

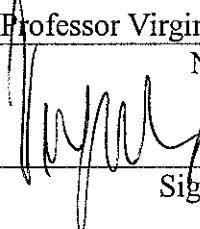


香港大學及醫管局港島西醫院聯網研究倫理委員會  
University of Hong Kong / Hospital Authority Hong Kong West Cluster

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HKU/HA HKW IRB

General Research Ethics Information and Definitions for  
Investigators and IRB Members

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 2003 March 3  
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Page 1 of 10

VERSION No: HKU/HA HKW IRB-2003 – (September)

## Contents

1. Local and International Ethical Regulations of Human Clinical Research
2. Definition of Research and Clinical Trials
  - 2.1 Definition of Research
  - 2.2 Definition of Clinical Trials
    - 2.2.1 Clinical Trial
    - 2.2.2 Investigational New Drug or Device
    - 2.2.3 Sponsor
    - 2.2.4 Phase I Drug Trial
    - 2.2.5 Phase II Drug Trial
    - 2.2.6 Phase III Drug Trial
    - 2.2.7 Phase IV Drug Trial
3. Responsibilities, Jurisdiction, Agreements and Submission Requirements of HKU/HA HKW IRB
  - 3.1 Responsibilities
  - 3.2 Jurisdiction
  - 3.3 Cooperative Agreements - Affiliated Medical Institutions
  - 3.4 HKU/HA HKW IRB Submission Requirements
4. Essentials of the ICH GCP Guidelines
  - 4.1 Institutional Review Board - Essentials of the ICH GCP Guidelines
    - 4.1.1 IRB Responsibilities
    - 4.1.2 IRB Composition, Functions and Operations
    - 4.1.3 IRB Procedures
    - 4.1.4 IRB Records
  - 4.2 Investigator – Essentials of the ICH GCP Guidelines
    - 4.2.1 Investigator's Qualifications and Agreements
    - 4.2.2 Adequate Resources
    - 4.2.3 Medical Care of Trial Subjects
    - 4.2.4 Communication with IRB
    - 4.2.5 Compliance with Protocol
    - 4.2.6 Informed Consent of Trial Subjects
5. GCP Glossary

## **1. Local and International Ethical Regulations of Human Clinical Research**

At present there is no local legal requirement in Hong Kong SAR for an institutional review board or ethics committee approval for the conduct of clinical research in humans. However, the Hong Kong SAR Government has advised any institution involved in research in humans to establish their own independent review process for such research studies, and to operate according to the Declaration of Helsinki (1996 version).

In 1996 the International Conference on Harmonisation Good Clinical Practice launched the ICH GCP Guidelines for the conduct of clinical trials. Good Clinical Practice (GCP) is 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.

The objective of the ICH GCP Guidelines is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The Guidelines were 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). Other countries have recently adopted the ICH GCP Guidelines or adopted a slightly modified GCP version such as in PR China, Singapore and Taiwan. Hong Kong has as yet not made any recommendations, but plan to introduce the ICH GCP or a set of similar Guidelines in the near future, first as a recommendation and by time may be as a legal requirement.

The ICH GCP Guidelines should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities in countries that have accepted the ICH GCP Guidelines. The principles established in these Guidelines may also be applied to other clinical investigations that may have an impact on the safety and well being of human subjects.

In order to make it possible for investigators to take part in the global development of new pharmaceutical compounds the HKU/HA HKW IRB complies with the ICH GCP Guidelines in the review, follow-up, reporting and auditing of clinical trials related to Investigational New Drug (IND) products (see section Clinical Trials). The ICH GCP Guidelines states in section 5.11.1 that the sponsor should obtain from the investigator/institution a statement obtained from IRB that it is organised and operates according to GCP and the applicable laws and regulations. GCP compliance is also more frequently needed for publication of the research results in international scientific journals.

