware of the key legislation that lays down requirements for trials conducted in their own country. For example in Europe, Regulations and Directives relevant to the conduct of clinical trials are implemented into national laws. It is therefore essential that investigators take account of their national laws when conducting clinical trials. US Federal Regulations and Japanese GCP requirements also place additional demands on investigators in other ICH regions. The ICH GCP principles outlined in this book should be followed, as a minimum requirement, to enhance the credibility of the study, facilitate data reliability and maximise human subject protection.

Who Can Be an Investigator?

Qualifications and experience

The investigator must be suitably qualified and have the appropriate experience. An up-to-date CV will be requested by the sponsor: this should describe the investigator's current appointment as well as providing any other relevant evidence of suitability to undertake the trial. Knowledge of GCP and the appropriate regulatory requirements will also be required, although new investigators can learn this.

National clinical trial laws or policies may provide more detail on who can be an investigator, particularly for those who are not medically qualified, or have little or no clinical trial experience.

Time and availability

The investigator must have time to do the study. Time is needed

- for regular meetings with the sponsor's monitor
- to identify and screen suitable subjects
- to spend with trial subjects, as appointment times will be much longer than usual
- to brief research team members and review the progress of the trial
- to supervise other individuals and parties delegated trial-related duties and functions
- to complete paperwork: trials generate numerous documents
- to spend with auditors and inspectors.

An investigator should also

- have the appropriate facilities and equipment

Relevant Extracts from the ICH GCP Guidelines

4.1.1
The investigator(s) 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 IRB/IEC, and/or the regulatory authority(ies).

4.1.3
The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.2.2
The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

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.

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.

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.

5.6.3
The sponsor should obtain the investigator's/institution's agreement:

(a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);

When an investigator is also a sponsor, a system needs to be in place to manage quality throughout all stages of the trial process. The quality management system should use a risk-based approach as described in section 5.0 of the ICH GCP E6(R2) guideline.

Know and Follow the Study Protocol

The protocol is a unique document that describes in detail how the study should be performed.

Read it

All research team members should read and be familiar with the protocol.

Agree it

The investigator should discuss any areas of concern with the sponsor before the study starts. Investigators need to agree with all aspects of the protocol.

Sign it

By signing the protocol you are making a formal agreement to adhere to it at all times.

Follow it

Non-adherence to the protocol, no matter how minor, may have a major effect on study outcome. All deviations from the protocol should be recorded. GCP inspectors consider protocol violations to be a significant finding, and this reflects on the quality of the investigator and research team.

If non-compliance with the protocol, GCP or regulatory requirements is identified, the sponsor should be informed. It is also good practice to identify the root cause and to implement corrective and preventative action plans. Always document any actions taken.

Make it available

The protocol should be available at all times to all members of the research team. Each researcher should be given a copy of the protocol.

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File it

A copy of the final protocol should be placed in the study file. Old versions should be clearly marked as being out of date and should be filed away from the current version to avoid confusion.

REMEMBER:

during the study, the protocol can only be amended by following a

and recorded.

Relevant Extracts from the ICH GCP Guidelines

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/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

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/favourable 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)).

4.5.3
The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4
The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

a) to the IRB/IEC for review and approval/favourable opinion,

b) to the sponsor for agreement and, if required,

sponsor.

RULE 4

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Ensure Study Equipment is Adequate

The study monitor will want to make sure that any equipment that needs to be used in the study (eg. sphygmomanometers, spirometers, fridges) is adequate. The investigator can use the acronym 'SMAC' to check that the study equipment meets requirements.

Suitable

Read the protocol to check that the correct equipment is being used.

Maintained

All equipment should be regularly maintained. Records should be available for inspection by the monitor.

Available

Make sure that equipment is available for use in the trial from start to finish – there may already be too great a demand for it!

Calibrated and checked

Some instruments require regular calibration to ensure that they perform correctly (eg. spirometers, patient-controlled analgesia equipment). Calibration records should be available for inspection.

