

CHAPTER 1

DEVELOPMENT OF THE ETHICAL GUIDELINES FOR RESEARCH IN HUMAN SUBJECTS IN THAILAND

1.1 Introduction

Nowadays, countries around the world, especially developed countries, have established human rights laws covering several aspects, including the law governing the conduct of researches in humans or animals. Developed countries also have attempted to stipulate regulations and guidelines for research in human subjects, and promote the adoption of the regulations/guidelines in developing countries, such as guidelines for manufacturing of pharmaceuticals or patent application. Prior to being accepted for publication or granted a patent, the scientific results derived from researches in human subjects are required to get ethical approval from an ethics committee. In addition, seminars, conferences have been conducted on the ethical principles or guidelines for research in human subjects in both developing and developed countries, the outcomes of which are several declarations. The most prominent and widely accepted and referred to is the Declaration of Helsinki of the World Medical Association (WMA), firstly adopted in Helsinki, Finland in B.E. 2507. The Declaration has been regularly amended to keep pace with advanced science and technology and social changes. The last amendment was done and adopted in Scotland in B.E. 2543. Later, several declarations concerning the conduct of a research in human subjects have also been adopted. The most essential element of those declarations is to protect the dignity, rights, safety, and well being of human volunteers or research participants.

Various institutions at national and international levels have been aware of the ethical issues of a research in human subjects. As a result, an ethics committee is appointed whose responsibility is to monitor that the research conducted within the institution is adherent to the ethical principles established in the Declaration of Helsinki or other declarations.

In Thailand, the Ministry of Public Health in co-operation with nine Faculties of Medicine had organized a series of seminars at the Faculty of Medicine, Chulalongkorn University. This resulted in the establishment of the Forum for Ethical Review Committees in Thailand or FERCIT. The FERCIT has served for the development of the plans for promoting ethics of research in human subjects. The Working Group was then appointed to draft the ethical guidelines for research in human subjects, which are intended to serve as the national guidelines. The national ethical guidelines were developed with the considerations of the ethical principles that have their origin in several international guidelines, such as the Declaration of Helsinki of the World Medical Association, the WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, the Council for International Organization of Medical Science (CIOMS), and the Canadian Ethical Conduct for Research involving Humans etc. The ethical guidelines has been published and distributed since B.E. 2545, and its English version was available in B.E. 2550.

1.2 Need for Research in Human Subjects

Research in human subjects is necessary for promoting scientific progress and building a better understanding in order to improve human's well-being. Researchers, universities, governments, and private organizations have various reasons for conducting or sponsoring researches in human subjects. Such reasons include, for example, alleviating sufferings from illness, evaluating social values or scientific theories, eliminating ignorance, analyzing policies, better understanding human behavior and related things. In summary, a research in human subjects serves 3 main purposes, i.e.,

1.2.1 To generate a new body of knowledge and new understandings;

1.2.2 To enhance scientific advancement that benefits the research subjects.

Through researches, the subjects may gain benefits from the development of new treatment, from new findings for their better living standard, from new discoveries, from writing, speech, and traditional culture, or from satisfaction in improving society;

- 1.2.3 Also, researches provide for benefits for a society at large or for certain groups of people or have influence on political behavior, which may lead to an improved health policy. The statistical information about the disease incidence may help to improve public health. The information about living conditions and behavior may lead to social development.

1.3 Objectives of the Ethical Guidelines for Research in Human Subjects in Thailand

- 1.3.1 To ensure that the dignity, rights, safety and well-being of subjects participating in research are protected, and the result of the researches are credible;
- 1.3.2 To serve as guidelines for researchers, ethics committees, organizations, institutions, and people who are related to research ethics;
- 1.3.3 To serve as a basis for an ethics committee to derive a standard operating procedure (SOP) for the review and approval of a biomedical research conducted within each institution.

1.4 Related Terms and Definitions

- 1.4.1 **Research in human subjects** means a research study, inquiry, interviews in social science, environments and environmental conditions, a clinical trial of pharmaceutical products and medical devices, a study of the nature of disease, the diagnosis of, the treatment of, the health promotion of, and the prevention of a disease which is related to humans or conducted in humans. Also, such researches include research studies using the information from patient's medical records or databases, laboratory specimens, body fluids, human tissues, and studies about the physiology, biochemistry, pathology, responses to treatment in physique, biochemistry, psychology of normal subjects and patients. These researches are collectively called **biomedical research**.
- 1.4.2 **Ethics Committee or Research Ethics Committee** means a committee appointed by an institution, an organization, or an agency whose responsibility is to review the ethical aspects of research studies and experiments in human subjects so that the rights, safety, and well-being of research subjects are protected. The ethics committee has been defined in the Medical Council's Regulation on the Preservation of Ethics of the Medical Profession (No. 5) B.E. 2545, Section 6. The ethics committee is also called differently, for example an Ethics Committee for Research in Human Subjects.
- 1.4.3 **Ethical Guidelines for Research in Human Subjects** mean ethical guidelines or criteria related to research studies or experiments in human subjects, for example, the Declaration of Helsinki and other ethical guidelines established by each institution.

1.5 Revision of the Ethical Guidelines for Research in Human Subjects in Thailand

Thanks to rapid advances in science and technology, the first version of the Ethical Guidelines published in B.E. 2545 cannot cover or keep pace with these advances. It is therefore necessary to revise the first Ethical Guidelines. The Medical Council of Thailand as a regulatory body has assigned the Sub-committee on the Promotion of the National Ethical

Guidelines for Research in Human Subjects to be in charge of the revision. The process was done by the Working Group for Revising the Ethical Guidelines, where the members of the working group were mainly from the Working Group for the Development of the Ethical Guidelines previously appointed in B.E. 2545. The Chairperson and the Secretary for the two Working Groups remain the same persons. Some new members joined in the revising working group, (Annex 10).

CHAPTER 2

ETHICS FOR RESEARCH IN HUMAN SUBJECTS

2.1 General Ethical Principles

Three basic ethical principles consist of:

First, **respect for person**;

Second, **beneficence**;

Third, **justice**

2.2 Principle of Respect for Person

The principle covers the following aspects.

- 2.2.1 Respect for human dignity. This aspect is the heart of research ethics, which provides for the protection of diverse interests relevant to the body, mind, and cultural security of a person. This is the foundation of the other following principles.
- 2.2.2 Respect for freely given informed consent. This means the subject needs to be fully informed of all aspects of the research without hidden or biased information by using an easy-to-understand language for the subjects. The information should cover the details of the procedures, rights, obligations, requirement for informed consent, and the freedom of decision making. Also, the subjects have the rights to withdraw the consent any time without giving any reason. In practice, the informed consent may appear in a form of conversation.
- 2.2.3 Respect for vulnerable persons. Respect for human dignity leads to an ethical requirement for vulnerable people who have inferior or lack physical capacities or have diminished capacities for making a reasonable decision, such as children, pregnant women, psychiatric patients, unconscious patients, and prisoners. These vulnerable people need to be protected from being forced to participate in a research involuntarily. In practice, a special treatment is needed for the protection of their benefits.
- 2.2.4 Respect for privacy and confidentiality. This principle is fundamental to the respect for human's dignity found in various cultures, and it helps to protect the security of mind. Therefore, the standards applied for the respect for privacy and confidentiality help to protect the access to, retention of, and distribution of personal information.

2.3 Principle of Beneficence

This principle covers the following aspects.

- 2.3.1 *Balancing between the risks and benefits*; An analysis of risks and benefits to be exposed to the subjects is a key ethical issue of a research in human subjects.

Research ethics in human subjects in modern times requires a balance between potential risks and benefits, with the desired goal being that the benefits must outweigh the risks and that the potential risks are acceptable for the subjects and received prior review and approval from an ethics committee. The analysis of the risks and benefits affects the welfare and rights of the subjects. However, sometimes the estimation of risks and benefits of all aspects of the research is difficult to achieve. Therefore, the key principle of respect for human's dignity always requires a proper and reliable research design, especially biomedical or health researches, which need prior research studies conducted in both laboratory and animal models to ensure safety. Moreover, it requires adequate review of the existing knowledge of the proposed research. Although, the analysis of risks and benefits may not be obvious in some research areas, such as political sciences, economics, or history (including a personal biography), the risks still remain as the research results may potentially destroy the credit or grace of an organization or individuals.

- 2.3.2 Minimizing harms; Researchers are required to protect the subjects from all possible harms or to minimize the dangers. The subjects must not be exposed to unnecessary risks. To achieve excellent scientific and social results, it is truly unavoidable to conduct researches in human subjects. The subject sample size should then be as small as possible, but still maintains scientific integrity, i.e., the smallest sample size adequate for a reliable statistical analysis of the results.
- 2.3.3 Maximizing benefits: The principle of beneficence relies on compassion, which mandates maximal benefits be entitled to others. This principle is actually supportive of the practice of researchers in certain professions, e.g. healthcare providers, psychologists, social workers, and educators. As mentioned above, the aims of a research in human subjects are to provide direct benefits to participating subjects and then to others or the society at large, or contribute to a scientific progress. Currently, most researches are primarily beneficial to society and the progress of science.

2.4 Principle of Justice

The principle of justice includes both fairness and equity. In term of procedural justice, a standardized procedure with a fair and independent review of a research protocol is required. Also, the justice intends to distribute both the burdens and the benefits of a research equally, which leads to the consideration that researches should not be performed simply to gain a scientific progress in vulnerable people who cannot protect their rights and benefits, as ever witnessed for several cases in the history. In addition, the subjects participating in a research should be entitled to a direct benefit from the research. The justice is then reflected by not neglecting or discriminating people or groups of people that may benefit the progress of the research.

CHAPTER 3

CONDUCTING RESEARCH ACCORDING TO THE PRINCIPLE OF RESPECT FOR PERSON

3.1 Informed Consent Process

Conducting a research in conformity with international standards requires correct and appropriate informed consent and invitation to be given to subjects. That is the process is not to force the subjects to participate in the research directly or indirectly without giving them a chance to be informed about the research procedures or giving no opportunity to make their own decision. Examples are that patients have a dependent relationship with physicians, or that physicians conduct experiments in patients using one or more medicines or new unproven treatment without informing the patients, or that payment or compensation in either money or gifts or the promise to give something beyond necessity is given, or that the instructions or explanation about research procedures are given in a technical language too difficult for the subjects to understand *etc.* In providing information or invitation to potential subjects to participate in a research, it is important to always adhere to the three ethical principles i.e., respect for person, beneficence, and justice.

In providing the information or invitation for decision making, the investigator may separate the documents into 2 parts i.e., the information sheet explaining research procedures, risks, benefits, what the subjects should be aware of in making their decision, and the informed consent form. The two parts can be combined into one, but it should cover the details of both parts. The language used should be suitable for lay persons to understand and cover medical information as appropriate, including legal and financial aspects of the study. The informed consent is not only to protect the research subjects, but also to protect the investigator, the sponsor, and the ethics committee. Therefore the investigator is responsible for preparing the details of the research procedures and the information sheet by himself/herself. In case the subjects cannot personally give a written informed consent, the informed consent given verbally with an impartial witness should be specified. In addition, it should specify in what case the legal guardian is to be informed and consented.

