Compliance

Clinical Research

Management and Compliance at Study Sites

A Practical Handbook for Investigators, Clinical Research Personnel and Administrators of the Hong Kong Hospital Authority

Legal Affairs

Resources Management

Quality Assurance

醫院管理局
HOSPITAL AUTHORITY

Clinical Research

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Hospital Authority Research Ethics Committee
AND
Clinical Effectiveness & Technology Management Department

Quality & Safety Division
Hospital Authority Head Office

Clinical Research Management and Compliance at Study Sites

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AND
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Brief Contents

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Preface by Chief Executive, HA

Clinical research is a cornerstone of evidence-based medicine. It is vital for improving human health and medical services. Being the major healthcare provider in Hong Kong, the Hospital Authority ("HA") is responsible for promoting and facilitating the conduct of clinical studies across the HA.

The objective of this handbook is to provide a comprehensive guide on management and regulatory compliance in clinical research. Investigators and research personnel are advised to comply with the principles contained in the guideline so that the public can be assured that the rights, safety, and well-being of research subjects are being protected and respected.

With the joint effort of our professional staff and partners, numerous clinical studies have been successfully completed throughout the years. In the future, the HA will continue to support and uphold the standard of clinical research with the ultimate aims of advancing healthcare technologies and services and improving the health and quality of life of people in Hong Kong.

Shane Solomon
Chief Executive, HA
January 2010

Preface by Chairperson, HA REC

Clinical research is an important type of medical research representing the final step in the development of novel therapies, prophylaxes and diagnostics, and is of great value to medical institutions, medical practitioners, patients and the society as a whole.

Being the largest healthcare services provider in Hong Kong, the Hospital Authority ("HA") provides the large majority of clinical study sites in Hong Kong and, with the support of its investigators and clinical research personnel, plays an important role in safeguarding the rights, safety and well-being of human subjects and the integrity of clinical study data and results.

This handbook covers the practical aspects of management and compliance relating to clinical research conducted under the HA, such as six-dimensional compliance, legal affairs, resources management and quality assurance, and offers detailed guidance to investigators, clinical research personnel, hospital management, administrators and research ethics committee members. I trust the publication of this handbook will help raise the standard and maximize the benefits of clinical research in the HA.

Dr. P Y Leung
Chairperson, HA REC
January 2010

Part 1:
Introduction

1. Scope and Applicability

1.1 Definition of Clinical Studies

1.1.1 A clinical study is any scientific investigation in human beings intended to discover or verify the efficacy and/or safety of one or more medical interventions (whether for the purpose of diagnosis, prophylaxis or therapy), or to investigate the causes, development, progress and effects of a disease or a medical condition. The terms “clinical study,” “clinical trial” and “clinical research” are often used interchangeably.

1.1.2 In this handbook, a clinical study may refer to any scientific investigation that is conducted on:

(a) Human beings (e.g. randomized controlled trial on a medical product or clinical procedure/method);
(b) Identifiable human materials (e.g. genetic analysis of archived human specimens); or
(c) Identifiable human data (e.g. questionnaire survey, medical chart review and case series).

1.1.3 Medical products may include (but not limited to):

(a) Drugs (e.g. chemical drugs, biologics and vaccines);
(b) Devices (e.g. implants, diagnostic kits, imaging machines and radiotherapy devices);
(c) Chinese medicines / herbal medicines;
(d) Health supplements (e.g. vitamins and nutritional supplements);
(e) Alternative therapies (e.g. acupuncture);

(f) Cell therapies (e.g. stem cells); and
(g) Gene therapies (e.g. viral vectors).

1.1.4 Clinical procedures and methods may include (but not limited to):

(a) Clinical examinations;
(b) Surgical procedures;
(c) Nursing procedures;
(d) Psycotherapies;
(e) Behavioral therapies; and
(f) Imaging methods.

1.2 Value of Clinical Studies

1.2.1 Clinical studies represent the final and the most important step in the development of novel therapies, prophylaxes and diagnostics, bringing new medical products, procedures and methods from laboratories to the bedside.

1.2.2 Clinical studies could bring along the following important benefits to medical institutions and their staff, as well as to patients and the society:

(a) Benefits to patients and the society: Clinical studies may benefit patients by providing access to new or modified medical products, procedures or methods, and may also benefit the entire society through successful development or modification of medical products, procedures or methods.
(b) Benefits to medical practitioners: Clinical studies offer medical practitioners the opportunities to learn and to practice clinical research, advancing their knowledge in the latest medical technologies and creating the culture of research and development of new technologies and services.

(c) Benefits to medical institutions and the healthcare system: Clinical studies improve understanding of the causes, development, progress and effects of diseases or medical conditions, contributing to the improvement in the cost-effectiveness of therapies, prophylaxes and diagnoses and enhancing the efficiency and effectiveness of medical institutions and the whole healthcare system.

1.3 Scope

1.3.1 This handbook outlines the major management and compliance issues in respect of clinical studies undertaken by the Hospital Authority ("HA") and its employees, officers and appointees under the employment or appointment of the HA. The main contents include:

(a) Compliance requirements;
(b) Legal affairs; and
(c) Resources management and quality assurance.

1.4 Applicability

1.4.1 This handbook is developed and published as a reference material for any HA personnel involved in overseeing, conducting, coordinating, facilitating or supporting clinical studies. The target readers include:

(a) Investigators (e.g. medical doctors and Chinese medicine practitioners);
(b) Clinical research coordinators (e.g. nurses and research assistants);
(c) Clinical and allied health professionals (e.g. radiologists, laboratory technologists and pharmacists);
(d) Management and administrators of hospitals/institutions

(e.g. Hospital Chief Executives, Chiefs of Service, department managers and hospital administrators); and

(e) Members of research ethics committees ("RECs").

1.4.2 This handbook is not an official policy document. In case of doubt and controversy, readers should refer to the HA's prevailing official policies, guidelines and requirements.

1.4.3 The HA is in close collaboration with the medical faculties of The University of Hong Kong ("HKU") and The Chinese University of Hong Kong ("CUHK") – especially through its two teaching hospitals (i.e. Queen Mary Hospital and Prince of Wales Hospital) – in education, research, and advancement of healthcare technologies and services. Without prejudice to the HA's applicable policies, guidelines and requirements, management and administration of clinical studies undertaken by or under the two universities shall be subject to their respective policies, guidelines and requirements.

2. Classification of Clinical Studies

2.1 Management Classification of Clinical Studies

2.1.1 Clinical studies could be classified from various perspectives. Common ways include classification by study phases (e.g. phase I, II, III and IV), by therapeutic areas (e.g. cardiology, endocrinology and oncology), by study articles (e.g. chemical drugs, biologics, herbal medicines and devices) and by study designs (e.g. double-blind, randomized controlled studies and open-label studies).

2.1.2 For the purpose of management and administration, clinical studies may be classified as:

(a) Interventional studies or non-interventional studies; or
(b) Sponsored studies or investigator/institution-initiated studies.

2.2 Interventional and Non-interventional Studies

2.2.1 An intervention is any medical product, procedure or method applied to humans and is intended to treat, mitigate, diagnose or prevent a disease or medical condition.

2.2.2 An interventional study is a clinical study that involves any extra medical intervention that is not part of the routine or necessary medical care for the human subjects involved and may include:

(a) The use of any investigational medical product or off-label use of any marketed medical product;

(b) Performance of any extra clinical procedure or method; and/or
(c) Study-specific assignment of human subjects to study arms (e.g. randomization).

2.2.3 A non-interventional study is a clinical study that involves no extra medical intervention or only medical intervention(s) with insignificant extra risk on the human subjects involved. Common non-interventional studies include (but not limited to):

(a) Surveys and epidemiology studies: Studies that involve only the collection of data or information from human subjects and without involving the use of any medical product or clinical procedure/method (e.g. questionnaire surveys, medical chart reviews and case series studies).
(b) Observational studies: Studies that involve the use of medical product(s) and/or clinical procedure(s)/method(s) without deviating from the normal clinical practices applicable to the human subjects involved, or to the furthest extent involve only noninvasive procedures/methods with insignificant extra risk (e.g. observation of patients on a normal treatment course during which a few extra small blood samples are collected).
(c) Medical product studies: Studies that involve investigation of any medical product, where (i) such medical product(s) has/have been officially approved or permitted for clinical use; (ii) such medical product(s) is/are prescribed according to the labeled indications and instructions; (iii) assignment of any human subject to any treatment or healthcare strategy is determined in accordance with normal clinical practices but not by randomization or other research specific methods; and (iv) no extra clinical procedure/method other than noninvasive

procedure(s)/method(s) of insignificant extra risk is involved (e.g. phase IV, single-arm drug trials).

2.2.4 Interventional studies are of higher risk and are therefore subject to more stringent ethical, regulatory and management requirements.

2.3 Sponsored and Investigator/Institution-initiated Studies

2.3.1 In the domain of clinical research, "sponsor" refers to any company, organization, institution or individual, whether for-profit or non-profit in nature, that is responsible for initiating, managing and/or financing a clinical study. The meaning of "sponsor" extends beyond somebody who simply provides financial sponsorship. It embodies a broad range of primary responsibilities, which usually includes the following:

(a) Scientific responsibilities: Developing and manufacturing an investigational product and designing a clinical study.
(b) Management responsibilities: Overall management of a clinical study – from study protocol development and identification of investigators to quality assurance/control and data analysis and reporting.
(c) Regulatory responsibilities: Ensuring compliance with applicable regulatory requirements.
(d) Legal responsibilities: Assuming the liabilities to human subjects and investigators for damages arising from a clinical study.
(e) Financial responsibilities: Financing the costs of running a clinical study.

2.3.2 A sponsored study is a clinical study sponsored by an external

party who is taking all or a large majority of the primary responsibilities outlined in section 2.3.1 above. In a sponsored study, a medical institution and its investigators only assume the role of research institution/investigator and are responsible for running the study at the study site. The sponsors, in return for the primary responsibilities taken, usually have full ownership over all the data, results and intellectual property rights derived from the studies. Clinical studies sponsored by commercial organizations (e.g. pharmaceutical, medical device and other healthcare companies) are commonly known as "industry-sponsored studies," "company-sponsored studies" or "commercially-sponsored studies."

2.3.3 An investigator/institution-initiated study is a clinical study initiated and managed primarily by a medical institution and/or its investigators. Without an external sponsor, the medical institution/investigators shall take all the aforesaid primary responsibilities and therefore assume the roles of both sponsor and research institution/investigator.

2.3.4 An investigator/institution-initiated studies may be organized either entirely by a medical institution and/or its investigators or with the support of one or more external organization(s) in the forms of funding, medical products, equipment, research services or otherwise. It is important to emphasize that responsibility, rather than the funding source, is the major criterion for differentiating investigator/institution-initiated studies from sponsored studies. Investigator/institution-initiated studies are also called "investigator/institution-sponsored studies" or "non-commercially sponsored studies." An investigator for an investigator-initiated study is sometimes referred to as a "sponsor-investigator."