## **2. Definition of Research and Clinical Trials**

### **2.1 Definition of Research**

There is sometimes a question of whether a planned activity is "research" and therefore requires IRB review and approval. Research is defined as "a systematic investigation, including research development, testing and evaluation, designed to develop or to contribute

to generalisable knowledge." Specific criteria that can be used to determine whether a planned activity is research include:

- ❑ the testing of a hypothesis or question for which an answer requires more clinical information.
- ❑ the prospective or retrospective collection of data from human subjects/patients with the intent to report findings in a scientific publication.
- ❑ the use of a standard procedure or an approved drug if its use is influenced by any consideration other than the direct welfare of the human research subject (e.g. a selection between different, although widely-accepted, procedures or therapies according to a predetermined plan such as randomisation; the administration of a standard procedure or an approved drug to a normal "control" subject).
- ❑ the use of an experimental (investigational) drug, biologic or device (e.g. a drug that is the subject of a drug regulatory authority approved investigational new drug (IND) exemption or a device that is not approved).

Innovative or newly introduced procedures or therapies do not require IRB review and approval except when they involve "research" as defined by the above criteria. The introduction of innovative procedures or therapies into clinical practice (i.e. independent of a research activity approved by the IRB) should, however, be reviewed by the Cluster Chief Executive of HKW prior to their implementation.

## **2.2 Definition of Clinical Trials**

### **2.2.1 Clinical Trial**

A clinical trial is a controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of investigational drugs or devices or of behavioural interventions. Clinical trials are conducted by clinical investigators who have entered into an agreement with a sponsor to conduct the study. For clinical drug and device trials, clinical investigators agree to conditions regarding the conduct of the study outlined by the ICH GCP (International Conference Harmonisation Good Clinical Practice) Guidelines. Clinical investigators agree to these conditions by signing a form that certifies that the investigator has obtained IRB review and approval prior to conducting the study.

### **2.2.2 Investigational New Drug or Device**

An investigational new drug or device is a drug or device permitted by the Drug Regulatory Authority (Department of Health in Hong Kong) to be tested in humans, but not yet determined to be safe and effective for a particular use in the general population.

### **2.2.3 Sponsor**

The sponsor is the person or entity that initiates the clinical trial. The sponsor is typically the manufacturer or research institute that developed the drug or device. In this case, the sponsor does not actually conduct the clinical trial but rather distributes the investigational new drug or device to a clinical investigator who directs the conduct of the trial. A clinical investigator may, however, serve as both the sponsor and investigator (investigator-sponsor) of a clinical trial. The sponsor assumes responsibility for the studies involving the investigational drug or device, including responsibility for compliance with applicable laws and regulations. The sponsor is responsible for obtaining approval to conduct a trial and for reporting the results of the trial to the appropriate regulatory authority.

#### **2.2.4 Phase I Drug Trial**

Phase I trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; however in certain situations where the drug is intended for use in patients with a specific disease, the Phase I trial may involve such patients. Phase I trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing dosages (to establish a safe dose range), and, if possible, to gain preliminary evidence of effectiveness. Phase I trials are performed at 1-2 sites, closely monitored, and involve a very small number of subjects (e.g. < 100).

#### **2.2.5 Phase II Drug Trial**

Phase II trials include controlled clinical studies conducted to evaluate the investigational drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically performed at a very limited number of sites, well controlled and closely monitored, and involve a small number of patients (e.g. 100-500).

#### **2.2.6 Phase III Drug Trial**

Phase III trials involve the administration of an investigational drug to a large number of patients in different clinical settings to determine its safety, effectiveness, and appropriate dosage. Phase III trials are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information to establish the overall benefit-risk relationship of the drug. Phase III trials usually involve multiple sites and patients (e.g. > 1000). When Phase III trials are completed, the sponsor of the drug submits an application to the appropriate regulatory authority for approval to market the drug for the specific use designated in its proposed labelling.