3.1.1 Advice for the preparation of the information sheet and informed consent form

The information sheet and the informed consent process to be given for the subject's decision making should contain the following elements:

- (1) the title of the study

- (2) an invitation describing why the subject should participate in the study;
- (3) the objective(s) and the research procedures that the investigator and the subject have to follow;
- (4) the duration of the subject's participation in the study;
- (5) the expected benefits of the study, which may directly benefit the subject, or the communities, or the society, or for gaining scientific knowledge ;
- (6) the plan for access to the products or the treatments that are proven from the research to be safe and effective for the subject or the community after the study;
- (7) the subject treatment, risks, discomforts, or any inconvenience that may happen to the subject (or others) participating in the study;
- (8) available alternative products or treatments that may be useful for the subject vis-à-vis the study product or treatment
- (9) the scope of confidentiality protection of the subject's records;
- (10) the disclosure policy for genetic study results at appropriate time;
- (11) the investigator's responsibilities (if any) in providing the services to the subject;
- (12) the availability of free medical treatment and care in case of study-related injuries or damages;
- (13) availability of payment/compensation for damages in the forms of either money or other offers for each subject (if any), and the type and quantity of which should be specified;
- (14) the funding resources, the sponsor, the participating institutions;
- (15) whether the results of the study will be disclosed to the subject and how;
- (16) whether the biological materials collected from the study will be destroyed; if not, the details of the storage and the plan for future use should be provided, and whether such a use is limited;
- (17) whether there would be any products derived from the biological materials collected from the study;
- (18) whether the subjects or their families or the persons under the subject's supervision will receive any compensation for the damage or death resulted from the study;
- (19) that the subject has the freedom to deny or withdraw from the study at anytime without losing any benefits, and must not affect standard treatments that the subject are normally entitled to;
- (20) that the study protocol has been reviewed and approved by the ethics committee for research in human subjects.

3.1.2. Practical guidelines that should be followed are

- (1) Obtaining informed consent is not merely having the subjects or their legally acceptable representatives sign on the consent form. Rather, the process should reflect a good relationship between the investigator and the subjects. The process should provide for full information sufficient for the subjects to make their decision. The investigator should pay attention to care and the physical and mental well being of the subjects during the course of the research.
- (2) The language used should be suitable to the subject's capacity and avoid technical terms;
- (3) The investigators must ensure that the potential subjects are aware of their participation in the study, and understand clearly the research procedures;
- (4) According to the principle of beneficence and non-maleficence, the researcher must inform in advance the subjects any procedures or treatments other than the diagnosis, treatments or prevention that are useful to the subjects. Advantages or disadvantages of participating in the study should be provided so that the subject can make their own decision;
- (5) Upon the completion of the study, whether the subjects are entitled to

continuous access to the medicines, the devices, or others should be specified.

3.2 Inducement

In recruiting the subjects into a study, the ethical principle that should be followed is that the subject should be invited to participate in the study. Please note that the words "invitation" and "volunteer" mean potential subjects are informed correctly, and voluntarily participate in the study. The information given should include both advantages, disadvantages to be incurred to the subjects themselves, to the community, or just for scientific benefits. The subjects should make their own decision, not be forced to do so, or are induced unduly. The subjects can also withdraw from the study any time. Several aspects of inducement that should receive considerations

- 3.2.1 Payment /compensation either money or other benefits to be given to the subjects should not be too much for the subject to decide to participate in the study without carefully considering the risks that may happen in the study;
- 3.2.2 For a phase I clinical trial usually conducted in normal subjects, the subjects would not obtain direct medical benefits from the study results. Therefore, it is necessary to compensate for travel expenses, loss of work or other payments, as appropriate. On the contrary, for a phase III study, the subjects usually obtain direct benefit from the study.
- 3.2.3 Enforced participation in a study may happen to institutionalized people, such as soldiers, prisoners, students who have to obey or cooperate with their corresponding authorities. In recruiting these people into a study, it is necessary that they are informed and are given opportunities to make their own decisions without any interference from the higher authority.
- 3.2.4 Payment given to investigators by pharmaceutical companies or sponsors in the form of money or other means that is excessive, or the payment methods, such as the given payment based on per head of subjects participating in the trial, may cause deviation in the way the investigator attempt to recruit the subjects as many as possible for their own benefit.

3.3 Privacy and Confidentiality Protection

No. 21 of the Declaration of Helsinki B.E. 2543 states, "The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information, and to minimize the impacts of the study on the subject's physical and mental integrity and on the personality of the subject."

3.3.1 Confidentiality protection

- (1) The subjects must be informed about the rights to have their personal information protected strictly.
- (2) During the informed consent discussion, the investigator must inform the subject in advance the measures used to protect their confidentiality before signing the consent form.
- (3) The subjects must sign on the informed consent form before the information is to be distributed in case the information can cause dangers to them.
- (4) The possible leakage of the research results containing the subject's confidentiality should be minimized to the lowest. In general, the best way to protect the subject's confidentiality is to remove the subject's identification from all stages of the study, and to control or restrict the access to the data.
- (5) The subjects should be made aware of the investigator's limitations in keeping their confidentiality. For example, the investigator has to transfer the subject's information from the case report forms to the national regulatory authorities or the sponsor. This also includes where there is a regulatory requirement to report

certain events, such as communicable disease, child molestation abuse, and child's negligence, directly to the responsible agency. Under these circumstances, the investigator must inform the subjects the limitations for keeping the confidentiality before the subjects participate in the study.

- (6) The subjects should be made aware of the social impacts having on them if there would be any leakage of the data. For example, if the subject's participation in the studies on AIDS medicines or vaccines is made public, it is risky for the subjects to be socially discriminated. Such risks should be carefully considered in the same manner as those being done for any treatment risks resulted from drug or vaccine studies.
- (7) In case where the ethics committee decides that signing in the informed consent form can be waived, the investigator should explore other means to protect the subject's confidentiality.

3.3.2 Confidentiality between physicians and patient subjects

The Declaration of Patients' Rights, issued by the four health professional associations and the Ministry of Public Health, states, "Patients have the rights to receive strict protection of their own information." Any disclosure of patient's information to anyone who needs the information, such as doctors, nurses, technical scientists, competent authority, or other researchers, can be made only if the patients or their legally acceptable representative give prior permission.

3.3.3 Data from medical records

- (1) In practice, it is quite difficult for a researcher who conducts a study using the information from medical records to have a patient's informed consent form kept in each patient's medical record either this is done by having patients sign the form in advance and keeping it in the medical record or by calling for patients to sign in later. In this case, therefore, the ethics committee may consider waiving for signing the informed consent form. However, the evidence should be provided to prove that the subjects are informed about the method for collecting the data. For example, the methods are included in the information sheet for patients being hospitalized, or the permission to use the data in medical records may be given from the hospital director or other authorized persons.
- (2) The collection of the data from the medical records must receive approval from the ethics committee, and the patient's confidentiality must be strictly protected.
- (3) The investigator is allowed to use the data from the patient's medical records only as specified in the research protocol.

3.3.4 Risks to Groups of People

Research results from certain fields such as epidemiology, genetics, and social sciences, whatever conclusions are reached, may cause risks to community, society, races or minors such as stigmatization, sin, or flaw. For example, the research results show that certain groups of people may be subjected to alcoholism at a greater rate. The investigator must take steps to protect the confidentiality of these groups of people both during the study and at the end of the study, including all related published articles. The ethics committee should review the impacts that may happen to groups of people, especially in a research study about people groups. Individual informed consent as well as community permission should be obtained.

3.4 Research Studies in Vulnerable Subjects

Vulnerable groups of people are those who need to depend on others, and are unable to express their opinion freely or to make their own decision. These include for example hospitalized patients, prisoners, children, the mentally impaired, critically ill patients, psychotic patients, pregnant women, and the disadvantaged. They are easily taken advantages of. As a consequence, the protection of vulnerable groups of people is of prime importance. Investigators should not select these groups of people simply because of easy management or convenience for the conduct of a research due to their economic or health constraints. However, if there would be a need to conduct a study in these people, some recommendations should be followed.

- 3.4.1 A irrefutable rationale for conducting a research in these groups of population should be clearly explained in the protocol.
- 3.4.2 Precautions against possible physical and mental harms should be exercised especially when the study is conducted in children.
- 3.4.3 The research procedures used in the study should be appropriate for the specific groups of these people.
- 3.4.4 In a study involving pregnant women, adequate information on the safety and impacts to the fetus should be available.
- 3.4.5 In a study involving minors, psychiatric patients, the incompetent, the informed consent should be obtained from their parents or legally acceptable representatives.
- 3.4.6 It should ensure that parents, guardians, or legally acceptable representatives are fully informed about the study.
- 3.4.7 The rights of the minors and the disadvantaged should be respected for their voluntary decision.
- 3.4.8 It should be shown that the research participants have a freedom in voluntarily participating in a research study, including for example a research study conducted in prisoners, inmates, and refugees.
- 3.4.9 Precautions against harms and protection of confidentiality should be strictly exercised when conducting research studies in subjects with illegal careers, such as sex workers or illegal drug users.
- 3.4.10 In case where a study is conducted in the vulnerable people without direct health benefit to them, the possible risks should not be greater than a minimal risk normally found in a general physical or psychiatric examination, or unless the research ethics committee allows for a greater-than-minimal risk.

CHAPTER 4

CONDUCTING RESEARCH ACCORDING TO THE PRINCIPLE OF BENEFICENCE

4.1 Nature and Scope of Risks and Benefits

The principle of beneficence requires that a research be justified to conduct in humans by an assessment of a favorable risk and benefit ratio. In the context of a research involving human subjects, the term "risk" means the possibility to get harm, whereas the term "benefit" denotes the thing that gives a positive value to health or well being.

Please note that benefits do not indicate the opportunity or the possibility. By this definition, a benefit is then opposite to a harm. An assessment of risk and benefit ratio requires the consideration of both probability and the dimension of possible harms and expected benefits.

The common types of harms that occur to the subjects include physical harms or injuries or psychological harms. In addition, there are other harms that may be overlooked such as legal, social, and economic impacts. Then, the types of the expected benefits may be consistent with the types of the potential harms that may happen.

Risks and benefits in a research may affect each subject directly, subject's family, and society at large, or special subject groups in a general society. Before initiating the study, an assessment of risks and discomfort that may happen to the subjects compared with the expected benefits is required. Please be aware that the rights, safety, and wellbeing of the subjects must prevail over the benefits of science and society.

4.2 Systematic Assessment of Risks and Benefits

In most cases, although it is very difficult to precisely assess a risk and benefit ratio because of the lack of a quantitative technique for such assessment, it is necessary to conduct the risk and benefit analysis systematically and reasonably as much as practicable. This can be done in practice by collecting and evaluating the data covering all aspects of the research, and other available alternatives should be considered systematically, which would help to evaluate the research precisely and rigorously.

4.3 Basic Guidelines for Justifying a Research Contain the Minimum Elements:

- 4.3.1 Whether there would be a real need to conduct a study in human subjects should be considered.
- 4.3.2 Brutal or cruel treatments to subject are not justified at all.
- 4.3.3 Risks should be minimized as much as possible, but still achieve the research's objective(s).
- 4.3.4 When a research involves a significant risk that can cause serious damages, special confirmations are needed in justifying the risk.
- 4.3.5 When a research is conducted in vulnerable people, rationale and need should be clearly explained and unavoidable.
- 4.3.6 The relevant risks and benefits should be clearly specified and fully provided in the informed consent form.