Part 2:
Compliance

3. Overview of Clinical Research Compliance

3.1 Three Bases for Regulating Clinical Research

3.1.1 Clinical research is a special kind of scientific experiment involving human beings. Through the collection of human data, it aims at evaluating the safety and/or efficacy of medical products, procedures or methods, as well as enhancing the understanding of diseases or medical conditions. Owing to its special nature, clinical research is heavily regulated worldwide for the following three key purposes:

(a) Protection of human subjects: Human research ethics is a core consideration in contemporary clinical research. Sponsors, investigators, clinical research personnel, research institutions and other parties participating in organizing and/or conducting clinical research are strictly required to take all necessary measures to safeguard the rights, safety and well-being of human subjects.

(b) Validation of scientific soundness: Clinical research is an important component of evidence-based medicine. Clinical studies must be well-designed, with valid scientific basis, to allow scientific evaluation of the safety and/or efficacy of medical products, procedures or methods and/or consideration for clinical use or the grant of marketing authorizations by regulatory authorities, as well as to avoid putting human subjects on unjustified risks and wastage of limited research resources.

(c) Assurance of data integrity: Scientific evaluation could not

be concluded without considering the quality and reliability of the data collected from clinical studies. Quality assurance systems must be established and quality control measures must be implemented to ensure data integrity and allow verification of study data wherever required.

3.2 Six Dimensions of Compliance by Investigators

3.2.1 Compliance is the act of conforming to certain established policies, regulations, rules, requirements, guidelines or standards. Investigators, being the key persons assuming the primary responsibilities to supervise and conduct clinical studies at their study sites, have to ensure compliance in the following six dimensions:

(a) Compliance with international guidelines
(b) Compliance with management policies
(c) Compliance with research ethics committees' requirements
(d) Compliance with regulatory requirements
(e) Compliance with public registration requirements
(f) Compliance with contractual requirements

3.2.2 Different kinds of clinical studies (e.g. interventional and non-interventional studies, sponsored and investigator/institution-initiated studies) are subject to different sets of compliance requirements. The requirements in each of the aforesaid dimensions are to be elaborated in the subsequent chapters.

4. Compliance with International Guidelines

4.1 International Guidelines for Clinical Research

4.1.1 The rapid advances in medical research and development over the last century has led to globalization of clinical research activities, which triggered the call for harmonization of ethical, regulatory and technical requirements for clinical research.

4.1.2 Established in 1947 (two years after the Second World War), the Nuremberg Code was the first important ethical document which emphasized the rights and safety of human subjects, including voluntary consent and avoidance of unnecessary injury or suffering. Whilst over the years various bodies tried to establish different guidelines for clinical research, the two most internationally recognized and prevailing guidelines, among all others, may still be:

(a) The Declaration of Helsinki; and
(b) The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use – Guideline for Good Clinical Practice ("ICH GCP").

4.1.3 Although these guidelines are neither laws nor regulations that are legally binding, over the years they have gained wide acceptance by the industry and clinical research professionals, and are generally regarded as the gold standards for clinical research, especially for international clinical studies.

Investigators and clinical research personnel are usually required to follow such guidelines in organizing and conducting clinical studies.

4.2 Declaration of Helsinki

4.2.1 The Declaration of Helsinki is probably one of the best-known policy statements issued by the World Medical Association ("WMA"), an international organization founded in 1947 by physicians from 27 countries and now representing about 80 national medical associations worldwide. First adopted in 1964 – 16 years after establishment of the Nuremberg Code – the Declaration of Helsinki provided a set of key ethical principles guiding the conduct of medical research involving human subjects. It has subsequently been amended in 1975, 1983, 1989, 1996, 2000, 2002, 2004 and 2008. The latest version could be obtained from the WMA homepage at www.wma.net.

4.2.2 Although the WMA only regards the latest version as the official version, individual institutions, RECs and sponsors may opt to use and follow the previous versions. Investigators should observe the most updated requirements of their affiliated institutions and RECs, and also the requirements of the relevant sponsors in case of participation in sponsored studies.

4.2.3 Owing to its comprehensiveness and broad representation, for decades the Declaration of Helsinki has been regarded and respected as the fundamental ethical standard for clinical research worldwide. Its underlying principles have also been embodied in subsequent international guidelines or regulations such as the ICH GCP (see section 4.3 below) and the U.S. Food and Drug Administration ("U.S. FDA") regulations.

4.2.4 Notwithstanding its recognized status, a few points incorporated into version 2000 and onward (e.g. the use of placebo and post-study access to beneficial interventions) triggered big and continuous controversy among various clinical research players.

4.2.5 In October 2008, the U.S. FDA removed the reference to the Declaration of Helsinki from its regulations and instead incorporated the standard of good clinical practice ("GCP"). The primary reason for the change, according to the U.S. FDA, is to eliminate any potential confusion resulting from different revisions of the Declaration of Helsinki, which is independent and beyond the control of the U.S. government. The U.S. is the world's biggest pharmaceutical and healthcare market and the U.S. FDA is among the most influential regulatory bodies worldwide. The aforesaid change by the U.S. FDA has unavoidably hampered the status of the Declaration of Helsinki.

4.3 ICH Guideline for Good Clinical Practice

4.3.1 GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical studies, which provides assurance of the creditability and accuracy of clinical study data and results and the protection of the rights, safety, well-being, integrity and confidentiality of human subjects.

4.3.2 The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") is a unique project that brings together the regulatory authorities and pharmaceutical industry experts from the U.S., Europe and Japan to discuss the scientific and technical aspects of pharmaceutical research and development, with the purposes of harmonizing the requirements for pharmaceutical product registration, avoiding or reducing

duplicated clinical trials, and accelerating the availability of new medicines that benefit the public.

4.3.3 The ICH GCP was adopted in 1996 and consists of eight chapters, covering the basic principles of GCP, the responsibilities of RECs, investigators and sponsors, the key components of clinical study protocols and investigator's brochures, and a summary of the essential documents for clinical studies. A complete version could be obtained from the ICH homepage at www.ich.org.

4.3.4 The ICH GCP is nowadays generally regarded as the international GCP standard applicable to clinical studies of pharmaceuticals and, to various extents, other medical research involving human subjects. It also forms the basis of the clinical research regulations in the ICH regions (i.e. the U.S., Europe and Japan) and the large majority of the countries and regions worldwide.

4.3.5 Replacement of the reference to the Declaration of Helsinki by GCP (as outlined in section 4.2.5 above) in the U.S. FDA regulations has made the ICH GCP being seen as a more important guideline in the international clinical research industry.

5. Compliance with Management Policies

5.1 Hospital Authority as a Research Institution

5.1.1 The HA is a body corporate established under the Hospital Authority Ordinance (Chapter 113 of the laws of Hong Kong). In addition to the primary responsibilities of establishing, managing, controlling and developing the public hospital system in Hong Kong and advising the Hong Kong government on healthcare policies and strategies, the HA also has the responsibility to promote, assist and take part in research relating to hospital services (Chapter 113, Section 4(f)(ii) of the laws of Hong Kong).

5.1.2 Being a public healthcare provider and a research institution, the HA, according to the Hospital Authority Guide on Research Ethics for Study Site & Research Ethics Committee (revision number 1, dated August 15, 2007), has to take into consideration the following aspects while promoting, assisting or taking part in clinical research:

(a) Healthcare services are accorded priority.
(b) The rights, safety and welfare of human subjects are properly protected.
(c) Clinical studies are conducted ethically and lawfully.
(d) Public confidence is sustained by an environment that upholds scientific and ethical integrity.
(e) Risks and potential liabilities to the HA are well-controlled and minimized.

5.2 Governance of Clinical Research in the Hospital Authority

5.2.1 To serve the role of a research institution, the HA has established a two-tier structure for governance of clinical research, including:

(a) Management governance by cluster/institution management; and
(b) Research ethics governance by RECs.

5.2.2 The HA is a large healthcare institution managing (as of December 2009) 41 public hospitals/institutions, 48 specialist outpatient clinics and 74 general outpatient clinics (for simplicity, HA hospitals, institutions and clinics are hereinafter referred to individually as an "institution" and jointly as "institutions"). In order to ensure that clinical research is managed in an effective and efficient manner, the HA has delegated its clinical research management governance responsibilities to different management levels within the HA management system, including:

(a) Cluster/institution management, represented by Cluster Chief Executives ("CCEs") and Hospital Chief Executives ("HCEs"), or their delegates; and
(b) Departmental management, represented by Chiefs of Service ("COSs") or their delegates.

5.2.3 Any clinical study undertaken by any HA institution and/or its employees, officers and appointees under the HA's employment/appointment is subject to initial management approval and continuous review and supervision by the management of the institution at where the study site is located.

The relevant cluster/institution management and departmental management shall have the joint responsibility to ensure that:

(a) Service priority of the institution will not be adversely affected by the study;
(b) The investigators and research team are competent to organize and conduct the study;
(c) Sufficient and suitable resources, manpower and facilities will be available for supporting the conduct of the study in a safe and proper manner;
(d) Qualified personnel, whether the investigators, research team members or other appropriate personnel, are available and prepared to manage any adverse medical conditions that may arise from the study; and
(e) Where external party(ies) is/are involved (e.g. in a sponsored study) and legal agreement(s) between such external party(ies) and the institution is/are required, a proper approval of such agreement(s) has been obtained from the HA Legal Services Section prior to execution by the institution's authorized representative(s).

5.2.4 The REC system is an added governance layer established by the HA for protection for human subjects participating in clinical research. Its structure and operations are to be outlined in the next chapter.

5.3 Governance by Cluster/Institution Management

5.3.1 Cluster/institution management is the official representative of the institution involved, and is responsible for overseeing the resources management and risk management aspects of clinical studies on cluster/institution level.

5.3.2 Any official document issued in relation to a study under the

capacity of a cluster/institution, including but not limited to legal agreements (e.g. clinical trial agreements and indemnity agreements for sponsored studies), shall be endorsed/signed by the cluster/institution management.

5.3.3 Cluster/institution management also has the responsibility to deal with any complain or claim received in relation to any clinical study. If circumstances warrant, the cluster/institution management may refer such complaints or claims to the HA Head Office ("HAHO").

5.4 Governance by Departmental Management

5.4.1 Departmental management is responsible for overseeing the clinical management, resources management and risk management aspects of clinical studies on departmental level.

5.4.2 Prior to submission of a study's clinical research ethics review application dossier (the list of major documents need to be included in the dossier will be set out in the next chapter) by the study's investigator to the relevant REC, the relevant departmental management shall review the dossier in order to verify that the criteria set out in section 5.2.3 above are properly conformed to. Signing of the dossier by the departmental management shall be deemed a valid and sufficient departmental management approval for the study.

5.4.3 If deemed required, the departmental management may discuss with the investigator to clarify any study particulars and, wherever necessary, to request for modifications of the study, its documents and/or arrangements to secure conformance to the said criteria.

5.4.4 In the circumstances the departmental management believes,

after reasonable evaluation, that the study may bring about extraordinary risk to human subjects, the investigators/research team, the institution and/or the HA, the departmental management shall consult with the cluster/institution management.

5.4.5 Management oversight is an ongoing process. Departmental management shall keep reviewing the status of each clinical study to safeguard continuous compliance with the aforesaid criteria.

5.4.6 Departmental management also has the responsibility to perform initial evaluation of any complaint or claim received in relation to any clinical study and, wherever circumstances warrant, to refer such compliant or claim to cluster/institution management for further handling.