REMEMBER:

Relevant Extracts from the ICH GCP Guidelines

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.

5.18.4 Monitor's Responsibilities
The monitor(s) 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:

b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

Meticulously Document Product Accountability

- Keep extremely detailed records of trial product
  - received from the sponsor
  - present at the study site
  - dispensed to each subject
  - returned from each subject
  - returned to the sponsor.
- Follow the instructions relating to the storage of study drugs.

- Encourage subjects to return both empty and unused treatment packs – these can be used to measure compliance.
- Do not destroy or dispose of returned medication packs – the study sponsor will advise you what to do with them.

Relevant Extracts from the ICH GCP Guidelines

4.6.1
Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2
Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3
The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4
The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5
The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6
The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

If you are also the sponsor of the study, always follow national laws relating to clinical trials. In Europe, a manufacturing or import authorisation is required for all investigational medicinal products (IMPs). The manufacture or preparation of IMPs according to Good Manufacturing Practice (GMP) is usually required.

Useful website:
http://ec.europa.eu/health/documents/eudralex/vol-10_en

Remember to consult national legislation.

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Ensure the Quality of Laboratory Evaluations

- Follow the method of sample collection described in the protocol – many trials require a vacutainer system to be used. Make sure that appropriate staff are familiar with the requirements.
- Focus on sample quality – avoid delays in analysis and handle samples as per the protocol. Transit by post or courier to a central laboratory is often necessary. In such cases, label samples carefully and ensure that the shipment is made as required.

- An appropriate person must review all laboratory results and abnormal results should be commented upon. Investigators should follow up abnormalities until resolution. Remember that some laboratory abnormalities might need to be recorded as adverse events – check the protocol for details.
- Remember that the investigator is responsible for supervising any party – for example a laboratory – who is delegated trial-related duties and functions. A basic requirement would be to check protocol compliance.
- Certain documentation will be required from the laboratory, including
  - reference ranges
  - details of analytical methods
  - quality assurance information.

Make sure that the laboratory management is fully briefed

Relevant Extracts from the ICH GCP Guidelines

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 incurrent illness(es) of which the investigator becomes aware.

8.2 [abbreviated] **Before the Clinical Phase of the Trial Commences**
During this planning stage the following documents should be generated and should be on file before the trial formally starts.

8.2.11
Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol

8.2.12
Medical/laboratory/technical procedures/tests – certification or, accreditation or, established quality control and/or external quality assessment or, other validation (where required)

8.3 [abbreviated] **During the Clinical Conduct of the Trial**

8.3.6
Updates to normal value(s)/range(s) for medical/laboratory/technical procedure(s)/test(s) included in the protocol

8.3.7
Updates of medical/laboratory/technical procedures/tests – certification or, accreditation or, established quality control and/or external quality assessment or, other validation (where required)

Keep Everyone Fully Informed

The investigator should

- read and refer to the investigator brochure that provides information about the test product.
- ensure that all personnel at the study site are fully informed about the trial (including any amendments as the trial progresses), and ensure that they have access to relevant trial documents.

- make clear what has been delegated and to whom.
- make sure that the trial subject is fully informed about the trial and what is expected of him/her.
- inform the subject's primary care physician that the subject is to participate in a trial (as appropriate).
- inform the study monitor if there are any problems.
- report serious adverse events immediately to the trial sponsor, and keep the sponsor informed of further developments and outcomes.
- inform the Ethics Committee of the trial status at least annually.
- inform the Ethics Committee when the trial is finished or if it is terminated earlier than planned.
- inform all members of the research team and other interested parties of the outcome of the study.
- follow up any outstanding matters at the end of the trial and keep the sponsor informed.

Relevant Extracts from the ICH GCP Guidelines

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.

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.

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.

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 given approval/favourable opinion by the IRB/IEC.

4.13 Final Report(s) by Investigator
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.

Also applicable: 4.1.3, 4.4, 4.10, 4.12.