4.4 Additional Guidelines for Considering Risks and Benefits of a Research Protocol

- 4.4.1. An ethics committee needs to assess both risks and benefits. A research protocol should maximize benefits and minimize risks or harm.
- 4.4.2. A research protocol should demonstrate measures used to reduce risks, including preventive measures and immediate treatment measures once a harm occurs to a research participant.
- 4.4.3. If the benefits do not directly go to the subjects, such as new knowledge, a rigorous review on the proper and careful design of the research that is worth for potential risks is required.
- 4.4.4. For a research conducting in a community, a private sponsor should provide for health services to the community, as appropriate. Or in case a clinical drug trial is conducted with the conclusion that the new drugs are more efficacious than or equal to the active control drugs, the sponsors should provide the benefits to the participating subjects in the control group or in all groups by giving them the new drugs for a certain period after the completion of the study. The research conducted to explore a new indication not previously approved in the product leaflet must be done in comparison with the approved drug.
- 4.4.5 In case the subjects cannot personally give an informed consent to participate in the study, the risk that may happen must be a minimal risk. Otherwise, the

research with slightly greater than a minimal risk would be acceptable only if the research's objective(s) are important enough, and the research provides only good effects to the participating subjects.

The assessment of risks and benefits will be very useful to the individuals involving a research in human subjects. For the investigator, the assessment helps to check if the research is properly designed. For the ethics committee, it helps to determine if the risks and benefits that may happen to the subjects are justified. And for the research subjects, it helps to decide whether to participate in the research or not.

CHAPTER 5

CONDUCTING RESEARCH ACCORDNG TO THE PRINCIPLE OF JUSTICE

The selection of groups of people of communities into a research should be based on a fair distribution of burdens and benefits. Exclusion of any people or communities from any research should be justified.

According to the Thai Dictionary of the Royal Academy of Thailand B.E. 2542, the word "justice" (or *yutti-tham* in the Thai language) is defined as fairness, legitimacy, or reasonably justified, which is a widely known or often referred to definition. In the context of a research in human subjects, however, the term "justice" is referred to as distributive justice, which requires that both burdens and benefits to be entitled to the subject participating in the research be distributed equally. Therefore, the key questions of this principle are that who bears the burdens and who receives the benefits from the research. Injustice then occurs when the benefits that one is entitled to receive are denied unreasonably, or when the subjects have to bears the burdens unreasonably.

Since the principle focuses on the distribution of the burdens and the benefits to the subjects participating in a research study, the application of this principle in reviewing a research in human subjects is clearly made in the process of subject selection. Fairness must serve for the selection of the research participants in both the practical procedures and the outcomes. The justice in the subject selection is considered in two levels i.e., individual and society.

Regarding the individual justice in the subject selection, the investigator is required to include the subjects based on the criteria with fairness and non-discrimination, i.e., there should be no offering of benefits to the favorite group of people or recruit those who are not favored into a risky study. The social justice requires that differences must be made among groups of people that should or should not be included into a particular research study. In doing so, the capacities of individuals in the groups or communities who can bear the potential burdens in the study, or the suitability of the individuals to bear further burdens must be considered. The social justice then deals with setting an order or a priority that needs to be considered before enrolling any groups of people into any studies (for example, adult before children, male before female).

Likewise, the principle of distributive justice can also be applied at community and country levels, i.e., that which community bears the burdens, or which community takes the benefits must be in accordance with the principle of distributive justice as well. A common problem of injustice occurred at a community level is exemplified in case of the trials for product development of drugs, vaccines or medical devices that are sponsored by companies or organizations in developed countries. The trials are conducted in developing countries, but after the end of the trials, drugs or vaccines or medical devices under the studies cannot be made beneficial to the participating populations or countries. One of the causes is due to the lack of access to those drugs or vaccines because of their high cost, or no disease or illness for such drugs or vaccines in those communities in developing countries occurs. Thus, the principle must be carefully and thoroughly considered to bring the justice into all levels from the individual to the country.

However, please be aware that in reviewing a research in human subjects based on this principle, deviation from the principle of distributive justice may sometimes happen reasonably as well, but the differences of related factors such as experiences, sex, physical impairment, capacity, and position must be taken into consideration carefully and appropriately. This is to serve as criteria for decision making in the case that different treatments are given to individuals, and the consideration should be made on an individual basis.

CHAPTER 6

ETHICS COMMITTEE FOR RESEARCH IN HUMAN SUBJECTS

A research protocol involving human subjects must be subject to review and approval by an ethics committee for research in human subject before initiating a study. Thus, institutions or organizations where there are research protocols or investigators have to appoint and authorize the ethics committee in making a decision about the research protocol. The institution or organization should establish the regulations on the appointment of the ethics committee, the submission of a research protocol for ethical review, the criteria for decision making, and the monitoring of the procedures or the results of ongoing studies.

6.1 Operational Guidelines

6.1.1 The institution or organization where there are investigators or research studies that involve human subjects should establish its own ethics committee or jointly organize it with other institutions or organization(s). Also, the institution should provide for protection and support for the operation of the ethics committee so that the committee can fulfill its functions fairly, independently, and without any intervention from any parties.

6.1.2 Upon the establishment of the ethics committee, the institution or organization has to determine the committee's scope of responsibilities, relation with the investigators both inside and outside the institution. Also, the mechanism for reporting the summary of the committee's performance and the member's term of holding the office should be established.

6.1.3 The institution or organization should provide for the ethics committee adequate resources, including stationary supplies, facility, staff personnel, training opportunity, and payment/honorarium (if any) so that it can function efficiently.

6.1.4 The institution or organization (alone or in collaboration with other institutions) should provide for legal liability protection for the ethics committee.

6.1.5 The institution or organization not having its own ethics committee should arrange for a written agreement with other institutions or organizations having their own ethics committees so that the institution can have its personnel to serve as the committee's member and share legal and other liabilities, as appropriate.

6.1.6 The institution or organization should appoint the ethics committee by its highest authority. But the number of the sub-committees under the ethics committee may vary based upon the workload for protocol review so that the committee can function efficiently.

6.1.7 The main function of the ethics committee is to protect the rights and well being of the research participants, whereas the key role of each member of the committee is to independently decide if the protocol provides for adequate protection of the rights and welfare of the research participants.

6.1.8 The ethics committee should advise the affiliated institution or organization concerning a system for ethical training to be given to the investigators within the institution.

6.1.9 The ethics committee in cooperation with its institution or organization should establish a database of experts, both inside and outside of the institution/organization, who can provide their advice on specific issues to the ethics committee. An honorarium paid for the experts should be determined, as appropriate.

6.1.10 The ethics committee should establish the requirements for protocol submission along with the required documents, such as an application form, the number of copies of a research protocol to be submitted, subject's information sheet, informed consent form, case report form for instance, and should thoroughly communicate to personnel or staff within the institution.

6.1.11 The institution or organization by the advice of the ethics committee should develop standard operating procedures (SOPs) and revise them at an appropriate time interval.

6.2 Composition of Ethics Committee

6.2.1 The ethics committee should consist of at least 5 members both male and female, and with the following qualifications:

(1) At least one member who should have knowledge and experiences in the current research field(s) regularly reviewed by the committee (e.g., medicine, public health, social science, epidemiology, as appropriate) in order to ensure that the proposed research methodology of the protocol can yield the correct result of the research problem, or is scientifically valid;

(2) At least one member who should be a lawyer or endowed with knowledge of law.

(3) At least one member who is independent of the institution or organization, and is an outsider whose current job is not in the field of medicine, science, or law. If possible, that member should be drawn from the community where the institution or organization is located.

(4) At least two members should have knowledge or experiences in the current practices of patient's care, counseling, or treatment to people (e.g., physician, psychiatrist, social worker, and nurse, as appropriate).

6.2.2 The institution or organization should ensure that at least one third of the total committee members are knowledgeable in research ethics or have ever been trained about the human research ethics.

6.2.3 The institution or organization should make available a list of the committee's members showing names and qualifications, dates of appointment and of termination from the office upon the request of the investigators or others.

6.3 Appointment of the Member of Ethics Committee

6.3.1 The institution or organization should establish the composition of the ethics committee, the term of service of the members, and the criteria for selecting the members of the ethics committee, as appropriate.

6.3.2 Each member must be appointed officially as evidenced by a written document. In addition, the member should have a document that assures legal protection in case of legal liability during the course of the duty as the ethics committee's member.

6.4 Ethical Review Process

6.4.1 The ethics committee should review the ethical aspect of a research protocol in accordance with the current international ethical guidelines taking into account of local or national laws, religions, traditions, and cultures.

6.4.2 The institution or organization and the ethics committee should establish the regulations or the operating guidelines for the committee's meeting, such as frequency of the meeting, announced dates of the meeting, timeframe for protocol review, quorum requirements, decision-making procedures, communicating the decision, complaints process, reviewing fee (if any), protection of confidentiality of the protocol, prevention of possible conflicts of interests.

6.4.3 In case that the ethics committee cannot reach a definite decision on any scientific aspects, the committee may seek for other expert's opinions. But it must ensure that the experts have no conflicts of interest with the research protocol, and that the experts can maintain the confidentiality of the protocol. Otherwise, the ethics committee may forward the protocol to the scientific committee or the epidemiology committee or the other committees within the institution or organization, asking for their opinions before conducting the ethical review.

6.4.4. The ethics committee may communicate its decision upon the protocol review to the investigators in 4 categories namely:

(1) approval/favorable opinion;

(2) approval after the investigator amends or modifies the protocol or clarifies points according to the committee's suggestions;

- (3) the investigator needs to amend the protocol as suggested by the committee and resubmits it for the next review meeting, or the review is postponed for a moment;
- (4) disapproval/negative opinion.

The ethics committee is required to provide an explanation for its disapproval decision so that the investigator can clarify and request the committee to review its decision.

6.4.5. The ethics committee should establish a system along with a procedure for an expedited review of the research protocol that imposes a minimal risk, or of the protocol amendment with no additional risk. The committee should also establish the criteria for what research protocols could fit the expedited review.

6.4.6 The ethics committee should determine the types of the protocol that can be conducted with no ethical review submission.

6.4.7 The ethics committee should establish the conditions where informed consent discussion and/or signing a consent form can be waived.

6.4.8 The ethics committee should implement an efficient system for minute recording and archiving to allow for an audit upon a request and received prior permission from the head of the institution or organization or from a competent authority. The duration for document storage should be in accordance with the applicable regulatory requirements *mutatis mutandis*, but at least for 3 years.

6.5 Committee Member with a Conflict of Interest

6.5.1 In case one or more members of the committee have a conflict of interest (e.g., being a principal investigator of, or being on a list of investigators of the protocol under the review, or being a competitive investigator of similar research areas), those committee members should not participate in the review and approval process. They, however, can provide relevant opinions, and disclose their conflict of interest with the protocol. The committee should respect for the rights of the applicant to oppose.

6.6 Review of an Ongoing Research

6.6.1 After the committee has approved the research study, the investigators have to report the progress of the research to the committee at an appropriate interval. For a research protocol with high risks, the investigator should report the progress more frequently than a low risk protocol. The applicant should propose the committee how often he/she will submit a research progress report to the committee from the date of protocol submission for ethical review, but at least once a year.

6.6.2 Upon the termination of the trial protocol for whatever reasons, the investigator should report the summary of the research results to the committee.