5.5 Investigator Accountability to Management

5.5.1 An investigator is the key person supervising the conduct of a clinical study at a study site and shall assume the final responsibility of ensuring compliance with all applicable management policies by himself/herself and also by his/her whole research team, including (but not limited to):

(a) Submitting the study's clinical research ethics application dossier to and seeking an approval for the study by the departmental management as described in section 5.4.2 above;
(b) Submitting any agreement (e.g. clinical trial agreement and indemnity agreement for sponsored studies) and official document to and seeking an endorsement from the cluster/institution management as described in section 5.3.2 above;

(c) Updating departmental management on the study status during the study period as described in section 5.4.5 above; and
(d) Informing the departmental management of any complaint or claim in relation to the study as described in section 5.4.6 above.

5.5.2 Notwithstanding the above, other research personnel, by agreeing to take part in conducting the study, shall have the responsibility to observe and help the investigator to comply with all relevant management policies.

5.5.3 If a study is conducted by a team of investigators at a study site, one of the investigators shall take the leading role and assume the final responsibility at the study site, and that leading investigator is commonly named a "principal investigator."

5.6 Approval by Collaborators

5.6.1 If a clinical study is conducted in collaboration with investigators at other hospitals/institutions outside the HA, the HA investigator shall make sure that the collaborating investigators obtain proper management approvals by the collaborating hospitals/institutions before study initiation and to continuously comply with the requirements of the collaborating hospitals/institutions.

6. Compliance with Research Ethics Committee Requirements

6.1 Research Ethics Committee System in the Hospital Authority

6.1.1 Human research ethics is a core consideration in contemporary clinical research. RECs have become a fundamental and essential infrastructure responsible for overseeing clinical research ethics and safeguarding the rights, safety and well-being of human subjects.

6.1.2 In the HA, its REC system is organized on two levels:

(a) HAHO Steering Committee on Research Ethics ("HA REC")
(b) Cluster-based RECs ("Cluster RECs")

6.1.3 The HA REC is responsible for establishing research ethics standards and guidelines, harmonizing research ethics standards and practices within the HA and with affiliated academic institutions, promulgating and monitoring the implementation of research ethics, administering a central clinical research database for risk management purpose, and handling appeals against the decisions of Cluster RECs.

6.1.4 Each Cluster REC is responsible for initial and continuing ethics review of clinical studies conducted in institutions under its jurisdiction, and has the power to:

(a) Approve, disapprove and require modifications or amendments to clinical studies and their related documents;

(b) Monitor the progress and conduct of clinical studies through review of progress reports and serious adverse event ("SAE") reports;
(c) Terminate or suspend clinical studies; and
(d) Audit study sites.

6.1.5 There are six Cluster RECs overseeing clinical studies in seven HA clusters (Table 6.1). The HKU/HA HKW IRB and the Joint CUHK-NTE CREC were established and are being operated jointly with HKU and CUHK respectively.

Table 6.1: Cluster RECs

REC	Abbreviation	Jurisdiction	U.S. OHRP Registration No.
Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong West Cluster (6 Panels)	HKU/HA HKW IRB	• HKU • HA Hong Kong West Cluster	IRB00005123 IRB00005124 IRB00005125 IRB00005126 IRB00005127 IRB00005128
Hong Kong East Cluster REC	HKE CREC	• HA Hong Kong East Cluster	IRB00006847
Kowloon Central / East Cluster REC (3 Panels)	KC/E CREC	• HA Kowloon Central Cluster • HA Kowloon East Cluster	IRB00005035 IRB00005036 IRB00005037
Kowloon West Cluster REC	KW CREC	• HA Kowloon West Cluster	IRB00004640
Joint CUHK-NTEC Clinical Research Ethics Committee	Joint CUHK-NTE CREC	• CUHK • HA New Territories East Cluster	IRB00002883
New Territories West Cluster REC	NTW CREC	• HA New Territories West Cluster	IRB00004753

6.1.6 According to the U.S. regulations, any organization that wishes to be involved in any clinical study funded by the U.S. federal government or any U.S. governmental agencies (e.g. the U.S. National Institutes of Health ("U.S. NIH")) must use REC(s) registered with the U.S. Office for Human Research Protections ("U.S. OHRP") for review and oversight of its clinical studies. For this purpose, all the six Cluster RECs have done their registrations with the U.S. OHRP and their registration numbers are listed in Table 6.1 above.

6.2 Initial Ethics Review

6.2.1 Each clinical study must first be approved by a REC before being initiated at a study site. An application for ethics review shall be submitted to a relevant REC secretariat and shall contain the following items:

(a) A duly completed and signed clinical research ethics review application form
(b) A study protocol
(c) An investigator's brochure (if available)
(d) An informed consent form and other information to be provided to human subjects (such as recruitment notice, invitation letter and safety information) in suitable language(s)
(e) Curricula vitae and relevant experience of investigators and key research personnel
(f) Other relevant documents, such as support from an academia for student projects

6.2.2 For sponsored clinical studies, the following additional items shall also be submitted:

(a) An investigator's conflict of interest declaration form

(b) A letter of indemnity for clinical trial
(c) A draft clinical trial agreement
(d) A cheque for the prevailing ethics review application fee

6.2.3 Initial ethics reviews are normally conducted in a meeting by a panel of at least five members. However, expedited reviews may be permitted for:

(a) Non-interventional studies that neither involve vulnerable subjects nor raise sensitive privacy concerns; or
(b) Studies that have been approved by another Cluster REC.

6.2.4 The following aspects in respect of ethics review applications shall be noted:

(a) Each REC may have different ethics review application requirements. An investigator shall check with the relevant Cluster REC secretariat for the detailed requirements.
(b) An application must be submitted before the submission deadline for the corresponding review meeting. An investigator shall check with the relevant Cluster REC for the exact meeting schedule and submission deadline for a particular review meeting.
(c) An investigator may be required to attend an ethics review meeting to present the key study information and to answer inquiries by the review panel.
(d) For each clinical study of pharmaceutical product(s), a Certificate for Clinical Trial needs to be obtained through the Hong Kong Department of Health and submitted to the relevant Cluster REC before the study is initiated. Details about the application will be provided in the next chapter.

6.2.5 In addition to initial ethics review applications, investigators

shall also comply with other requirements of Cluster RECs, such as submitting serious adverse event reports, protocol amendments, progress reports and final reports.

6.3 Reporting of Serious Adverse Events

6.3.1 A serious adverse event ("SAE") is an adverse event observed during a clinical study, which:

(a) Results in death;
(b) Is life-threatening;
(c) Requires inpatient hospitalization or prolongation of existing hospitalization;
(d) Results in persistent or significant disability or incapacity; or
(e) Results in a congenital anomaly or birth defect.

6.3.2 All unexpected SAEs shall be reported to the Cluster RECs promptly. Other SAEs may be reported in accordance with the standard operating procedures of individual Cluster RECs. Investigators shall note and comply with the reporting requirements and timelines stipulated by the relevant Cluster RECs.

6.3.3 Acknowledgements or notices from the relevant Cluster RECs for any SAE reports shall be retained properly by investigators and (if applicable and required) copied to the relevant sponsors or supporting organizations.

6.4 Progress Reports and Final Reports

6.4.1 Investigators shall update the relevant Cluster RECs on the status of their clinical studies through submission of progress reports (at least annually during the period of the study) and a

final report (at the end of the study).

6.4.2 Approvals from the relevant Cluster RECs for any progress or final reports shall be retained properly by investigators and (if applicable and required) copied to the relevant sponsors or supporting organizations.

6.5 Ethics Compliance by Investigators

6.5.1 Investigators shall be responsible for observing, understanding and complying with the latest requirements of the relevant Cluster RECs, including (but not limited to) making required submissions and obtaining corresponding approvals or acknowledgements.

7. Compliance with Regulatory Requirements

7.1 Local Regulation on Clinical Studies of Pharmaceutical Products

7.1.1 Clinical studies of pharmaceutical products are regulated in Hong Kong under the Pharmacy and Poisons Regulations (Chapter 138A Regulation 36B of the laws of Hong Kong).

7.1.2 Under the regulation, a "pharmaceutical product" means any substance or mixture of substances manufactured, sold, supplied or offered for sale or supply for use in (i) the diagnosis, treatment, mitigation, alleviation or prevention of disease or any symptom thereof; (ii) the diagnosis, treatment, mitigation, alleviation of any abnormal physical or physiological state or any symptom thereof; or (iii) altering, modifying, correcting or restoring any organic function in human beings.

7.1.3 The regulation not only applies to clinical studies of unapproved, investigational pharmaceutical products but also to clinical studies of any pharmaceutical products irrespective of their marketing registration status in Hong Kong.

7.2 Applications for Certificates for Clinical Trials

7.2.1 For the purpose of regulatory compliance, a Certificate for Clinical Trial ("CTC") shall be obtained before initiation of any clinical study of any pharmaceutical product. An application for a CTC shall be submitted to the Pharmaceutical Registration Section of the Hong Kong Department of Health ("DOH") and

shall contain the following items (according to the current requirements):

(a) A completed application form and a completed checklist of clinical study documents
(b) The prescribed application fee
(c) A copy of the proposed protocol for the clinical study
(d) Information on the pharmaceutical product (e.g. its pharmaceutical data, pharmacological action, toxicology, previous studies on human (if any) and package insert), in case of investigational pharmaceutical product unapproved in Hong Kong
(e) Copies of pre-clinical studies
(f) A sample of the pharmaceutical product
(g) A letter from the investigator confirming his/her involvement in the clinical study
(h) A curriculum vitae of the investigator
(i) Documentary evidence that the clinical study has been approved by the REC affiliated with the institution in which the study is to be conducted
(j) The proposed patient information sheet and patient consent form (in both English and Chinese, or in Chinese only)
(k) Evidence that the pharmaceutical product is manufactured in accordance with Good Manufacturing Practice ("GMP") (e.g. a copy of the GMP certificate of the manufacturer)
(l) A sample certificate of analysis of the pharmaceutical product

7.2.2 The following key aspects in respect of applications for CTCs shall be noted:

(a) In case of sponsored clinical studies, the applicants are normally the sponsors. For investigator/institution-initiated

studies, the applicants are usually the investigators or the institutions. Whoever the applicant is, an investigator shall always ensure that a valid CTC is obtained prior to initiation of a study and maintained during the period of the study.

(b) If a sample pharmaceutical product (as referred to in section 7.2.1(f)) needs to be imported into Hong Kong, an import license is needed. Import Licence Form 3 (TRA 187) shall be completed and submitted to the Pharmaceutical Registration and Import/Export Control Section of the DOH.

(c) An application for a CTC and an application for ethics review could be submitted in parallel, although a CTC will not be issued before an approval by the relevant REC is granted.

(d) Each CTC is valid for two years. An applicant shall obtain a new CTC every two years during the period of a study if the study continues for over two years.

7.3 Reporting of Adverse Drug Reactions

7.3.1 Adverse drug reactions ("ADRs") that are both serious and unexpected shall be reported to the DOH promptly. The reporting timelines for different kinds of ADRs are as follows:

(a) For fatal or life-threatening ADRs that are unexpected, initial reporting should be done as soon as possible but no later than seven (7) calendar days after first knowledge by the CTC holder and followed by a complete assessment report within eight (8) additional calendar days.