#### **2.2.7 Phase IV Drug Trial**

Concurrent with marketing approval, the regulatory authority may seek agreement from the sponsor to conduct certain post marketing studies (Phase IV trials) to delineate additional information about the drug's risks, benefits, and optimal use. These studies may include, but are not limited to, evaluating different dosages or schedules of administration, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

### **3. Essentials of the ICH GCP Guidelines**

#### **3.1 Institutional Review Board - Essentials of the ICH GCP Guidelines**

##### **3.1.1 IRB Responsibilities**

- An IRB should safeguard the rights, safety, and well being of all trial subjects.
- The IRB should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates.
- The IRB should consider the qualifications of the investigator for the proposed trial.
- The IRB should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

### **3.1.2 IRB Composition, Functions and Operations**

- The IRB should consist of a reasonable number of members.
- A list of IRB members and their qualifications should be maintained.
- The IRB should perform its functions according to written operating procedures,
- The IRB should maintain written records of its activities and minutes of its meetings.
- The IRB should comply with GCP and with the applicable regulatory requirement(s).
- An IRB should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

### **3.1.3 IRB Procedures**

The IRB should establish, document in writing, and follow its procedures, which should include:

- Determining its composition and the authority under which it is established.
- Scheduling, notifying its members of, and conducting its meetings.
- Conducting initial and continuing review of trials.
- Determining the frequency of continuing review, as appropriate.
- Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB approval.
- Specifying that the investigator should promptly report to the IRB: (a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects, (b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial, (c) All adverse drug reactions that are both serious and unexpected, (d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

### **3.1.4 IRB Records**

- The IRB should retain all relevant records for a period of at least 3 years after completion of the trial.
- The IRB may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

## **4. Investigator – Essentials of the ICH GCP Guidelines**

### **4.1 Investigator's Qualifications and Agreements**

- The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications.
- The investigator should be thoroughly familiar with the appropriate use of the investigational product(s),
- The investigator should be aware of, and comply with, GCP and the applicable regulatory requirements.
- The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

#### **4.1.1 Adequate Resources**

- The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
- The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- 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.
- 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.

#### **4.1.2 Medical Care of Trial Subjects**

- A qualified physician who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical decisions.

#### **4.1.3 Communication with IRB**

- Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC.
- During the trial the investigator/institution should provide to the IRB all documents subject to review.

#### **4.1.4 Compliance with Protocol**

- 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. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.
- 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 of an amendment.

#### **4.1.5 Informed Consent of Trial Subjects**

- Prior to the beginning of the trial, the investigator should have the written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.
- Any revised written informed consent form, and written information should receive the IRB's approval/favourable opinion in advance of use.

### **5. GCP Glossary**

#### **Clinical Trial/Study**

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study

absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

### **Device**

A device is an instrument, apparatus, implement, machine, contrivance, in vitro reagent or other similar or related article, including a component part, or accessory, which is:

- recognised in the official National Formulary, of the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependant upon being metabolised for the achievement of any of its primary intended purposes.

### **Good Clinical Practice (GCP)**

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.

### **Institutional Review Board (IRB)**

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. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in the ICH GCP Guidelines.

### **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.

### **Investigational New Drug (IND)**

A new drug, antibiotic or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The term "investigational drug" and "investigational new drug" are deemed to be synonymous.

### **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. See also Sub investigator.

### **Investigator's Brochure**

A compilation of the clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

### **NDA**

New Drug Application.

### **Protocol**

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guidelines the term protocol refers to protocol and protocol amendments.

### **Protocol Amendment**

A written description of a change(s) to or formal clarification of a protocol.

### **Regulatory Authorities**

Bodies having the power to regulate. In the ICH GCP Guidelines the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

### **Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)**

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

**Standard Operating Procedures (SOPs)**

Detailed, written instructions to achieve uniformity of the performance of a specific function.

**Co-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).

**Unexpected Adverse Drug Reaction**

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).