6.7 Ethical Review of a Multi-center Trial

6.7.1 A multi-center trial may be referred to as a trial that is conducted in more than one institution or organization by a single or several investigators. It may also be defined as a trial conducted by a group of investigators from different institutions or from jointly collaborated organizations, and as a trial conducted by the investigators who later change their original affiliated institution or organization to a new affiliation.

6.7.2 The multi-center protocol submitted to each institution or organization should contain the same details and meaning of the text, and should specify the quality control techniques of the research procedures to ensure the same practices in each institution in order to obtain credible data.

6.7.3 The ethics committee in each institution or organization should be free to decide about the multi-center protocol, the outcome of which may not necessarily be the same as those of the committees in the other institutions. The research protocol should specify what part(s) of the protocol cannot be amended as it may affect the validity of the data and what part(s) can be modified by the committees as it does not affect the data as a whole. However, it is advised that the committee in each institution or organization consult among one another

in case of any possible different opinions about the main principle so as to reach a clear agreed decision. The investigator should amend the protocol's minor details as suggested by the committee in his/her institution.

6.7.4. The ethics committee of each institution or organization may accept entirely the decision made by other institutions or organizations, or accept only the scientific aspect, but requests minor amendment for the ethical aspect. This is to facilitate the efficient review and approval of the multi-center protocol.

6.7.5 The investigator should inform the ethics committee where the protocol has been submitted for ethical review as well as the review's outcome.

6.8 Monitoring of a Research

6.8.1 The institution or organization should appoint a committee independent of the ethics committee to monitor the progress of the research.

6.8.2 The purpose of the research monitoring committee is ensure that the research is complied with the proposed procedures specified in the protocol, and that the advice is given to the subject, as appropriate.

6.8.3 The research monitoring committee should establish its own criteria and mechanisms for monitoring the research protocol.

6.9 Termination or Suspension of a Research

6.9.1 The ethics committee may withdraw or suspend its approval given to the research so as to protect the rights and welfare of the research participants. For example, when serious adverse effects are reported, or when the conduct of the research is not complied with the protocol approved by the committee.

6.9.2 In case of premature termination of any research protocols made by the investigator, the reasons for the termination must be reported to the ethics committee.

CHAPTER 7

SPECIFIC TYPES OF RESEARCH in HUMAN SUBJECTS

7.1 CLINICAL DRUG TRIAL

A clinical drug trial is a study of drug in either patients or healthy people in order to study the therapeutic or preventive effects of the drug.

In general, an investigational drug used in the clinical trial falls into one of the 4 categories, namely: (1) new drugs; (2) unregistered drugs in Thailand (3) registered drugs by the national drug authority, but being studied in new doses or indications not previously approved; and (4) locally produced drugs which are required for their efficacy testing.

Phases of Clinical Drug Trials

For new drugs, adequate evidence derived from animal studies must be available to ensure safety and toxicity prior to conducting a study in humans.

A Clinical Drug Trail Can Be Classified in 4 Phases.

Phase I

This is a first-in-human trial using a new chemical entity that is usually conducted in healthy volunteers to study acute toxicity that is associated with the dose range of the drug. Because of drug side effects, the study should be conducted in well-equipped facilities in the hospital, and should not be conducted in children, the elderly, women with childbearing potential. Anesthesia or anticancer drugs should not be used in the healthy volunteers as a result of its high toxicity. Approximately, the number of the subjects should not exceed 30

subjects. Every subject should give a written informed consent before participating in the study. The study in this phase is usually an open study without any control group i.e., both subjects and investigators know the trial drug. Studies in the phase I also involves two stages. Stage I studies employ a small dose i.e., about 1/50 or 1/100 of the dose used successfully in the animal studies. When the results demonstrate safety, a second stage is then followed by gradually escalating the dose. Once the results are satisfactory, phase II studies are conducted.

Phase I trials also include the studies done in the patients suffering from a specific disease with no hope from currently available treatments, such as studies in terminally ill cancer patients.

Phase II

Phase II studies are conducted in patients with the target treatment of the drug that was satisfactorily studied in phase I. The primary objective of the trial in this phase is to study short-term pharmacological toxicity in details, while the secondary objective is about the drug's preliminary efficacy. Anesthesia and anticancer drugs are allowed in the phase II trials. If possible, a trial design should be randomized and open label. The subjects and investigators may not know whether the drugs received are investigational drugs or comparator drugs. Approximately, 100-200 subjects are employed in the phase II trials. If serious adverse events are reported frequently, the trials should be stopped temporarily. Once the safety is confirmed, a phase III trial can then be conducted.

Phase III

Phase III studies are conducted in patients with the target treatment using the new chemical entity being tested successfully in the phase II. The primary and secondary objectives are to evaluate the pharmacological effectiveness and to study a short-term toxicity, respectively. The number of the subjects in the phase II trials may considerably increase up to several thousands depending on sample size determination using a statistical method in conjunction with the existing preliminary data. Most phase III trials involve a comparative control group, which is usually the group receiving no investigational new drugs. In the phase III trials, control procedures are implemented beginning from subject selection, group randomization, treatment allocation, follow up, and evaluation. The trial in this phase is aimed to increase patient's survival or to improve patient's quality of life. Then, the trial design should be randomized, double blinded, i.e., both the investigators and the subjects do not know what drugs either investigational or comparator are given. When the drug gives the favorable results under the phase III trials, they are likely authorized for marketing.

Phase IV

This phase is also called a post marketing surveillance study. The study is done after the drug has been registered, with the objectives being to study the therapeutic uses, any adverse effects, and toxicity of the drug in a larger number of patients who have been using the drug for a longer period of time, or to explore additional effectiveness for other indications other than the approved ones. Also, the study in this phase can be done in other groups of population that have never been studied.

Ethical Considerations on Each Phase of the Clinical Drug Trial

7.1.1 Phase I Clinical Trials

- (1) The ethics committee should be independent of the trial sponsor, conduct a rigorous review of a research protocol, and continuously monitor the trial.
- (2) As the trial in this phase is conducted in healthy subjects where the sponsor of new drugs pay for the study, the ethical review should focus on the following aspects:
 - a. the subject sample selection;

- b. a freely given informed consent process;
 - c. the meaning of the message in the consent form;
 - d. the qualifications of the committee's members and performance of the ethics committee;
 - e. applicable regulatory requirements (if any).
- (3) Specific ethical considerations are needed for the review of the drug trial conducted in patients suffering from the illness with no hope from currently available treatments. As the conduct of the trial under this situation may distort the awareness of the patients, the family, and the investigator in weighing out the risks and the benefits of the trial, and may affect the freely given informed consent and the termination or the withdrawal criteria, therefore, both the investigator and the ethics committee should co-operate and consult each other throughout the course of the trial.

7.1.2 Phase II and Phase III Clinical Trials

Generally, the trials in these phases involve the use of a placebo as a control group. Placebo should not be used as a control group if standard treatments are available because the subjects will lose medical benefits from participating in the trial. In addition to the focus on the freely informed consent process, ethical considerations in a placebo-controlled trial should be paid attention to an appropriate design so as to maximize the benefits and minimize harms to patients.

7.1.3 Phase IV

The trial in this phase is usually conducted in the private practice of physicians who use the drugs already available on the market. Frequently, the sponsor pays the investigator based on per capita of patient recruited in order to study the side effects of drugs and to build acceptance in using the drugs among patients and other physicians. This case may impose an obligation to the investigator. Therefore, the investigator and the ethics committee should consider appropriate benefits and payment to be given to the subjects for their participation.

7.1.4 Clinical Trial of Medical Equipment

A clinical trial using a medical device for human use, either invasive or non invasive, requires similar ethical considerations as for the clinical drug trials in 4 phases, in particular the medical device that is to insert into the body. In such a case, a specific consideration is required depending on types of the devices. For example, the conduct of a trial using a cardiac pace maker, which is a very expensive device, requires a surgery to evaluate its safety and effectiveness. Considerations are also extended to the costs of the surgery and of a patent license requested by the device's manufacturer.

Slight differences between the clinical trials of drugs and devices can be noted. The ethics committee should pay attention to the differences as well, such as

- (1) A medical device for human use may not be tested previously in animal models such as retractors because of different human and animal anatomies.
- (2) Certain types of medical devices should not be studied in healthy human subjects because of the research procedures and/or the use of the device may impose extremely high risks and harms, but create no benefits to the subjects. For example, the trials using artificial joints, artificial cardiac valves, or a cardiac pace maker.
- (3) The clinical trial of a new drug is not regarded as a trial with a minimal risk because the mechanism of action may not be clear. As a result, it is impossible

to predict possible side effects. On the contrary, the trial using an external medical device which is known for its mechanism of action allow us to predict the possible side effects. The trial can be regarded as imposing a minimal risk. Details will be discussed later.

- (4) A comparative study using a medical device and a placebo or other comparators to evaluate the effectiveness or efficiency of the treatments may not be conducted because of ethical justification if the use of that device is the only opportunity for the subject to obtain the benefit from the treatment, such as the surgery to insert the artificial joint to replace the irreversibly impaired joints.

In general, a sham surgery in the comparator group is regarded as ethically inappropriate as it can greatly impose risks and harms to the subjects, while it provides no benefits to the subjects. The sham surgery, however, used in the clinical trial of a medical device may be conducted under certain circumstances of extreme necessity, provided that the risks must be minimized as small as possible and the subject must be given full and correct information before freely deciding to participate in the trial.

As mentioned above, in several cases, a medical device that has clear mechanisms of action may be designed by the physician who directly takes care of the patient. Or a device available on the market may be altered or further developed and used in the treatment for the patients hopeless from other available treatments. The investigator or the sponsor of this type of trial may get less financial support than that from drug companies in case of a clinical drug trial. Hence, the design of clinical study of a medical device to prove the effectiveness or efficiency and safety may be an observational study instead of a randomized controlled trial, which is a standard of a clinical trial of new drugs. The observational study allows for collecting the data completely and completing the follow-up for all patients for sufficiently long time. This is demonstrated by the study of artificial joints and cardiac valves that are widely recognized.

Systematic consideration of a research using a medical device may start from the division of the devices into two categories i.e., devices with minimal risk or non significant risk and devices with significant risk, by considering the general characteristics and the use of the devices.

Medical devices with significant risks are referred to as the devices that

- are risky to death upon usage;
- are risky to permanent disability upon usage;
- require a surgery or certain drugs to prevent from death and/or disability that may be caused by that device.

The risks related to the use of the devices also include the risks that are caused by the procedures and techniques used, for example, the risk caused by a surgery and general anesthesia used in the process of inserting the devices into the body.

If the device to be used in a research is similar to or has been used under the approved indications as that of the device available on the market, the advantages and disadvantages of the device to be studied in comparison with the available device should be considered.

For example, the conduct of a trial using an electrical pacemaker, despite its high risk, inserted into the patient's body which contain the property and usage not significantly different from those of the available device on the market may be ethically acceptable according to the principle of beneficence (see list of devices with classified risks in the annex)

Deciding if the trial of a medical device or the device itself falls into what types of risks is the responsibility of the human research ethics committee. If the committee decides that the trial and the device used impose a minimal risk, the trial of the device should pass ethical clearance according to the principle of

beneficence.

However, if the committee decides that the clinical trial of a device imposes a high risk, comparison should be made with similar devices available on the market. Just as exemplified previously, if the device to be used in the trial are greatly different from the devices on the market, the trial should be reviewed according to the general ethical principles applied in clinical trials taking into account of the specific characteristics of the trial of medical devices as explained earlier.