(b) Other serious, unexpected ADRs that are not fatal or life-threatening shall also be reported as soon as possible but within fifteen (15) calendar days after first knowledge by the CTC holder.

(c) Non-serious ADRs and serious ADRs that are expected shall be reported in a brief summary at the conclusion of a study.

7.4 Progress Reports and Final Reports

7.4.1 CTC holders shall have the responsibility to notify the DOH of the updated status of their clinical studies. Progress reports shall be submitted annually during the period of a study. A final report shall also be submitted at the end of a study.

7.5 Local Regulation on Other Clinical Studies

7.5.1 Clinical studies of medical procedures, methods, or medical products other than pharmaceutical products (e.g. traditional Chinese medicines, medical devices and cell therapies) are not currently regulated by laws or regulations in Hong Kong. Investigators, however, need to observe the latest regulatory requirements and ensure that their clinical studies are conducted in compliance with all applicable regulatory requirements in Hong Kong.

7.6 Applicability of Overseas Regulations

7.6.1 From a legal perspective, clinical studies conducted in Hong Kong are subject only to local laws and regulations. However, harmonization of regulations has triggered the globalization trend, transforming contemporary clinical research into an international collaborative effort. Clinical studies conducted in Hong Kong may therefore also be subject to overseas regulations in many circumstances. Examples include:

(a) Clinical studies targeted at supporting marketing applications to overseas regulatory agencies (e.g. multicentre, multinational drug trials targeted at global

registration).

(b) Clinical studies supported and/or funded by overseas governmental or funding bodies (e.g. clinical studies funded by the U.S. NIH).

(c) Clinical studies conducted in collaboration with overseas organizations (e.g. collaborative multicentre clinical studies conducted in alliance with overseas research institutions).

7.7 Investigators' Roles in Regulatory Compliance

7.7.1 Investigators shall have the responsibility to observe, understand and ensure compliance with the latest regulatory requirements.

7.7.2 In investigator/institution-initiated studies, investigators are normally the CTC holders and are therefore fully responsible for compliance with applicable local regulatory requirements, which includes making applications for CTCs, reporting of ADRs and submitting progress reports and final reports.

7.7.3 In sponsored studies, sponsors are normally the CTC holders and hence need to take the regulatory responsibilities. However, investigators still need to make appropriate efforts to ensure compliance by the sponsors with applicable local regulations.

7.7.4 Different kinds of clinical studies may be regulated differently in different countries or places. Investigators considering participation in international clinical studies shall pay special attention to the applicable overseas regulatory requirements and ensure that they understand and have the ability to comply with the regulations before committing to such studies. Local investigators participating in clinical studies targeting at supporting an application for marketing authorization by the U.S. FDA, for instance, are required to commit to complying

with the applicable U.S. FDA regulations by signing a Statement of Investigator (i.e. Form FDA 1572). Investigators who fail to comply with the commitment may be subject to disqualification or debarment sanction under U.S. regulations, and be restricted or prohibited from participating in clinical studies supported by any U.S. governmental agency or targeted at supporting any marketing authorization application.

8. Compliance with Public Registration Requirements

8.1 Bases for Public Registration of Clinical Trials

8.1.1 Since the call for more transparent disclosure of clinical trial activities by the International Committee of Medical Journal Editors ("ICMJE") in September 2004, registration of clinical trials with public clinical trial registries has become a common practice worldwide.

8.1.2 Public registration of clinical trials is deemed an effective way to help achieve the following objectives:

(a) Avoidance of publication bias through selective reporting of clinical trials with positive results.
(b) Increasing the awareness of clinical trial activities by the general public, especially local societies.
(c) Offering a convenient and open channel for people who are interested in participating in clinical trials.

8.1.3 For the purpose of achieving the above objectives, public registration of clinical trials is made an essential requirement in many important regulations and international policies, including (but not limited to):

(a) The Uniform Requirements for Manuscripts Submitted to Biomedical Journals ("URM") of the ICMJE;
(b) Food and Drug Administration Amendments Act ("FDAAA") of the U.S.; and

(c) The Declaration of Helsinki of the WMA.

8.2 Requirements under the URM of the ICMJE

8.2.1 To promote public registration of clinical trials, the ICMJE requires that, with effect from July 1, 2005, any clinical trial must be registered with a recognized public clinical trial registry before recruitment of the first trial subject in order to be qualified for consideration for publication by its member journals. The ICMJE defines a clinical trial as "any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome." Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like.

Table 8.1: Primary clinical trial registries recognized under the ICTRP of the WHO (as of January 2010). An updated list is available on the ICTRP website at www.who.int/ictrp/network/primary.

Registry	Website
Australian New Zealand Clinical Trials Registry (ANZCTR)	www.anzctr.org.au
Chinese Clinical Trial Register (ChiCTR)	www.chictr.org
Clinical Trials Registry - India (CTRI)	www.ctri.in
German Clinical Trials Register (DRKS)	www.germanctr.de
Iranian Registry of Clinical Trials (IRCT)	www.irct.ir
ISRCTN.org	www.isrctn.org
Japan Primary Registries Network	rctportal.niph.go.jp
The Netherlands National Trial Register (NTR)	www.trialregister.nl
Pan African Clinical Trial Registry (PACTR)	www.pactr.org
Sri Lanka Clinical Trials Registry (SLCTR)	www.slctr.lk

8.2.2 To comply with the ICMJE requirement and ensure a clinical trial will be considered for publication by ICMJE member journals (or other medical journals that adopt the same or similar requirements), a clinical trial needs to be registered with ClinicalTrials.gov (i.e. the registry developed by the U.S. NIH) or other "primary registries" recognized by the World Health Organization ("WHO") under the WHO International Clinical Trials Registry Platform ("ICTRP"). A list of recognized primary registries (as of December 2009) is set out in Table 8.1 and an updated list could be accessed to from the ICTRP website at www.who.int/ictrp/network/primary. It is important to note that the ICMJE only considers registrations with complete and accurate information as valid registrations.

8.3 Requirements under the U.S. FDAAA

8.3.1 On September 27, 2007, the U.S. government passed the FDAAA (i.e. U.S. Public Law 110-85) which includes a section on clinical trial databases requiring registration of "applicable clinical trials" with ClinicalTrials.gov.

8.3.2 "Applicable clinical trials" means interventional clinical trials subject to U.S. FDA's regulation (i.e. clinical trials that have one or more sites in the U.S, involve a drug, biologic or device that is manufactured in the U.S., or are conducted under an U.S. investigational new drug application ("IND") or investigational device exemption ("IDE")), including:

(a) Controlled clinical investigations (other than phase I investigations) of drugs and biologics subject to the U.S. FDA's regulation; and
(b) Controlled device trials with health outcomes (other than small feasibility studies) and pediatric postmarket surveillance.

8.3.3 The timelines for registration are as follows:

(a) Clinical trials initiated after September 27, 2007 must be registered within 21 days after the first subject is enrolled, or by December 26, 2007, whichever is later.
(b) Clinical trials for "serious or life threatening diseases or conditions" that were initiated on or before September 27, 2007 and ongoing as of December 26, 2007 must be registered by December 26, 2007.
(c) Clinical trials not for "serious or life threatening diseases or conditions" that were initiated on or before September 27, 2007 and ongoing as of December 26, 2007 must be registered by September 27, 2008.

8.3.4 A "serious and life-threatening disease or condition" generally means (i) a disease or condition where the likelihood of death is high unless the course of the disease is interrupted; or (ii) a disease or condition where the endpoint of clinical trial analysis is survival. Examples of serious and life-threatening disease or condition include cancers, HIV infection and heart failure.

8.4 Requirements under the Declaration of Helsinki

8.4.1 In line with the international trend, the WMA for the first time incorporated the requirement for public registration of clinical trials into the Declaration of Helsinki during its General Assembly in Seoul, Korea in October 2008, requiring that every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

8.4.2 The WMA takes the registration requirement as a general principle and does not specify any particular registry. Registration with any of the WHO-recognized registries is generally deemed sufficient for fulfilling the requirement under

the Declaration of Helsinki.

8.5 Registration of Investigator/Institution-initiated Studies

8.5.1 Investigators shall be responsible for registering their investigator/institution-initiated studies with recognized public clinical trial registries. For compliance with the ICMJE's requirement, a clinical study must be registered before recruitment of the first trial subject. For compliance with the U.S. FDAAA, registration must be completed within 21 days following recruitment of the first subject.

8.5.2 For collaborative clinical studies involving more than one investigator or institution, the participating investigators or institutions shall come to a consensus about who should the responsible party be. Each study shall only be registered once and repeated registrations should be avoided.

8.6 Registration of Sponsored Studies

8.6.1 For sponsored studies, sponsors are usually the responsible parties for study registration. If for any reason investigators wish to register their sponsored studies, they shall pay special attention to the following:

(a) Disclosure of study information is usually subject to confidentiality and non-disclosure obligations under legally-binding contracts with sponsors (e.g. clinical trial agreement or confidentiality agreement). Sponsors' prior written permissions may need to be obtained wherever necessary.
(b) Sponsors may have their own policies and practices in public registration of clinical studies. Investigators shall

check with the relevant sponsors if they have already registered their clinical studies with any recognized public clinical trial registry. Repeated registrations shall be avoided.

9. Compliance with Contractual Requirements

9.1 Contractual Requirements for Sponsored or Collaborative Studies

9.1.1 In the preceding chapters, general requirements applicable to apparently all clinical studies conducted under the HA have been outlined. Sponsored or collaborative clinical studies involving parties outside the HA, whether sponsors, collaborators or supporting organizations, may however be subject to additional requirements under contracts or other legal instruments.

9.1.2 Contracts and legal instruments commonly used in sponsored or collaborative clinical studies include (but not limited to):

(a) Confidentiality agreements;
(b) Clinical trial agreements;
(c) Indemnity agreements;
(d) Financial disclosure statements; and
(e) Investigator's personal data processing agreements.

Such legal instruments are to be introduced in part 3 of this handbook.

9.1.3 It should be noted that contracts are not necessarily in the format of formally signed original legal documents. A contract is made where two or more parties have reached agreement (or where they are deemed to have reached agreement) and the law

recognizes their rights and obligations arising from the agreement. A contract may be made in writing (e.g. by letters, facsimiles and e-mails), by word of mouth (e.g. by face-to-face conversations and telephone communications), by inference from the conduct of the parties and the circumstances of the case (e.g. by the actions taken by the parties), or by any combination of the above.

9.2 Acceptability of Proposed Contractual Requirements

9.2.1 Unlike the other requirements described in the preceding chapters, which are generally mandatory and have to be complied with, contractual requirements may reflect the subjective desires of outside parties and may therefore be negotiable.

9.2.2 Before making any commitment under any contract, the following key factors need to be considered:

(a) Compatibility with other requirements: Mandatory requirements (i.e. HA's management policies, REC requirements, regulatory requirements, international guidelines and, if applicable, public registration requirements) shall always prevail and shall not be overridden by any contract. Any proposed contract term or condition which is in conflict or inconsistent with any mandatory requirement shall be removed or properly modified for alignment with such requirement.
(b) Operational viability: Every person or organization is facing certain practical limitations or restrictions, whether internally or externally. A contract requirement could only be accepted if it is practically feasible considering all the internal conditions and the external environment.
(c) Availability of resources: Some contractual requirements

may be both compatible with other mandatory requirements and practically feasible, but only on condition that extra resources are provided. Acceptance of such contractual requirements shall therefore be subject to availability of suitable and sufficient resources.

9.3 Contractual Compliance by Investigators and Institutions

9.3.1 A contract shall become effective once it is fully executed by all the contract parties. Each person signing on a contract shall ensure that he/she has the authority or has been duly authorized to enter into the contract.

9.3.2 Depending on the nature of a contract, the contract party(ies) on the side of a study site may be an investigator, a HA institution, or both. For instance, a confidentiality agreement may be signed under the personal capacity of an investigator, an indemnity agreement may be endorsed by an institution, and a clinical trial agreement is normally entered into by both an investigator and his/her affiliated institution. Each contract party shall have the responsibility to observe, understand and duly comply with the relevant terms and conditions under a contract.

Part 3:
Legal Affairs

10. Personal Data Protection

10.1 Privacy and Personal Data Protection

10.1.1 Privacy is a cornerstone of human dignity and is generally regarded as a fundamental human right in modern societies. Respect for privacy is addressed in many international documents such as the Universal Declaration of Human Rights adopted by the United Nations in 1948. In the past decades, laws for protection of privacy and personal data have been enacted in many jurisdictions especially in developed countries.

10.1.2 In Hong Kong, privacy and personal data are protected under the Personal Data (Privacy) Ordinance (Chapter 486 of the laws of Hong Kong). Under the ordinance, personal data are defined as any data:

(a) relating directly or indirectly to a living individual (i.e. a data subject);
(b) from which it is practicable for the identity of the data subject to be directly or indirectly ascertained; and
(c) in a form in which access to or processing of the data is practicable.

10.1.3 The Personal Data (Privacy) Ordinance states six basic principles that need to be complied with in any activity involving the collection, holding, processing or use of personal data, including:

(a) Purpose and manner of collection of personal data;
(b) Accuracy and duration of retention of personal data;

(c) Use of personal data;
(d) Security of personal data;
(e) Information to be generally available to data subjects; and
(f) Access to personal data by data subjects.

10.2 Purpose and Manner of Collection of Personal Data

10.2.1 The first principle underlying personal data protection is that personal data shall not be collected unless:

(a) The data are collected for a lawful purpose;
(b) The collection of the data is necessary for the purpose or directly related to that purpose; and
(c) The data to be collected are adequate but not excessive in relation to that purpose.

10.2.2 Where personal data must be collected from a data subject, all practicable steps shall be taken by the data user to ensure that the data subject is informed of:

(a) Whether it is obligatory or voluntary to supply the data, and if it is obligatory to supply the data, the consequences for not supplying the data;
(b) The purpose for which the data are to be used;
(c) The classes of persons or parties to whom the data may be transferred; and
(d) The rights to request access to and correction of the data, and the name(s) and address(es) of the individual(s) to whom any such request may be made.

10.3 Accuracy and Duration of Retention of Personal Data

10.3.1 Where personal data have been collected from a data subject, all

practicable steps shall be taken by the data user to ensure that:

(a) Such personal data are accurate having regard to the purpose for which the personal data are used or to be used;
(b) Where there are reasonable grounds for believing that certain personal data are inaccurate, such data shall either (i) not be used unless and until such data are rectified or those grounds are proven to be inapplicable; or (ii) be erased; and
(c) Where certain personal data disclosed to a third party are found to be inaccurate or to become inaccurate, the third party shall be informed of the inaccuracy of such data and be provided with such necessary particulars as it will enable the third party to rectify such data.

10.3.2 Personal data shall not be kept longer than it is necessary for the fulfillment of the purpose for which the data are used or are to be used.

10.4 Use of Personal Data

10.4.1 Personal data shall not be used for any purpose other than the prescribed purpose(s) informed to the data subject at the time of data collection or a purpose directly related to the prescribed purpose.

10.4.2 Any alternative use of personal data other than for the purposes stated in section 10.4.1 above shall be subject to the express consent of the data subject concerned.

10.5 Security of Personal Data

10.5.1 Whilst personal data are being held by a data user, all practicable steps shall be taken to ensure that such data are protected against unauthorized or accidental access, processing,

erasure or other use.

10.5.2 In particular, the following aspects regarding data security shall be considered and addressed:

(a) The kind of data that may be influenced and the harm that could result if any of those incidents set out in section 10.5.1 occurs.
(b) The physical location where the data are stored.
(c) Any security measures incorporated into any equipment in which the data are stored.
(d) Any measure taken for ensuring the integrity, prudence and competence of the persons having access to the data.
(e) Any measure taken for ensuring the secure transmission of the data.

10.6 Information to Be Generally Available to Data Subjects

10.6.1 With regard to personal data collected, all practicable steps shall be taken by the data user to ensure that a data subject can:

(a) Ascertain the data user's policies and practices in relation to his/her personal data;
(b) Be informed of the kind of personal data held by the data user; and
(c) Be informed of the main purposes for which his/her personal data held by the data user are used or are to be used.

10.7 Access to Personal Data by Data Subjects

10.7.1 A data subject shall be entitled to:

(a) Ascertain whether a person or party is a data user and is

holding his/her personal data;

(b) Request access to his/her personal data within a reasonable time, at a reasonable fee (if any), in a reasonable manner, and in a form that is intelligible;

(c) Request the correction of his/her personal data; and

(d) Be given reasons if any request referred to in items (b) and (c) above is refused, and object to any such refusal.

10.8 Personal Data Protection in Clinical Research

10.8.1 Clinical research is about collection of data from or relating to human subjects and obviously the issue of privacy and personal data protection needs to be addressed.

10.8.2 Subjects participating in clinical studies performed in the HA are mostly patients who seek medical treatments or other healthcare services in the hospitals or clinics under the HA. By default, their personal data should only be used for these purposes. Recruiting a patient into a clinical study or using a patient's data in a medical research would change the patient's role to a research subject and therefore the collection, holding, processing and use of personal data will be subject to separate prior consent of the subject, according to the requirements under the Personal Data (Privacy) Ordinance.

10.8.3 Personal data of human subjects in clinical studies may need to be disclosed or transmitted to third parties for various purposes including (but not limited to) inspection by local or overseas regulatory agencies and auditing/monitoring by auditors/monitors designated by sponsors, collaborators or supporting organizations (for sponsored studies or studies conducted in collaboration with or with the support of outside parties). Express prior consent must be obtained from the

subjects for such specified purposes.

10.8.4 Unless otherwise necessary and expressly permitted by the human subjects, where personal data are to be presented, whether in the form of published results or otherwise, such data shall be presented in a way from which the subjects could not be identified.

10.8.5 The requirements for obtaining subjects' consent will be discussed in the next chapter.

10.9 Protection of Investigators' Personal Data

10.9.1 In addition to collection of data from human subjects, sponsors also need to collect, hold, process and use investigators' personal data (e.g. investigators' curricula vitae) for various purposes such as regulatory compliance or retention in sponsors' databases for future feasibility assessments.

10.9.2 For the avoidance of contravening with any privacy law or regulation, sponsors may request each investigator to sign an investigator's personal data processing agreement which permits sponsors to collect, hold, process and use investigators' personal data.

11. Informed Consent

11.1 Concepts of Informed Consent

11.1.1 Informed consent is a process by which a subject is informed of the known and potential risks and benefits as well as all other relevant aspects of a clinical study and voluntarily confirms his/her willingness to participate in the study. It became a major requirement in clinical research since it was first made a legal requirement in the U.S. through adoption of the Kefauver-Harris Drug Amendments in 1962. The requirement was subsequently incorporated into the Declaration of Helsinki in 1964 and the ICH GCP in 1996. Nowadays, it is a core element of human research ethics and has been included as a legal requirement in many jurisdictions.

11.1.2 An informed consent process must consist of two undividable parts – informing (by investigators and/or study personnel) and consenting (by a human subject or his/her legally acceptable representative) – which are of equal importance. Although nowadays written informed consent is mandatorily required and used for documenting human subjects' informed consent in the large majority of clinical studies, strictly speaking an informed consent process starts from the moment when a potential human subject first learns about a clinical study, whether through a subject recruitment advertisement on a newspaper, a public clinical trial registry on the Internet, a subject recruitment poster in a clinic or a face-to-face invitation by an investigator at a study site. It is important to emphasize that an informed consent is not simply a written informed consent form carrying a human subject's signature.

11.2 Investigators' Responsibilities in Informed Consent

11.2.1 An investigator has the ultimate responsibility in an informed consent process, and shall ensure that:

(a) the informed consent form(s) and any other written information (including any subsequent amendment of such documents) to be provided to each human subject are submitted to and approved by the relevant REC(s) and the local regulatory authority (if needed) before they are used (see chapters 6 and 7 for the detailed requirements);
(b) The informed consent discussion with each human subject is conducted either personally by the investigator or through a qualified person designated by the investigator;
(c) Each human subject is provided with sufficient opportunity to ask any question he/she may have in relation to the study and sufficient time to consider his/her participation in the study;
(d) Each informed consent form is signed and dated personally by the human subject and the person who conducted the informed consent discussion (i.e. either the investigator or his/her designee); and
(e) Each fully signed informed consent form shall be properly kept.

11.3 Essential Elements of Informed Consent

11.3.1 To facilitate a potential human subject to make a reasoned decision about his/her participation in a clinical study, sufficient details about the study must be provided, and such details must be conveyed and explained in an easily understandable manner in terms of the contents, the presentation and the language used.

11.3.2 The ICH GCP Section 4.8.10 lists out 20 essential elements that

must be incorporated into the informed consent process in respect of any human subject for any clinical study, including statements or descriptions about:

(a) Study purposes and arrangements
- The research nature of the study
- The purposes of the study
- The details of the study treatment and any randomization arrangement
- The experimental aspects of the study
- The detailed study procedures
- The expected duration of participation in the study by the subject
- The circumstances where the subject's participation in the study will be terminated
- The approximate number of subjects involved or to be involved in the study

(b) Potential risks and benefits
- The potential benefits of the study
- The foreseeable risks of the study

(c) Subject's rights and responsibilities
- The right of voluntary participation in and free withdrawal from the study
- The availability and details of any alternative treatment
- The right to be promptly informed of any new information that may affect the subject's willingness of continuous participation in the study
- The right to contact a designated person for study-related matters and his/her contact details
- The subject's responsibilities in the study

(d) Personal data protection
- The measures to be taken to protect the subject's privacy
- The subject's permission to provide access to his/her

personal data by certain designated parties and regulatory authorities

(e) Compensation and costs
- Any payment to the subject
- The compensation and treatment available in the event of study-related injury
- Any cost that may need to be borne by the subject

11.3.3 Informed consent is a localized process and must reflect the local ethics, culture and regulations. For example, different countries and places may have different legal requirements for personal data protection. The measures to be taken to protect personal data and to be informed to the human subjects during the informed consent process should therefore never be less stringent than the requirements under local laws and regulations. In sponsored, multinational, multicentre clinical studies, sponsors usually prepare and provide sample informed consent forms for use by individual investigators. Investigators shall review such samples and to make necessary adaptations to reflect the local situations.