Finally, the investigator and the subject should always realize that the devices inserted into the human body undergo failure both in short and long term. The failure of the device may result in damages, even death. When there is such the event, the investigator is responsible for objectively reporting the event to the sponsor, the ethics committee, and the subjects.

7.1.5 Research Budget

The ethics committee should review a research budget to ensure that the issue of benefits has been taken into account. In general, the sponsor will pay the investigator based on a per capita of subjects. The payment calculated based on a per capita of the recruited subject is an ethical issue, because it is possible that the investigator has conflicts of thoughts between the payment to receive and good and appropriate health service to be given to the subject. This is the case in particular when the patient or the subject trusts the investigator.

Researches conducted in public hospitals or public health care facilities involve expenditures to cover such as laboratory tests, lump sum fees determined by the institution. The disclosure of the payment and the other budget items helps the ethics committee to evaluate the conflict of interest, and helps the investigator to decide whether to conduct the trial.

7.1.6 Placebo-Controlled Trial

It is generally unacceptable to use a placebo as a control group in a trial where standard treatments or medically proven medicines are available, because patients will lose medical benefits entitled to obtain from participating in the clinical trial. However, the use of a placebo as a control group may be allowed in the following cases.

- (1) no standard drug medically recognized for the treatment of the disease is available;
- (2) the available drug for the treatment yields uncertain outcomes;
- (3) the standard drug for the treatment is available, but it causes serious adverse drug reactions or adverse events that the subjects cannot tolerate;
- (4) the illness to be studied is recovered itself due to a placebo effect;
- (5) the disease to be studied is a minor condition and treating with the placebo causes the only discomfort or the illness is alleviated slower negligibly, and causes no serious or irreversible harm to the subjects;
- (6) there are compelling scientific and methodological reasons that are necessary to use a placebo-controlled group in determining the effectiveness and the safety of a study drug.

In addition to the focus on freely informed consent, the ethical consideration of a placebo-controlled trial should be paid on an appropriate design to maximize benefits and minimize harms to patients.

7.1.7 Analysis and Distribution of Research Results

In most clinical trials, the sponsor has the rights as agreed for the analysis and the interpretation of research results. However, the investigator and the ethics committee should ensure that:

- (1) The final analysis and interpretation of the research results will rest with the investigator to ensure that the results would be actually complete and accurate.
- (2) When the trial of phase I, II and III is required to stop according to the stopping rules, there must be an independent interim analysis. However, prior to implementing the stopping rules, it should be aware that either positive or negative long-term effects of the drug may be obscured by either good or bad short term drug effects.
- (3) The main responsibility of the investigator is to circulate the research findings to the community of investigators. However, it is found that frequently the research results of several trials, in particular the negative results, are not published or distributed. Not only does the case create an inappropriate scientific conduct and produce no actual research results, but also the research results and the resources invested in the research become in vain.

7.2 EPIDEMIOLOGICAL RESEARCH

An epidemiological research is an integral part of public health or health service researches, which are necessary for the prevention of and the control of diseases or for improving the efficiency and the performance of a health care system. This leads to the improved health of the population. Certain epidemiological researches may be required to study in a large population, and thus a multi-center study is needed.

The epidemiological research is different from other types of research in that it involves the use and the keeping of medical information and the tissue samples of patients or population. Then, there is a need for an ethical consideration for the use of the data or the tissues regardless of whether the data or the tissues would be stored for the purpose of the treatment.

Types of Personal Information

Epidemiological researches involve the use of the following types of data.

- a. identified data which are referred to as, for example, name, date of birth, or address, including such a minor detail as a zip code that may be used as an identifier;
- b. potentially identifiable, coded, reidentifiable data which are referred to as the data the identifier of which has been removed and replaced by a new code that can re-identify the individuals. They are then regarded as “identifiable data” ;
- c. de-identified, not re-identifiable, anonymous data which are referred to as the data that have been permanently removed their identifiers, and as a consequence, the data cannot identify any individuals if the existing identifiers are permanently destroyed or the data are collected without any identifiers.

7.2.1 It is required that all epidemiological researches be reviewed by an ethics committee, based on international ethical guidelines. In the epidemiological study that needs to use identified or identifiable data, the individual informed consent from each subject for his/her participation should be obtained. The ethics committee should ensure that:

- (1) the research is conducted according to the applicable policy / laws / regulations related to the personal rights, the privacy, and the disclosure of information, etc.
- (2) searching for medical records or other records or patients’ reports for research purposes should be restricted to only the investigators knowledgeable in the relevant fields or to the attending physicians.

However, research assistants may be allowed when there are many records to search for.

- 7.2.2 The ethics committee may approve for the search for identified or identifiable data from the records if the following criteria are fulfilled.
- (1) the informed consent process possibly causes excessive worries to the subjects or reduces the scientific value of the research, whereas the subjects or the relatives or the involved communities do not gain any benefits or the informed consent cannot practically be obtained;
 - (2) the research is conducted by the attending physician of the patients, and the risks are minimal, and the research is not involving any abnormality of the genetics;
 - (3) the public benefits is of high degree for the proposed research topic;
 - (4) the informed consent process possibly causes excessive worries to the subjects or reduces the scientific value of the research, whereas the subjects or the relatives or the involved communities do not gain any benefits or the informed consent cannot practically be obtained because of too many and too old the medical records, or it is difficult to contact for the informed consent; or
 - (5) the public interests from the research prevail over the private interests
- 7.2.3 When the ethics committee allows the use of coded identifiable data, it should be decided whether a third party should hold the code.
- 7.2.4 When the research is conducted in a community, it should be sure that the conduct is complied completely with the requirements on the research in community.
- 7.2.5 When the identified or the re-identifiable data are used in a research, the ethics committee should ensure that the collection of, handle of, and storage of the data are complied with the principle of rights of personal information. If the data are to be used for purposes other than those specified in the approved protocol, a new protocol should be submitted for ethical review.
- 7.2.6 If the research involves the linkage of a set of data, the ethics committee may approve for the use of the identifier to assure the correct linkage. When the linkage is finished, the ethics committee should require that the emerging data be coded or the identifier be removed.
- 7.2.7 If the identified or identifiable data are used for other purposes in the research or by other people other than those listed in the previously approved protocol, a new protocol needs to be submitted for ethical review.
- 7.2.8 The information derived from the epidemiological researches both short- and long-term should be securely kept from the access of unauthorized people.
- 7.2.9. When screening the data for the statistical analysis and conclusion, the investigator should maintain the confidentiality of the research participants.
- 7.2.10 The research results should not be published in a manner that can identify the individuals participating in the research and can affect the cultural or other sensitivity.
- 7.2.11 If the emerging new knowledge during the course of the research has clinical implications or indicates the adjustment of the current treatment, the new knowledge should be disclosed to the relevant competent authority. If possible, both the research participants and the attending physician should be informed as well.

7.3 SOCIAL SCIENCE RESEARCH

Similarly, the ethical principles applied in a social science research consist of the principles of respect for person, beneficence, and justice.

- 7.3.1 The investigator should protect each subject from any physical or mental harm.
- 7.3.2 The investigator should respect for the faith, belief, culture, religion, and basic rights of the subject.
- 7.3.3 The investigator should conduct only the research that benefits mankind.
- 7.3.4 The investigator should ensure that the design of the study is suitable to the objectives of the study.
- 7.3.5 The investigator should fully inform the subjects so that they can freely decide whether to participate in the research.
- 7.3.6 The investigator should protect the confidentiality and undisclosed names of the subjects.
- 7.3.7 The investigator should provide for health care to the subject as maximum as possible.
- 7.3.8 If the inclusion criteria are sensitive issues, the investigator should carefully conduct the study to avoid the disclosure of the subjects' identity. The investigators may sometimes conduct the study in a non-targeted population to prevent the members of the community from being aware of what is conducted.
- 7.3.9 In case the study is conducted using the medical record consisting of the confidentiality of patients, only the authorized medical personnel are allowed to access to the data in the records, which can identify the patients. The access should be permitted by the highest authority of the institution.
- 7.3.10 The investigator should provide for an appropriate payment, benefits, or privileges to the subjects, and ensure that it should not be too much to induce the subjects to participate in the study.

7.4 VACCINE TRIAL

The guidelines for conducting clinical drug trials are also applied to vaccine trials. However, the phase of the vaccine study may have additional details as explained below.

- 7.4.1 Phase I: This is a first-in-human trial to study the safety and biological effects, in particular the immunogenicity of a vaccine. Doses and route of administration will be studied in this phase, and the trial is conducted in a low risk population.
- 7.4.2 Phase II: The trial is conducted in a limited number of patients to firstly explore the efficacy of a vaccine. The vaccine trial also serves for preventive purposes. Therefore, the trial involving a preventive vaccine must be conducted in healthy volunteers, while the trial involving a treatment vaccine is done in the patients of targeted disease.
- 7.4.3 Phase III: The trial in this phase focuses on the effectiveness of a vaccine for disease prevention. More subjects are then needed for the study in this phase (a thousand subjects and up). The trial is usually a multi-center trial, including a control group.
- 7.4.4 Precautions in a vaccine trial where the vaccines are produced from live-attenuated microorganisms should be exercised as the vaccines may cause infection in the subjects, despite its low possibility. Therefore, it is essential to inform the potential subjects in advance about the risk. The subjects in the control group not receiving the real vaccine must also be protected from the disease or be informed that they have a chance to contact the disease from the experimental subject group.
- 7.4.5 In case of the trial using a recombinant DNA vaccine, the adverse effects of which are not yet clear, the investigator has to strictly follow the regulation of the Ministry of Public Health.

7.5 USE OF HUMAN TISSUE SAMPLES

Human tissue samples mean anything being taken out or excreted from a human body or a corpse. The tissue samples also include other tissues, blood, secretion, and excretion from all organ systems. The objective of using the tissue samples is for diagnosis of a disease or for serving other purposes.

The human tissue samples may be obtained by one of the following means e.g.,

- a. being taken directly from the body of the subject for the research's use where the donors of the tissues give the informed consent;
- b. being taken from the body for treatment, diagnosis, or other objectives (e.g., learning and teaching, organ donation for transplantation);
- c. from either of the aforementioned sources above, and have been kept under the applicable regulatory requirements or the institutional regulations or by the subject's approval. In this case, the donors of the tissue samples usually do not know the objectives of the use of the samples of future research.

In a research protocol that uses the human tissue samples, the ethics committee should review it according to the international ethical guidelines at least those as described below.

7.5.1 Prospective studies

The investigator should do the followings.

- (1) obtain the written informed consent to use the samples from the donor or giver of the tissue samples or from the legal owner of the corpse;
- (2) provide detailed information to the donor or giver of the tissue samples or legal owner of the corpse about the objectives of the use of the samples in research or the overall research plan. The information sheet should specify the possibility or the plan to use the samples for future research, storage duration of the samples, and the rights of the subject to request for destruction of the samples when the research is complete;
- (3) collect the samples from the body of the owner by a specialist with correct and appropriate medical practice;
- (4) utilize the technique and system for the storage of the tissue samples that are appropriate and secured from the access by unauthorized persons;
- (5) use the appropriate data recording, storing, and retrieving system that ensure the protection of the confidentiality of the owner of the tissue samples;
- (6) appoint a personnel staff responsible for the handle and storage of the tissue samples;
- (7) The institution or organization that allows the use of human tissue samples for research purposes should lay down the guidelines for the conduct of the researches using the tissue samples and for the ethical review and approval of the research protocol. The guidelines should be in compliance with the applicable laws and regulations, and the institutional ethical guidelines should provide detailed procedures and possible conditions for the use of the tissue samples in the research. The guidelines will be used for the investigator to follow when asking for the subject's donation of the tissue samples used in the research, and for the ethics committee to review the protocol taking into consideration of the international ethical principles i.e., respect for person, beneficence, and justice;
- (8) A material transfer agreement should be made in case the tissue samples are

transferred to other institutions to ensure the consistence with the principle of respect for person.