11.3.4 Human subjects' legal rights shall never be restricted by informed consent. In no circumstances shall any human subject be required during an informed consent process to waive any of their legal rights or to release any investigator, institution, sponsor or any party participating in the organization, conduct or coordination of a clinical study from any liability for negligence.

11.4 Subjects Incapable of Providing Informed Consent

11.4.1 Some human subjects may be incapable of providing informed consent. Common examples include pediatric subjects,

emergency patients (e.g. unconscious patients admitted to a hospital's emergency department) and patients with severe mental disorders or neurological diseases (e.g. severe Alzheimer's disease). Obtaining informed consent in respect of clinical research on those vulnerable subjects has always been a controversial issue in human research ethics. Lacking the possibility of obtaining informed consent directly from them, compliance with the fundamental ethical principle of informed and voluntary participation is difficult to be demonstrated and protection of those subjects becomes a bigger challenge. For the advancement of medical care for those specific groups of patients, however, clinical research involving them is unavoidable. To balance the needs for healthcare advancement and protection of human subjects, alternative arrangements shall be implemented to facilitate the informed consent process whilst without compromising those subjects' rights, safety and well-being.

11.4.2 Many organizations, initiatives and regulatory agencies have attempted to address this issue by establishing guidelines or regulations. The Declaration of Helsinki, for instance, outlines a few key principles:

(a) Informed consent by subjects' legally authorized representatives: If a subject is incapable of giving informed consent, the informed consent of his/her legally authorized representative shall be obtained. As soon as the subject becomes capable of giving consent, an informed consent to continue participating in the study shall be obtained from the subject.
(b) Potential benefits to subjects or the population represented by the subjects: A subject should not be included in a clinical study unless he/she or the population represented

by him/her could be potentially benefited from the study.

(c) Minimal risk and burden: A subject incapable of giving informed consent should not be included in a clinical study unless the study entails no more than minimal risk and burden to him/her.

(d) Assent by subjects: If a subject is deemed to have sufficient intellectual ability to understand the key aspects of a study, his/her assent shall also be obtained. Whilst the subject's assent alone does not establish a sufficient informed consent, his/her refusal is sufficient to exclude him/her from a study.

11.4.3 Informed consent in respect of clinical research is generally seen as a research ethics issue in Hong Kong and the responsibility of overseeing and governing informed consent for clinical research has been staying mainly with the local RECs. Any arrangement to recruit subjects incapable of giving informed consent shall only be practiced with the prior written approval of the relevant REC(s).

11.4.4 In the absence of a specific law or regulation about informed consent for clinical research, investigators and RECs in Hong Kong have to be especially vigilant in considering any measure applying to obtaining consent in respect of subjects who are incapable of providing informed consent. In addition to the relevant principles set out in international guidelines such as the Declaration of Helsinki, the following principles underlying the local requirements of obtaining consent in relation to provision of medical treatments to mentally incapacitated persons under the Mental Health Ordinance (Chapter 136 of the laws of Hong Kong) may also be taken as a reference:

(a) Consent to the carrying out of treatment for a mentally

incapacitated person may be given by the guardian of that person appointed under the ordinance.

(b) Any proposed treatment for a mentally incapacitated person shall be in the best interests of, or considered to be in the best interests of, that person.

11.4.5 One key principle, among the others outlined above, is that subjects incapable of providing informed consent shall not be deprived of the opportunity of treatment and therefore not be assigned, by randomization or otherwise, to receive only placebo or any other treatment that is considered inferior to the best standard treatment offered by the HA to the population of patients represented by those subjects.

12. Confidentiality

12.1 Concepts of Confidentiality

12.1.1 Confidentiality is the state where certain information – which is confidential in nature – is being kept secret. It is defined by the International Standards Organization ("ISO"), in ISO-17799, as "ensuring that information is accessible only to those authorized to have access."

12.1.2 Confidential information is information that is not publicly available, and must not be disclosed without the permission of the information owner or controller. It is a broad concept which does not have a general definition, and therefore needs to be specifically defined with respect to the subject matters and individual circumstances. It may embrace commercial secrets (e.g. patents and other intellectual properties) and technical information (e.g. knowhow and manufacturing methods), as well as general information having special importance to the information owner or controller (e.g. personal medical records).

12.1.3 Confidential information is not necessarily carried in written documents. It may be recorded in other media such as electronic storage device and video tapes, in the form of physical items such as models or apparatus, or even in non-material forms such as by word of mouth or simply by observation.

12.1.4 Confidential information may carry great value, whether commercial (e.g. proprietary information), ethical (e.g. personal data) or otherwise. Breach of confidentiality may cause losses, harms or damages to the information owner or controller.

12.2 Confidentiality in Clinical Research

12.2.1 During the preparation for and the conduct of a clinical study, confidential information may need to be utilized or generated. There are three main kinds of information that may be utilized by or generated from clinical studies and may be subject to confidentiality:

(a) Scientific and technical information: Information relating to research, development and manufacturing of investigational medical products, procedures or methods, which may be proprietary in nature (e.g. study protocols, investigator's brochures and chemical, manufacturing and control documents of investigational products).
(b) Business and operational information: Information in relation to the business and operations of the participating parties (e.g. business secrets, business plans, pricing strategies, client information and standard operating procedures).
(c) Personal information: The personal data of human subjects, investigators and other research personnel (e.g. human subjects' medical records and investigators' and research personnel's curricula vitae).

12.2.2 In sponsored clinical studies, sponsors are normally the owners of the proprietary information relating to their investigational products and therefore are especially concerned about the protection of confidentiality.

12.2.3 To ensure that confidential information is kept confidential in a proper manner, written confidentiality agreements ("CDAs") are commonly used to document the terms and conditions of confidentiality.

12.3 Confidentiality Agreement

12.3.1 A CDA is a legal contract which binds one or more of the contract parties to confidentiality obligations in respect of disclosure or use of confidential information received from the other contract parties for a particular purpose. A CDA may also be called a "secrecy agreement" or a "non-disclosure agreement."

12.3.2 A CDA may be unilateral (i.e. binding only one contract party to confidentiality obligations) or mutual (i.e. binding all contract parties to confidentiality obligations), depending on which party is going to disclose confidential information. A party disclosing confidential information is a "discloser" or "disclosing party" and a party receiving confidential information is a "recipient" or "receiving party." In a mutual CDA, a party could be both a discloser and a recipient.

12.3.3 CDAs commonly impose the following three confidentiality obligations on recipients of confidential information:

(a) A recipient shall not disclose confidential information of a discloser to any third party.
(b) A recipient shall only disclose confidential information of a discloser to his/her employees, officers, agents and affiliates on a "need-to-know" basis for fulfilling the purposes specified in a CDA.
(c) A recipient shall not use confidential information of a discloser for his/her own benefits or for any purpose other than the purposes specified in a CDA.

12.3.4 Notwithstanding the above, it should be noted that not all the information disclosed by a discloser is confidential in nature and such information shall be excluded from the scope of

confidentiality obligations. Such information may include:

(a) Information that was already in the public domain before its disclosure by the discloser to the recipient;
(b) Information that was already in the possession of the recipient before receipt of the information from the discloser,
(c) Information that becomes known to the public through no fault of the recipient;
(d) Information that becomes known to the recipient from a third party that has a lawful right to disclose such information; and
(e) Information that is independently developed by the recipient.

12.3.5 Time is of the essence to the performance of confidentiality obligations under a CDA. To make a CDA enforceable, there are two important time periods that need to be specified:

(a) The period during which confidential information may be disclosed (e.g. one year from the date of a CDA).
(b) The period during which the confidentiality obligations shall apply (e.g. three years from the time of disclosure).

Perpetual confidentiality obligations are difficult to enforce practically and should be avoided unless with special grounds.

12.4 Confidentiality Obligations of Investigators and Institutions

12.4.1 For sponsored studies, sponsors normally require execution of CDAs as early as in study sites identification and feasibility assessment stage to make sure that all their confidential

information is protected. Since investigators' affiliated institutions are normally not yet involved in such an early stage, sponsors usually enter into CDAs directly and only with investigators. Being a contract party under a CDA, an investigator has the full responsibility to comply with all the confidentiality requirements and will be personally liable for any breach of his/her confidentiality obligations. An investigator has to make sure that he/she fully understands the confidentiality requirements and is able to comply with such requirements.

12.4.2 In the event that a CDA is entered into between a sponsor and an investigator's affiliated institution, the CDA shall be signed by an authorized representative of the institution, who is the institution's CCE/HCE or designee, and the institution shall assume the confidentiality obligations. As an employee of the institution, an investigator shall be bound by the CDA in the same manner as the institution.

12.4.3 Investigators and institutions shall take reasonable measures, at a standard no less stringent than the prevailing mechanism for protection of their own confidential information, to comply with the confidentiality obligations under CDAs.

12.4.4 Where confidential information needs to be disclosed to any of the investigator's colleagues or the institution's employees, officers, agents or affiliates through the investigator or the institution, the investigator or the institution (as the case may be) shall fully inform them of the confidentiality requirements under the CDA and take necessary steps to bind them to the obligations, whether by a statement made by the recipients to follow the obligations under the CDA or by a separate CDA between the recipient and the investigator or institution (as the case may be).

13. Clinical Trial Agreements

13.1 Six Principles Underlying Clinical Trial Agreements

13.1.1 Clinical trial agreements ("CTAs") normally need to be entered for sponsored clinical studies for the purpose of setting out the rights and responsibilities of sponsors, institutions, investigators and other research personnel.

13.1.2 All CTAs shall be so drafted and entered into to reflect the following six key principles:

(a) Study site interests: The interests of the institutions, investigators and research personnel shall be fairly protected.
(b) Controlled risk: The risk exposure of the institutions, investigators and research personnel shall be limited within a reasonably acceptable level.
(c) Operational viability: All the study-specific operational requirements shall be reasonably practicable in respect of the specific environment, conditions, manpower and resources of the study teams and study sites.
(d) Services priority: The normal healthcare services of the institutions shall not be adversely affected.
(e) Ethics: Nothing shall directly or indirectly compromise the rights, safety or well-being of any human subject.
(f) Compliance: No terms or conditions shall be in conflict or inconsistent with any applicable law or regulation, REC requirement and international guideline, as well as the institutions' management policy.

13.2 Major Contents in Clinical Trial Agreements

13.2.1 Whilst each clinical study is different and the terms and conditions of CTAs may vary, harmonization of international requirements for clinical research has set the ground for standardization of CTAs. In spite of the need to adapt for study-specific or local requirements, a CTA should normally address the following aspects:

(a) Study management
- Supply of investigational products and study materials
- Safety reporting
- Appointment of contract research organization (if any)
- Monitoring, auditing and inspection
- Financial arrangements

(b) Study site operations
- Recruitment of human subjects and informed consent
- Completion and verification of case report forms
- Archiving of study records

(c) Handling of study information
- Ownership of study data and intellectual property rights
- Confidentiality
- Registration of study and publication of study results
- Use of parties' names

(d) Liability management
- Indemnity and insurance
- Limitation of liability

(e) Legal procedures
- Amendment and assignment of agreement
- Termination of agreement
- Disputes resolution
- Governing law

13.2.2 The above list of topics shall however not be construed as an exhaustive list of requirements for all CTAs. Any other specific aspects that deem to have special importance to a study shall also be addressed in a CTA.