7.5.2 Retrospective Studies Using Stored Human Tissue Samples

- (1) The institution and the ethics committee should established the rules and regulations that determine what circumstances the investigator can waive the informed consent from the owner of the tissue samples so as to use the stored samples for the research;
- (2) Whenever a physician has received a human tissue sample for purposes of the treatment or diagnosis of the patient's disease, the physician should make best attempt to maintain the confidentiality of the patient. When the research is conducted using the stored tissue samples, searching for the patients or the patients' information should be made as least as possible and as necessary as for achieving the research objectives only.
- (3) If the results of the research may affect the health of patients, the ethics committee may require the investigator to search for the patients and contact them for treatment or follow-up;
- (4) Under certain situations, the ethics committee may agree for the waiver of the informed consent from the tissue owners in using the stored tissue samples for the research by taking into considerations of:
 - a. the modes of obtaining the tissue samples (e.g., from pathology storage, blood bank);
 - b. the scope and content of the informed consent given previously by the owner of the samples (if any);
 - c. the reasons behind the waiver of the informed consent by the investigator, including difficulty of obtaining the informed consent;
 - d. the possibility that the process of obtaining the informed consent may violate the privacy of the owners of the tissues, or cause damages to the physical and/or mental health of the donor or to the donor's social status;
 - e. the proposal to protect the privacy and confidentiality of the tissue owners;
 - f. the risk that may happen is a minimal risk;
 - g. the relationship between the previously approved protocol and the new protocol;
 - h. the potential commercial benefits or intellectual property;
 - i. the regulatory requirements.
- (5) A material transfer agreement should be made in case the tissue samples are transferred to other institutions to ensure the consistence with the principle of respect for person.

7.6 HUMAN GENETIC RESEARCH

A human genetic research is the study of genes and their interactions with the surrounding factors that affect the health of individuals and a population. Not only does the research enlarge the body of knowledge that impacts the individual's health, but it may also affect the health of the individuals and their families in the future, which paves the way for the protection from genetic diseases.

Regarding the ethics in human genetic research, there are some additional elements that need to be considered apart from those applied for other researches involving human subjects because of the specific nature of this type of research. For example, the cooperation of the subjects and their families is very much needed for a genetic research, and the data or the research results collected from one family may not only benefit those who participate in the research, but also those who do not directly join the research, but they are the relatives of the subjects involving in the research. Therefore, in certain situations, those relatives have to be informed of the data collected from the other related groups for the benefit of their own families' health care, such as a married couple who pays attention to the health of their unborn baby.

In addition, the information generated by the results of the human genetic researches may directly impact the subjects, e.g., causing social stigma or being treated with discrimination. Therefore, the investigator should be aware of these potential impacts, and should have measures for solving the problems that may arise. The procedures for strictly protecting the subject's privacy and the confidentiality of the data should be implemented.

Generally, it should be aware of the following important considerations when conducting the human genetic researches.

7.6.1 Individuals, Families, and Biological Relatives:

- (1) The investigator should provide the information and obtain the individual informed consent from relevant people.
- (2) The outcomes of the research are to be disclosed to appropriate persons for free of charge (appropriate persons mean the research participants who inform in advance that they need to know the results).
- (3) The human genetic researches are often conducted in the groups of families or in the communities that are related one another, e.g., the study of a family tree or history or the linkage study on the same chromosome. In case that the study causes a conflict between the family members, the investigator must take responsibility for solving the problem by communicating and informing correctly and honestly the information regarding the purposes, benefits, and disadvantages of the research to the families in question.

7.6.2 Privacy, Confidentiality, Loss of Benefits, and Danger

- (1) The investigator and the ethics committee should ensure that the confidentiality and the results of the genetic research be securely kept from unauthorized

access by a third party, such as employer or insurance companies.

- (2) The investigator studying about the family's or population's genetics should review the scope of possible physical and mental impacts that may happen to the relevant persons, and demonstrate those to the ethics committee.

7.6.3 Genetic Counseling

The investigator and the ethics committee should ensure that the research protocol provides correct and appropriate genetic counseling for the potential subjects.

7.6.4 Genetic Alterations

A genetic alteration of a human embryonic cell or a human gamete is regarded as violation of research ethics. The research study on gene alteration then must not be approved, except for the gene therapy that may need to be considered on a case by case basis if it would receive ethical approval for the research.

7.6.5 Eugenic Concern

The objectives of the human genetic research are related to improved knowledge and understandings of genetic diseases that may affect human health only, including health care, and not for eugenic purposes. And it should be aware of the subjects' free decision making on the problems that may arise, in particular for the married couple who needs to make a decision after being formed about a risk imposing the intrauterine fetus to develop a disease. The investigator should provide moral support for the married couple who decides to carry on the pregnancy after they are aware that the fetus would develop a disease.

7.6.6 Banking of Genetic Materials

Although establishing a bank for collecting genetic materials is expected to benefit the future, it may impose risks to individuals who are the owners of the genetic materials and their families. Therefore, the followings are recommended.

- (1) The investigator involving the storage of the genetic materials in the bank should demonstrate the ethics committee and the subjects the operating procedures used for keeping the confidentiality, the privacy, and the retention of the materials as well the data and the research results.
- (2) The duration of storing the genetics materials should be specified, including the operating procedures for destruction of the materials upon completing the storage time.
- (3) The duration of storing the genetics materials should be specified, including the operating procedures for destruction of the materials upon completing storage time. Uses of the materials for the purposes other than those specified in the approved protocol should receive the informed consent from the research participants or their heir. And their families are able to contact for the data or for the withdrawal from the research at anytime without any conditions.

7.6.7 Commercial use of genetic data

The investigator must specify the commercial benefits that may be derived from the results or the data of the research using human genetics in a research protocol to allow the ethics committee and the subjects to be aware of.

7.7 RESEARCH ON HUMAN GAMETES, EMBRYO, EMBRYONIC STEM CELL, AND FETUS

Researches using advanced reproductive health technology have influenced on the practices of research ethics, researcher's ethics, and people at large. The regulation issued by the Medical Council, by the advice of the Royal College of Obstetrics and Gynecology of Thailand, has already laid down the medical practice guidelines on the standards of services concerning reproduction technology. In addition, in conducting the research involving human gametes, embryo, and fetus, the risks imposed to the embryo or fetus, the informed consent, and the respect for the rights of the embryo and fetus should be considered. The following criteria should then be considered.

7.7.1 Research involving human gametes

- (1) Obtaining the informed consent from the owners of the gametes is required in the researches using the human gametes, which follows the principles and practices applied in other researches involving human subjects.
- (2) The collection of the human gametes from a deceased person is not allowed, as the informed consent from the donor of the gametes cannot be obtained. If there would be any research conducted using commercialized gametes, or inducing artificial cross-fertilization between the human gamete and an animal gamete, this is unethical.

7.7.2 Research on human embryo and embryonic stem cells

- (1) The fertilization of human gamete results in an embryo, and it is unethical to create the human embryos merely for research purposes. However, if the research is conducted for the benefit of reproductive health according to the principles and practices mentioned previously, it would be considered ethical.
- (2) Researches on alteration of human genes or the internal compositions of the human gametes or in the human embryo must not be conducted. When the research using an embryo is conducted, while no information about the future problem being likely to happen to the fetus is available, the embryo must not be implanted in the uterus to induce pregnancy. The experiment on the human embryo is allowed within the period of fourteen days after its fertilization.

- (3) A human cloning research for reproduction is not approved. Also, induced cross-fertilization between the human gamete and an animal gamete is unethical.

7.7.3 Research involving intrauterine fetus

Researches designed for the diagnosis or treatment of the intrauterine fetus that suffers from genetic diseases or congenital anomaly could be conducted if the mother has given her consent after being thoroughly informed about the treatment in detail, since the diagnosis or treatment of the fetus cannot be done separately from that of the mother, and both need to be treated simultaneously.

7.7.4 Research involving the use of fetal tissues, placenta and its blood

A research that uses fetal tissues must be conducted in accordance with the ethical principles as applied in other human experimentations. The fetus is a human, not merely tissues. Therefore, obtaining the informed consent from the parents, who are considered the legally acceptable representatives of the tissues, is required.

The conduct of a research using the fetal tissues to generate stem cells must adhere to the practice guidelines established in the Medical Council's Regulation on the Preservation of the Ethics of Medical Profession (NO. 6) B.E. 2545, Section 9 on the Medical Practice of Blood Stem Cell Transplantation from Donors.

ANNEXES

ANNEX 1

THE MEDICAL COUNCIL'S REGULATION ON RESEARCH STUDIES AND EXPERIMENTS IN HUMAN SUBJECTS B.E. 2525

1. **“Research study and experiment in human subjects”** refers to a research study and an experiment using a pharmaceutical product or medical devices, or a study of a natural course of a disease, or the diagnosis, treatment, health promotion, and prevention of a disease which is conducted in human subjects. This also includes a research study conducted using the information from medical records and any specimens taken from the human body.

“Ethics Committee” refers to a committee or board appointed by an institution, organization, or agency, which is responsible for conducting an ethical review of researches and experiments in human subjects. This is to protect the rights, safety, and well being of the subjects who participate in the researches and experiments.

“Ethical Guidelines for Research Studies and Experiments in Human Subjects” refer to ethical guidelines or ethical principles for researches and experiments in human subjects, such as the Declaration of Helsinki and any ethical guidelines for a research study in human subjects established by an institution.

“Ethics for Researchers,” refers to the Ethical Guidelines of the National Research Council of Thailand.

2. Medical practitioners who conduct a research or experiment in human subjects must obtain informed consent from potential subjects, and ready to protect the subjects from any harm that occurs from the experiment.

3. Medical practitioners must treat the subjects in the same manner that they treat a patient during the course of the medical practice as applied *mutatis mutandis* by Section 3 of the Council's Regulations.

4. Medical practitioners must be responsible for the dangers and damages that happen to the subjects in the experiment and such dangers or damages are not due to the subjects' mistakes.

5. Medical practitioners who conduct or participate in research studies or experiments in human subjects can initiate the research studies only if the research or experimental proposals have been reviewed and approved by an ethics committee.

6. Medical practitioners who conduct or participate in research studies or experiments in human subjects must adhere to the **Ethical Guidelines for Research Studies and Experiments in Human Subjects and the Ethics for Researchers**.

ANNEX 2

THE MEDICAL COUNCIL'S REGULATION ON THE PRESERVATION OF THE ETHICS OF MEDICAL PROFESSION B.E. 2545

By virtue of Section 21 (3) (๙) and with the approval of the Special Council of Chairman according to Section 25 of the Medical Profession Act BE 2525, which contains some provisions that restrict the rights and freedom of individuals, however, Sections 29 and 50 of the Constitution of the Kingdom of Thailand allow the act according to the provisions of the Act. The Medical Council Committee hereby issues the regulation as follows.

1. This regulation shall be called, "the Medical Council's Regulation on the Preservation of the Ethics of Medical Profession (No.6) B.E. 2545"

2. The following statements shall be added as Section 9 of the Medical Council's Regulation on the Preservation of the Ethics of Medical Profession B.E. 2526.

"Section 9"

Medical Practice involving Blood Stem Cell Transplantation from Donors

1. In this Section

“Blood Stem Cell Transplantation” means the medical practice that involves blood stem cell transplantation from bone marrow, blood, or placenta’s blood.

“Donors” mean an individual who donates blood stem cells or placenta’s blood for the blood stem cells transplantation to other people.

2. Medical practitioners who conduct the blood stem cell transplantation shall have the following qualifications.

- (1) being a hematologist or hematological pediatrician who has received a certificate or diploma from the Medical Council; or
- (2) being either an internist or a pediatrician who has been trained in a blood stem cell transplantation course approved by the Medical Council.

3. Medical practitioners who conduct the blood stem cell transplantation shall have additional qualifications apart from those described in 2 if the donors and the recipients of the stem cells are unrelated donors.

- (1) having experiences in the bone marrow transplantation not less than 2 years;

and

- (2) having been certified by the Subcommittee on Blood Stem Cell

Transplantation

4. There shall be a Subcommittee on Blood Stem Cell Transplantation consisting of one representative from the Bone Marrow Transplantation Association of Thailand, one representative from the Hematology Association of Thailand, one representative from the National Blood Center, Thai Red Cross Society, and a total of at least 4 but not more than 5 representatives from the institutes experienced in the bone marrow transplantation with one representative being from each institute, and 2 members of the Medical Council.

The Subcommittee in the first paragraph shall have the following authorities.

- (1) certify the medical practitioners according to 3.
- (2) revoke the certification in case the medical practitioners are not qualified or do not comply with the criteria established under this Section

5. The Subcommittee on Blood Stem Cell Transplantation shall grant the certification of the medical practice described in 3 according to the following criteria.

(1) the medical practice is done in a clinic where the number of patients under the bone marrow transplantation from brothers and/or sisters with the same HLA not less than 10 patients annually;

- (2) the medical practice is done in clinics which have the following qualifications

2.1 having other medical specialists e.g.,

(a) pediatrics and /or internists in cardiology, infectious disease, gastrointestinal disease, kidney disease, and pulmonary disease;

(b) surgery;

(c) blood bank

2.2 having permanent nurses at the bone marrow transplantation ward

at the proportion between nurses and patients not less than 1:3

2.3 other components

(a) having a separate room for the treatment of patients with low white blood cells

(b) having an intensive care unit

(c) able to provide laboratory testing and radiology for 24 hours

(d) able to provide blood and blood component infusion for 24

hours

6. In case the bone marrow or blood stem cell transplantation is to be done where the donors and the recipients are not biological relatives, the National Blood Service Center, Thai

Red Cross Society, shall make a donor registration list by establishing the National Stem Cell Donor Program under the supervision of the Medical Council.

7. In blood stem cell transplantation, the medical practitioners who conduct the transplantation shall comply with the following criteria.

(1) conduct a physical examination of the donor to check if he/she is healthy, and is suitable for donating blood stem cells

(2) inform and explain the donors of possible risks of harm that may occur to the donors both during and after the donation. Once the donors understand and are willing to donate the stem cells, then the donors sign an informed consent form for donating the blood stem cells. The written informed consent form is attached to this regulation.

In case the blood stem cell transplantation is done using the blood from the umbilical cord, the donor or her husband shall sign the informed consent form.

(3) written document shall be made to show that no payment is given to the donors of blood stem cells.

8. The medical practitioners who transplant the blood stem cells can store the blood stem cells in the laboratory for future transplantation, as appropriate.

3. This regulation shall come into force when the period of 60 days after the publication date in the Government Gazette has lapsed.

It is hereby announced.

Given on the Thirtieth Day of April B.E. 2545.

Somsak Lohlaekha, M.D.
Chairman, Medical Council

ANNEX 3

THE MEDICAL COUNCIL'S ANNOUNCEMENT NO. 21/2545 ON THE STANDARDS OF SERVICES INVOLVING REPRODUCTION TECHNOLOGY (NO.2)

As the Medical Council had issued the announcement no. 1/2540 dated 22 October B.E. 2540 on establishing the standards of services involving reproduction technology by medical

practitioners, it is now time to additionally establish the standards of services to provide for more appropriate protection to service receivers.

By virtue of Section 21(1) of the Medical Profession Act B.E. 2525 where the Act contains certain provisions that restrict the rights and freedom of individuals, however, Sections 29 and 50 of the Constitution of the Kingdom of Thailand allow for the act according to the provisions of the Act. The Medical Council then reached its resolution at the 10/2545 meeting dated 11 October B.E. 2545 to issue the announcement as follows.

1. The following statements shall be added as no. 4/1 and no. 4/2 of the Medical Council's Announcement No. 1/2540 on Standards of Services involving Reproduction Technology dated 22 October 2540 as follows.

"No. 4/1 The services involving reproduction technology shall not be conducted in a way of human cloning for reproduction.

No. 4/2 Medical practitioners who are responsible for the services according to (3), or are the providers of the services involving the reproduction technology shall maintain the standard of services that involve the donation of male or female gametes or an embryo to be employed in a reproductive process as follows.

- (1) In case a married couple would like to have a baby by having his wife to carry out pregnancy, the medical practitioner may provide the services
 - (a) using the donor's gamete for fertilization either *in vivo* or *in vitro*;
 - (b) requesting for donation of an embryo for pregnancy
 - (2) In case a married couple who wishes to have a baby by having the other woman who is not his wife to carry out the pregnancy instead, the medical practitioner shall provide for the services by using only the embryo derived from the fertilization of the gametes of the married couple.
 - (3) Providing the services in (1) and (2) shall adhere to the following conditions.
 - (a) no payment is given to the donor of the gamete in a manner that can be mistaken as selling-buying;
 - (b) no payment is given to the other woman who carries out the pregnancy instead that may be misunderstood as hired pregnancy;
 - (c) the woman who carries out the pregnancy instead must be a biological relative of the couple either the husband or the wife;
 - (d) Pre-implantation genetic diagnosis of an embryo shall be conducted only for serving diagnosis purposes, as necessary and as appropriate. Such a conduct shall not be made in a way that may be understood as gender selection, and shall obtain a written informed consent according to the form attached to this regulation.
 - (4) For any services other than the standards established in (1), (2), and (3), the medical practitioners who are responsible for, or are the service providers shall obtain an approval from the Royal College of Obstetrics and Gynecology of Thailand prior to providing all the services."
2. This announcement shall come into force since the date next to the publication date in the Royal Gazette.

It is hereby announced.

Given on the Twentieth Day of June B.E. 2545.

(Somsak Lohlaekha, M.D.)
Chairman, Medical Council

ANNEX 4

THE ETHICAL GUIDELINES FOR RESEARCHERS,

THE OFFICE OF NATIONAL RESEARCH COUNCIL OF THAILAND

The Office of National Research Council of Thailand has established the following ethical guidelines for researchers.

1. Researchers must be honest and hold morally responsibility in both science and management.
2. Researchers must be aware of the obligation for the conduct of a research as agreed with a sponsoring agency and their affiliated institution.
3. Researchers must be knowledgeable in the field of their research.
4. Researchers must be responsible for the subjects used in studies, either living or non-living things.
5. Researchers must pay respect to the dignity and rights of human subjects participating in a research.
6. Researchers must hold freedom of thought without any biases throughout all stages of researches.
7. Researchers should utilize their research results in an appropriate manner.
8. Researchers should respect the scientific opinions of other researchers.
9. Researchers should be responsible for society at all levels.

ANNEX 5

ROLES AND RESPONSIBILITIES OF SPONSOR¹

1. Quality Assurance and Quality Control

1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

2. Contract Research Organization (CRO)

2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

3. Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

4. Trial Design

4.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

* This part is adopted from the Chapter on Sponsor of the ICH GCP Guidelines, as the Thai version is directly translated from the ICH GCP Guidelines. Re-translating the Thai version back to the English language may cause slight deviation from the original meaning. Therefore, adopting the original English version is made to best preserve the accuracy of the text.

4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

5. Trial Management, Data Handling, and Record Keeping

5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

(b) Maintains SOPs for using these systems.

(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.8 If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.11 The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

6. Investigator Selection

6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multi-centre trials, their organization and/or selection are the sponsor's responsibility.

6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

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

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

(b) to comply with procedures for data recording/reporting;

(c) to permit monitoring, auditing and inspection (see 4.1.4) and

(d) to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

7. Allocation of Responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

8. Compensation to Subjects and Investigators

8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

9. Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

10. Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

11. Confirmation of Review by IRB/IEC

11.1 The sponsor should obtain from the investigator/institution:

- (a) The name and address of the investigator's/institution's IRB/IEC.
- (b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.
- (c) Documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

11.2 If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC.

11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC re-approvals/re-evaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

12. Information on Investigational Product(s)

12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from non-clinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

13. Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)

13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

14. Supplying and Handling Investigational Product(s)

14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

14.4 The sponsor should:

- (a) Ensure timely delivery of investigational product(s) to the investigator(s).
- (b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).
- (c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).
- (d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

14.5 The sponsor should:

- (a) Take steps to ensure that the investigational product(s) are stable over the period of use.
- (b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as

required by the applicable regulatory requirement(s), whichever represents the longer retention period.

15. Record Access

15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

16. Safety Information

16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial.

17. Adverse Drug Reaction Reporting

17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

18. Monitoring

18.1 Purpose

The purposes of trial monitoring are to verify that:

- (a) The rights and well-being of human subjects are protected.
- (b) The reported trial data are accurate, complete, and verifiable from source documents.
- (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

18.2 Selection and Qualifications of Monitors

- (a) Monitors should be appointed by the sponsor.
- (b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.
- (c) Monitors should be thoroughly familiar with the investigational product(s), the

protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

18.4 Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

- (a) Acting as the main line of communication between the sponsor and the investigator.
- (b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
- (c) Verifying, for the investigational product(s):
 - That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
 - That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
 - That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
 - That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
 - That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.
- (d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
- (e) Verifying that written informed consent was obtained before each subject's participation in the trial.
- (f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
- (g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.
- (h) Verifying that the investigator and the investigator's trial staff are performing

the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enrolling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

- The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
- Any dose and/or therapy modifications are well documented for each of the trial subjects.
- Adverse events, concomitant medications and inter-current illnesses are reported in accordance with the protocol on the CRFs.
- Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
- All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

18.5 Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

18.6 Monitoring Report

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

19. Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

19.2 Selection and Qualification of Auditors

(a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

19.3 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

20. Noncompliance

20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

21. Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

22. Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

23. Multi-centre Trials

For multi-centre trials, the sponsor should ensure that:

23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favorable opinion by the IRB/IEC.

23.2 The CRFs are designed to capture the required data at all multi-centre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

23.3 The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

23.5 Communication between investigators is facilitated.

ANNEX 6

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)²

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

1. General Information

1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

1.2 Name and address of the sponsor and monitor (if other than the sponsor).

1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

2. Background Information

2.1 Name and description of the investigational product(s).

2.2 A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

2.4 Description of and justification for the route of administration, dosage, dosage

* This part is adopted from the Chapter on Clinical Trial Protocol and Protocol Amendment(s) of the ICH GCP Guidelines, as the Thai version is directly translated from the ICH GCP Guidelines. Re-translating the Thai version back to the English language may cause slight deviation from the original meaning. Therefore, adopting the original English version is made to best preserve the accuracy of the text.

regimen, and treatment period(s).