13.2.3 The HA Legal Services Section has prepared a standard CTA template reflecting the principles set out in section 13.1.2 and the major contents listed out in section 13.2.1 above. A copy of the standard CTA template is available from each Cluster REC secretariat.

13.3 Legal Review and Approval

13.3.1 Whenever a CTA is required for a clinical study, the investigator shall have the responsibility to request the sponsor to provide a draft CTA and to include it in the clinical research ethics review application dossier for submission to the relevant Cluster REC. The Cluster REC secretariat will further submit the draft CTA to the HA Legal Services Section for legal review.

13.3.2 The HA Legal Services Section will verify if the draft CTA has been prepared based on the HA standard CTA template or a pre-approved CTA template, and if so return a confirmation of the draft CTA to the Cluster REC secretariat. Otherwise, it will start a negotiation with the sponsor and send to the Cluster REC secretariat a mutually acceptable CTA once a conclusion is reached with the sponsor.

13.4 Investigator and Management Review and Approval

13.4.1 It is important to note that the HA Legal Services Section is only responsible for reviewing and approving the legal contents of CTAs. Investigators and institutions (including cluster/institution management and departmental management,

where appropriate) shall evaluate the operational and financial arrangements and determine if those requirements are acceptable and in line with the principles under section 13.1.2.

13.4.2 A CTA is normally structured as a three-party agreement involving the sponsor as a contract party on one end and the investigator and the institution as the other two contract parties on the other end. The investigator shall sign a CTA on his/her own capacity. The institution management, represented by the CCE or HCE (or delegate), shall sign on behalf of the institution.

13.4.3 Whilst the other research personnel are not contract parties to a CTA, the investigator shall have the responsibility to fully inform them of their respective responsibilities in the study and to ensure that they comply with the contractual requirements.

14. Indemnity and Insurance

14.1 Risk Management in Clinical Research

14.1.1 Clinical studies involve testing of investigational products, procedures or methods which have not been proven safe or effective, and hence usually carry a higher degree of risk than normal medical care. Additional risks associated with clinical studies could be managed by various risk management measures such as development of standard operating procedures, continuous ethics and regulatory review, regular study monitoring, independent study audits and additional safety monitoring by data and safety monitoring committees, as well as provision of continuous training for investigators and clinical research personnel. Such measures are effective in avoiding or minimizing certain risks.

14.1.2 Bodily injuries and deaths are among the most severe incidents that may occur in clinical studies in spite of the implementation of the aforesaid risk management measures. Such incidents may arise from or associated with:

(a) Adverse effects or manufacturing defects of investigational products;
(b) Wrongful or inappropriate design of study protocols;
(c) Violation of study protocols; or
(d) Negligence or malpractice of any participating party or personnel.

14.1.3 The costs, losses or damages arising from any claim in connection with any of the aforesaid incidents may be controlled

by transfer of potential liabilities to outside parties through indemnity and insurance.

14.2 Indemnity for Clinical Studies

14.2.1 An indemnity is a promise by one party (i.e. indemnifier) to another party (i.e. indemnitee) to bear certain liabilities on occurrence of certain specified events.

14.2.2 In a sponsored clinical study, the sponsor is the party who develops and owns all the rights in its investigational products and the study protocol. Obviously the sponsor has the responsibility to bear all the risks in association with its investigational products and the study protocol and shall indemnify the HA, the institution at where the study is conducted, the investigators and other study site personnel from any claim made based on any of the reasons referred to in sections 14.1.2(a) and 14.1.2(b) above.

14.2.3 The costs, losses or damages that may arise form the aforesaid claims may include:

(a) The medical costs for providing medical treatments and care to the affected human subjects;
(b) The legal and administrative costs for dealing with such claims; and
(c) The financial compensations for the affected human subjects or their family members.

14.2.4 It is important to note that claims arising from the wrongdoings of the investigators, other study site personnel or the institution, including protocol violations and negligence/malpractice committed by any of them, have to be borne by the respective parties and hence do not fall under the scope of indemnity

coverage by the sponsor.

14.2.5 Since November 2001 the HA has adopted a standard indemnity policy for sponsored clinical studies. Any sponsor that wishes to carry out a clinical study in any HA institution is required to enter into a standard indemnity agreement, and a fully executed indemnity agreement is a condition precedent to effectiveness of a REC approval for the study.

14.2.6 For investigator/institution-initiated clinical studies, however, the non-existence of external sponsors implies that indemnity by outside parties will not be available and therefore investigators and institutions have to rely on insurance as a risk transfer strategy.

14.3 Medical Malpractice Insurance

14.3.1 Medical malpractice insurance is a kind of insurance covering claims arising from bodily injury or death of patients or healthcare service users as a result of negligence or malpractice committed by medical institutions or medical personnel during performance of their medical duties. The HA is maintaining a general medical malpractice insurance policy covering its institutions and medical staff.

14.3.2 A major characteristic of medical malpractice insurance is that it is triggered only by negligence or malpractice. As outlined in section 14.1.2, claims in connection with clinical studies may arise from investigational products or study protocols, which have nothing to do with negligence or malpractice. It means that medical malpractice insurance is not sufficient to cover the potential liabilities arising out of clinical studies and coverage by separate clinical trial insurance is needed.

14.4 Clinical Trial Insurance

14.4.1 Clinical trial insurance is a special kind of insurance product offering "no-fault" coverage for clinical studies on a "claims-made" basis. It responses to claims for bodily injuries or deaths in relation to clinical studies rather than relying on negligence or malpractice as the triggers, and is able to cover liabilities associated with adverse effects or manufacturing quality of investigational products and designs of study protocols.

14.4.2 Since every sponsored study is covered by a standard indemnity in accordance with the HA's requirements, separate clinical trial insurance is not necessary.

14.4.3 The HA is not maintaining a general clinical trial insurance for covering investigator/institution-initiated studies. Individual institutions and investigators need to assess the risks underlying each investigator/institution-initiated study and secure suitable clinical trial insurance coverage wherever necessary. For instance, interventional studies usually carry a higher level of risk and arrangement for clinical trial insurance coverage is strongly recommended.

14.4.4 The exact clinical trial insurance coverage could be tailored to the specific conditions of each study and the specific needs of each investigator or institution. Investigators and institutions shall discuss with insurers to arrange insurance policies that are most suitable for their studies. Some important conditions that need to be considered include (but not limited to):

(a) Policy limits: The limits of indemnity provided by the insurer – for any one claim and in aggregate under the policy.
(b) Deductible or excess: The amount of money which is not

covered by the insurer and must be paid out of pocket by the insured party before the insurance coverage comes into effect.

(c) Period of coverage: The period during which any claim under the insurance should be reported to the insurer in order to warrant a valid coverage.

(d) Excluded events: Any specific event or circumstance that is excluded from the insurance coverage.

(e) Availability of legal liability extension: An extended coverage which covers compensations and legal costs incurred from litigations or formal legal proceedings (rather than by settlement only).

14.4.5 In order to secure and to maintain the validity of a clinical trial insurance, investigators need to submit any major updated study documents and information to the insurer, including (but not limited to) the study protocol, investigator's brochure and informed consent forms (including any subsequent amendments of such documents), as well as the progress of human subject recruitment and the latest study status. Failure to provide the accurate and updated information may jeopardize the validity of the insurance coverage.

14.5 Reporting of Claims

14.5.1 Investigators and institutions shall be responsible for reporting any claim or potential claim to the HA Legal Services Section and/or the insurers (as applicable) as soon as possible following the receipt of a claim or awareness of a potential claim. Failure or delay in reporting a claim or potential claim may jeopardize the validity of the relevant indemnity or insurance coverage.

15. Conflicts of Interest and Financial Disclosure

15.1 Concepts of Conflicts of Interest

15.1.1 A conflict of interest is the co-existence of multiple interests, where pursuing one interest could compromise the other. In the evaluation of such conflicts of interest, special attention should be paid to differentiate the following two related but different concepts:

(a) Potential conflict of interest: A situation where a party is involved in multiple interests that might come into conflict.
(b) Real conflict of interest: A situation where a party cannot pursue one interest without compromising another interest.

15.1.2 It is important to note that there is nothing intrinsically wrong with potential conflicts of interest. The key is how potential conflicts of interest could be prevented from transforming into real conflicts of interest, and how they could be avoided from being perceived by different stakeholders and the public as real conflicts of interest.

15.2 Conflicts of Interest in Clinical Research

15.2.1 In clinical studies, investigators are playing the key role in testing investigational medical products, procedures or methods on human subjects. Having the dual roles of a researcher and a medical practitioner, an investigator on one hand desires to pursue a successful clinical study and on the other hand has the

responsibilities to safeguard the rights, safety and well-being of human subjects and to ensure unbiased study designs and reporting of results. In sponsored clinical studies, the ties between investigators and sponsors, whether financial or otherwise, may create another dimension of potential conflicts of interest.

15.2.2 Significant interests of investigators that may potentially lead to conflicts of interest in clinical studies include (but not limited to):

(a) Proprietary interest in an investigational product (e.g. any form of ownership or any right in any patent, trademark or other intellectual property);
(b) Equity interest in an organization which has ownership over the investigational product or the results of a study (e.g. stocks and stock options of a sponsor);
(c) Financial payments or valuables in addition to the costs for conducting a study (e.g. honoraria and donation of equipment);
(d) Financial arrangements linking to the outcomes of a study (e.g. royalty interests in the sales of an investigational product); and
(e) Decision-making or consulting position in an organization which has ownership over the investigational product or the results of a study (e.g. directorship or scientific committee membership in a sponsor).

15.2.3 Disclosure of potential conflicts of interest is generally regarded as an effective way to avoid or minimize real conflicts of interest and is commonly practiced nowadays by many regulatory agencies, RECs and research institutions worldwide.

15.3 Disclosure Requirements by the U.S. FDA

15.3.1 The U.S. FDA has clear requirements about financial disclosure by investigators. Under the U.S. Code of Federal Regulations Title 21 Part 54 (i.e. 21 CFR 54), each investigator participating in a clinical study targeted at supporting an application for marketing authorization by the U.S. FDA (whether investigators within or outside the U.S.) is required to disclose the following significant financial interests in relation of a clinical study:

(a) Any financial arrangement linked to the outcomes of the study;
(b) Any financial payment or compensation of over US$25,000 in addition to the costs of conducting the study;
(c) Any proprietary interest in the investigational product; and
(d) Any equity interest in the sponsor that exceeds US$50,000.

15.3.2 In order to fulfill the above requirements, sponsors typically require each investigator to submit a financial disclosure form to disclose any of those significant financial interests or to certify the absence of such interests.

15.4 Disclosure Requirements by the Hospital Authority

15.4.1 In the HA, potential conflicts of interest is an essential element for review and approval of clinical studies by the Cluster RECs. Each investigator participating in a sponsored clinical study is required to declare any potentially conflicting interest to the relevant Cluster REC by completing an investigator's conflict of interest declaration form and include it in the initial clinical research ethics review application dossier. Potential conflicts of interest that arise during the period of the study, if any, shall also be disclosed actively by the investigator to the Cluster REC for consideration.

15.4.2 The presence of potential conflicts of interest does not necessarily prohibit an investigator from participating in a clinical study, provided that appropriate steps are taken to avoid any potential bias or impairment that may result from any of the disclosed interests. Cluster RECs have the authority to request investigators to provide more detailed information about any disclosed interest and to demand precautionary actions be taken to avoid occurrence of real conflicts of interest.

Part 4:
Resources Management and Quality Assurance

16. Resources Management at Study Sites

16.1 Overview of Resources Management at Study Sites

16.1.1 Clinical studies are complicated activities requiring utilization of different kinds of resources. Investigators, being the key persons holding the final responsibilities at study sites, shall manage such resources carefully in order to ensure successful initiation and completion of the clinical studies.

16.1.2 Resources management at study sites include (but not limited to) the following key aspects:

(a) Human resources management
(b) Facilities management
(c) Financial management

16.2 Human Resources Management

16.2.1 The conduct of clinical studies usually requires different kinds of expertise and a lot of manpower. Without a team of research personnel, the studies normally could not be carried out and completed properly.

16.2.2 A clinical study team usually consists of the following kinds of members:

(a) Principal investigator: A medical professional (usually a medical doctor) who assumes the role of a responsible leader and is holding the final responsibilities at a study site.

(b) Co-investigators: Other investigators (maybe medical doctors or other medical or scientific professionals such as radiologists, pharmacists, laboratory technologists and medical statisticians) who are responsible to and share part of the responsibilities of the principal investigator.
(c) Clinical research coordinators: Other research personnel (usually nurses or research assistants) who assist the investigators in coordinating and facilitating the operational and administrative duties in relation to a clinical study, such as scheduling study visits, completing case report forms, collecting blood specimens and performing certain study procedures as designated by the principal investigator.

16.2.3 The principal investigator shall ensure that sufficient manpower and expertise are available, during the entire study period, for the proper conduct and completion of the study, and shall have the authority to assign duties to his/her team members, provided that:

(a) An updated list of study team members is maintained and the main duties assigned to each of the members are clearly documented;
(b) All study team members are qualified by education, training and experience in the area of the study and in respect of the duties assigned, and such qualifications are documented in their respective updated curricula vitae and training records;
(c) All study team members are well-informed of the key elements of the study (such as the study design and the nature of the investigational products) and the requirements for the duties assigned; and
(d) The principal investigator is finally responsible for the performance of his/her study team members.

16.2.4 Special attention shall be paid to balancing study team members' regular duties under their employments and the clinical study duties assigned. If necessary, employment of short-term staff may be considered subject to availability of funding and approval by the institution's human resources department.

16.3 Facilities Management

16.3.1 An investigator shall evaluate the requirements of a clinical study in order to determine the necessary facilities needed for the conduct of the study, be it spaces, equipment or otherwise.

16.3.2 Use of facilities in an institution is subject to approval by the institution and/or the relevant departments. An investigator shall discuss with the responsible parties and obtain approval before committing to carrying out a study.

16.3.3 Investigators shall ensure that the facilities used in a clinical study are under appropriate maintenance wherever required. Maintenance records, if any, shall be kept properly.

16.3.4 For sponsored studies, a sponsor may supply to investigators and institutions with equipment or other facilities necessary for the conduct of a study. Investigators shall keep and handle such equipment or facilities with care and shall use reasonable efforts to safeguard them from accidental loss or damage.

16.4 Financial Management

16.4.1 The conduct of clinical studies may require extra financial resources that are not covered by the institutions' regular operating budgets. An investigator shall be responsible for financial management in respect of his/her clinical study in

accordance with his/her institution's policies and requirements, including (but not limited to):

(a) Budgeting for the study;
(b) Securing sufficient funding for running the study;
(c) Managing the incomes and expenses in relation to the study; and
(d) Communicating with his/her institution's finance department on administration of all financial transactions.

16.4.2 Investigators shall take into account all study-induced costs in budgeting for their clinical studies. In the event that a study is conducted in parallel to the patients' routine care in an institution, all extra costs incurred on top of standard care or routine clinical services shall be considered study-induced costs and additional funding shall be secured to cover such costs. Investigators shall discuss with the institution's finance department and/or the relevant service departments to assess the study-induced costs for study budgeting purpose.

16.4.3 Sponsorship or funding received from outside parties for supporting clinical studies, whether from commercial sponsors or other research funding bodies, are normally accounted as "alternative sources of income" ("ASOI") according to the HA's accounting system. Investigators shall report all study-related incomes to their institutions' finance departments and distribute the incomes according to the institutions' policies.

17. Retention of Study Documents and Records

17.1 Purpose of Study Documents and Records Retention

17.1.1 All clinical studies aim at collecting data to answer the research questions set out in study protocols. Clinical research is the basis of evidence-based medicine, and evidence must be supported by documentation. It is therefore important that major documents and records are properly kept during and after completion of a clinical study to allow verification, analysis and reporting of study results and data, as well as reconstruction and evaluation of clinical studies.

17.1.2 Investigators and institutions have the responsibility to retain documents and records that are used for or created from the conduct of clinical studies at their study sites. Such documents and records could be divided into two categories:

(a) Study specific documents and records: All the documents and records that are specifically used for conducting a clinical study or generated specifically for a study (e.g. study protocols, ethics submission and approval documents, case report forms and other worksheets used for collection of study data).

(b) Medical records: The medical records of human subjects (e.g. hospital patient records, medical charts, laboratory testing results and X-ray films) which carry the common identifiers (e.g. names, identity card numbers, dates of birth and genders) and therefore could be directly used to identify

individual subjects.

17.2 Records Retention for Investigator/Institution-initiated Studies

17.2.1 In Hong Kong, there is no regulatory requirement in respect of retention of study documents and records.

17.2.2 The Cluster RECs, however, require investigators to retain all study documents and records during each study and for a period of at least three years after study closure.

17.2.3 Medical records are the properties of HA institutions and therefore have to be kept in accordance with the HA's policies. The HA has developed a central electronic clinical management system which stores the large majority of the medical records for its patients. Paper medical records are retained in accordance with the Manual of Good Practices in Medical Records Management (version March 2009) issued by the Health Informatics Section of the HA Information Technology Services. In normal circumstances, hospital inpatient and specialist clinic outpatient paper medical records are retained for six years and general outpatient paper medical records are kept for three years after the last follow up of a patient. Radiological films are stored only for one to four years. Investigators and/or institutions should check from the updated version of the aforesaid manual from time to time for the latest arrangements.

17.2.4 Investigators and/or institutions shall determine for how long study documents and records should be retained. If extended retention of medical records is required, investigators shall communicate with the Health Information and Records Department of the relevant HA institution.

17.3 Records Retention for Sponsored Studies

17.3.1 The ICH GCP aims at the harmonization of regulations for clinical studies targeted at supporting applications for marketing authorization of investigational products by regulatory authorities, and therefore requires all study documents and records to be retained for at least two years after the last approval of a marketing application in the ICH region and until there are no pending or contemplated marketing applications in the ICH region or at least two years after the formal discontinuation of clinical development of an investigational product.

17.3.2 Since the ICH GCP does not specify a definite timeline for the retention of study documents and records, the requirement is difficult to follow in practice. For this reason, the industry now tends to set a defined archiving period, usually up to 10 to 15 years after study closure, which is generally longer than enough for fulfilling the ICH GCP requirement.

17.3.3 Investigators and institutions shall assess that whether or not there is sufficient storage space and proper mechanism established to fulfill the long-term archiving requirements of sponsors. In the event that such requirements could not be met, the following alternative arrangements may be considered:

(a) The sponsor may be requested to archive, on behalf of the investigator and the institution, the study specific documents and records in the sponsor's own storage facility or an independent third-party storage facility, provided that all such documents are placed and sealed in carton boxes at the study site before being transported to any outside storage facility and shall not be retrieved, transferred to another place, or accessed to for whatever purpose without

the prior written consent of the investigator or the institution.

(b) The sponsor may be requested to provide reasonable funding to facilitate archiving of such study specific documents and records in a third-party storage facility according to the sponsor's requirements.

17.3.4 Notwithstanding the above, it should be emphasized that medical records shall always be kept by HA institutions. Investigators shall coordinate with the Health Information and Records Department of the relevant institution for extended retention of medical records.

18. Monitoring, Auditing and Inspection

18.1 Quality Assurance through Monitoring, Auditing and Inspection

18.1.1 Compliance and data integrity are the key aspects reflecting the quality of clinical studies. To ensure compliance with relevant requirements and integrity of study data, the following measures are normally taken:

(a) Monitoring
(b) Audit
(c) Inspection

18.2 Monitoring

18.2.1 Monitoring is the act of overseeing the progress of a clinical study, verifying the proper documentation and reporting of study data, and ensuring that the study is properly conducted by the investigators and other research personnel in accordance with the study protocol and other relevant requirements.

18.2.2 For sponsored studies, monitoring is normally performed regularly during the period of study by study monitors (also commonly called clinical research associates) designated by a sponsor's clinical research team.

18.3 Auditing

18.3.1 An audit is a systematic and independent examination of clinical

study activities, documents and facilities, during or after completion of a study, to determine whether a study was conducted according to its protocol and applicable requirements.

18.3.2 For sponsored studies, an audit may be performed by an auditor of the sponsor's quality assurance department, which is independent from the clinical research team, or by an external auditor appointed by the sponsor.

18.4 Inspection

18.4.1 Inspection is the act by a regulatory agency of conducting an official review of documents, facilities, records and other resources related to a clinical study for the purpose of verifying the reliability of study data and compliance with applicable regulatory requirements.

18.4.2 In addition to the local regulatory agency which has the authority to perform inspection in relation to a clinical study, a study site may also be subject to inspections by overseas regulatory agencies (e.g. U.S. FDA) in the event that the study data are used for submission to such overseas regulatory agencies.

18.5 Investigators' Roles in Monitoring, Auditing and Inspection

18.5.1 For investigator/institution-initiated studies, investigators and/or institutions shall be responsible for establishing appropriate quality assurance mechanisms, such as monitoring and auditing, for safeguarding the quality of the studies.

18.5.2 In sponsored studies, investigators and institutions have the responsibilities to facilitate monitoring and auditing activities

reasonably requested by sponsors. The detailed arrangements may be agreed upon and documented in a CTA if deemed necessary.

18.5.3 Investigators and institutions shall also have the responsibilities to allow and facilitate inspections required by competent regulatory agencies according to applicable laws or regulations.

18.5.4 Since monitoring, auditing and inspection activities usually involve disclosure of human subjects' identities and personal data to monitors, auditors and inspectors, special attention should be paid in respect of personal data protection. Investigators shall ensure that the human subjects are fully informed of the requirements to allow access to their personal data by such designated persons for the purposes of monitoring, auditing and inspection, and that their express permissions are obtained through the informed consent process.

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