2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

2.6 Description of the population to be studied.

2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

3. Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

4. Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

4.3 A description of the measures taken to minimize/avoid bias, including:

(a) Randomization.

(b) Blinding.

4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

5. Selection and Withdrawal of Subjects

5.1 Subject inclusion criteria.

5.2 Subject exclusion criteria.

5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6. Treatment of Subjects

6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.3 Procedures for monitoring subject compliance.

7. Assessment of Efficacy

7.1 Specification of the efficacy parameters.

7.2 Methods and timing for assessing, recording, and analyzing of efficacy parameters.

8. Assessment of Safety

8.1 Specification of safety parameters.

8.2 The methods and timing for assessing, recording, and analyzing safety parameters.

8.3 Procedures for eliciting reports of and for recording and reporting adverse event and inter-current illnesses.

8.4 The type and duration of the follow-up of subjects after adverse events.

9. Statistics

9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(es).

9.2 The number of subjects planned to be enrolled. In multi-centre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

9.3 The level of significance to be used.

9.4 Criteria for the termination of the trial.

9.5 Procedure for accounting for missing, unused, and spurious data.

9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluated subjects).

10. Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits,

IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

11. Quality Control and Quality Assurance

12. Ethics

Description of ethical considerations relating to the trial.

13. Data Handling and Record Keeping

14. Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

15. Publication Policy

Publication policy, if not addressed in a separate agreement.

16. Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

ANNEX 7

EXAMPLES OF MEDICAL DEVICES AND INHERENT RISKS

Examples of medical devices that may be regarded as being highly risky

- Artificial organs or tissues such as artificial cochlear, injectable collagen, all types of artificial joints, artificial lenses, artificial bones, blood vessel stents and internal stents, including for example stents used in the gall bladder duct, or in the urinary tract system, artificial valve, and artificial blood vessels
- Devices used for cardiovascular system, such as cardiac pace maker
- Cardiopulmonary resuscitation, laser used for dilating clotted blood vessels and devices for cardiopulmonary bypass used in the open heart operation
- Devices for stone destruction
- Devices for haemodialysis
- The intestinal stapler
- Absorbable haemostatic agents
- Infusion pumps etc.

Examples of medical devices that may be regarded as being low risky

- Contact lenses
- Gastroscope and Colonoscope; Cystoscope
- Laparoscope and hysteroscope

- Dressing devices for external wound, except burns
- Urinary and gall bladder ducts catheter connected to an external bag
- Nerve stimulator

ANNEX 8

MODEL TEMPLATE FOR MATERIAL TRANSFER AGREEMENT

MTA No.....

1. The parties to this Agreement are:
 - 1.1[1].....(hereinafter referred to as[2].....);
 - 1.2[3].....(hereinafter referred to as the RECIPIENT) and ;
 - 1.3 The RECIPIENT includes RECIPIENT's Scientists as well as Principal Investigator / Laboratory Supervisor/ Instructor

....[2]..... agrees to provide the RECIPIENT with MATERIAL, as hereinafter defined, for use in accordance with the terms and conditions of this agreement.

2. In this agreement:

Material means original material, progeny, and unmodified derivatives.

Progeny means unmodified descendant from the MATERIAL, for example, virus from virus, cell from cell, or organism from organism.

Unmodified Derivatives mean substances created by RECIPIENT, which constitute an unmodified functional sub-unit or an expression product of the original MATERIAL, such as purified or fractionated sub-sets of the original MATERIAL, sub-clones of unmodified cell lines, monoclonal antibodies secreted by a hybridoma cell line, proteins expressed by DNA/RNA supplied by[2]....., sub-sets of the original MATERIAL, for example, novel plasmids or vectors.

Modifications mean substances created by RECIPIENT, which contain or incorporate the MATERIAL (Original Material, Progeny or Unmodified Derivatives).

Commercial purposes mean the sale, patenting, obtaining or transferring intellectual property rights or other tangible or intangible rights by sale or license, product development and seeking pre-marketing approval.

3. The MATERIAL covered by this agreement includes:
 - 3.1 All biological materials, living or dead, originated from within the Kingdom of Thailand/or else where as listed in Attachment A
 - 3.2 Any associated know-how, data and information
 - 3.3 Any Progeny, Unmodified Derivatives and Modifications
 - 3.4 Any cells or DNA, molecules replicated or derived there from

4. The RECIPIENT agrees that:
 - 4.1 The MATERIAL is the property of[2]..... and is to be used by the RECIPIENT solely for (check only one that applies)
 - research purposes.
 - test, reference, bioassay and control (covering only their use within the framework of corresponding official international test, bioassay and control protocols)
 - training and teaching purposes

at the RECIPIENT' s institution and only under the direction of the RECIPIENT.

The research / test to be conducted by the RECIPIENT is restricted to the project/ test described in Attachment B, Entitled, “.....”
(Principal Investigator / Laboratory Supervisor / Instructor :
.....)

- 4.2 The MATERIAL will not be used in human subjects or in clinical trials involving human subjects without the written permission of[2].....
5. The RECIPIENT agrees not to transfer the MATERIAL to anyone who does not work under his or her direct supervision at the RECIPIENT' s institution without the prior written consent of[2]..... The RECIPIENT shall refer nay request for the MATERIAL to[2].....
6. The RECIPIENT agrees to use the MATERIAL in appropriate containment facilities by fully trained and competent staff.
7. The RECIPIENT will notify....[2]..... of all research results related to the MATERIAL in writing within one year after completion of the research project.
8. The RECIPIENT agrees to acknowledge....[2]..... as the source of the MATERIAL and data in any and all publications and patent applications based on or relating to the MATERIAL, replicas, or derivatives there of and any research thereon.
9. The RECIPIENT acknowledges that the MATERIAL is or may be the subject of a patent application. Except provided in this agreement, no expressed or implied licenses or other rights are provided to the RECIPIENT under any patents, patent applications, trade secrets or other proprietary rights of[2]....., including any altered forms of the MATERIAL made by[2]..... In particular, no expressed or implied licenses or other rights are provided to use the MATERIAL, modifications, or any related patents of the MATERIAL for commercial purposes.
10. If the RECIPIENT desires to use or license the MATERIAL or Modifications for commercial purposes.[2]..... AGREES, IN ADVANCE OF SUCH USE, TO NEGOTIATE IN GOOD FAITH WITH RECIPIENT TO ESTABLISH THE TERMS OF A COMMERCIAL LICENSE.
11. The RECIPIENT will use the MATERIAL in compliance with all his/her national and international laws and regulations, including Pathogens and Animal Toxins Act B.E.2525 as amended by Pathogens and Animal Toxins Act (No.2) B.E. 2544. The MATERIAL is experimental in nature and it is provided by[2]..... without warranty of any sort, expressed or implied.[2]..... makes no representation the use of the MATERIAL will not infringe any patent or other proprietary right. The RECIPIENT will indemnify[2]..... and its employees and hold[2]..... and its employees from any claims or liabilities which may arise as a result of the use of the MATERIAL by the RECIPIENT.
12. The MATERIAL is provided at no cost; however, fee is requested solely for its preparation and distribution cost. The amount shall be indicated in Attachment A
13. The RECIPIENT shall promptly return or destroy all information and the MATERIAL upon demand therefore by[2].....
14. The agreement shall be effective on the date of last signing below, apply to all information and the MATERIAL received from[2]..... and terminate on completion of the RECIPIENT' s current research with the MATERIAL (within.....years after the effective date) unless the parties agree in writing to extend the agreement
15.[2]..... and the RECIPIENT shall use their best efforts to settle in a fair and reasonable manner any disputes arising in connection with this Agreement. If such dispute cannot be

settled by the parties between themselves, it shall be first submitted to mediation by a mediator chosen jointly by the parties.

In the event that mediation does not bring a resolution of the dispute within 30 days, the dispute shall be submitted to arbitration before a single arbitrator pursuant to the Arbitration Rule of Thailand. Any such arbitration will be subject to such rules.

Signed for and on behalf of the RECIPIENT

Signed for and on behalf of the ...[2].....

Name.....
(.....)
Position:

Date.....

Name.....
(.....)
Position:

Date.....

Signature of Witness

Signature of Witness

Name.....
(.....)
Position :
Date.....

Name.....
(.....)
Position:
Date.....

Attachment A

MTA No.....

Material Transfer Record

.....[1]..... agrees to transfer the following materials to ...[3]... as follows:

No.	Material	Quantity	Remark
1			
2			
3			
4			
5			
6			

Preparation costsBaht/.....unit Total.....Baht

Distribution fees.....Baht

[] The materials will be picked up on/...../.....(Please notify.....days/weeks in advance.)

[] The materials are requested to be shipped to Recipient’s investigators/ Laboratory supervisor/ Instructor shown below.

FOM SCIENTIST

RECIPIENT SCIENTIST

Signature:

Signature:

Printed Name:

Printed Name:

Unit/Dept:

Unit/Dept:

Faculty

/ Address:

Institute.....

Date:

Date:

BIBLIOGRAPHY

Bioethics and Advanced Biomedical Research: *Draft, Bioethical Issues and Guidelines on Modern Biomedical Research Involving Humans*, Thai National Health Foundation and National Center for Genetic Engineering and Biotechnology, 2003,(Thai)

Singhaneti, B., *Fundamental Principles of Rights, Freedom, and Dignity of Humans according to the Constitution of the Kingdom of Thailand*, Vinyuchon, B.E. 2543 (2000), p. 231 (Thai).

Office of National Research Council, Ministry of Science, Technology, and Environment, *The Ethical Guideline for Researcher*, National Research Council, B.E. 2541 (1998) (Thai).

Institute for Population and Social Research, Mahidol University, Handouts of the “*Ethics in Human Research*” Workshop, September 2-3, 1998 (B.E.2541), Amarin Room, Third Floor, SD Avenue Hotel, Boromracchonani Road, Bangkok.

Canada Tri-council Policy Statement. *Ethical Conduct for Research Involving Humans*, 1998.

Code of Federal Regulations Title 45 Part 6 - *Protection of Human Subjects* (45 CFR 46) Revised June 18, 1991 (Effective August 19, 1991) Edition October 1, 1993.

Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subject*, (1993 and a draft version 2001).

Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Ethical Review of Epidemiological Studies* (1991).

Kittaporn, D., *Ethical Issues in Social Science Research*, Handouts for the First Training Workshop on Ethical Guideline in Clinical Research or Experiments Involving Human Subjects, hosted by the Faculty of Medicine, Khonkaen University and the Forum for Ethical Review Committee in Thailand (FERCIT), June 20-22, 2001 (B.E. 2544), Faculty of Medicine, Khonkaen University.

European Epidemiology Group, *Good Scientific Practice: Proper Conduct of Epidemiological Research*.

Drug Control Division, Food and Drug Administration, Ministry of Public Health, Thailand, *ICH- Good Clinical Practice Guideline* (Thai version), July, B.E. 2543.

ICH Harmonized Guideline for Good Clinical Practice. London: EMEA, 1998.

National Health and Medical Research Council, Australia, *National Statement on Ethical conduct in Research Involving Humans*, 1999.

Office for Human Research Protections (OHRP), *Institutional Review Board Guidebook*, 1993.