

The Ethical Guidelines for Research on Human Subject in Thailand, 2007



Forum for Ethical Review Committees in Thailand

Editors

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Foreword and Acknowledgement

The Ethical Guidelines for Research on Human Subjects in Thailand, B.E. 2550 follow the revised edition of the National Guidelines for Ethical Research on Human Subjects, B.E. 2545. Apart from a minor change in the Thai title, major revisions of Chapter 7, Specific Types of Research on Human Subjects, have been made. Ethical issues in modern biomedical research, i.e., medical devices, vaccine trials, epidemiology, human genetics, research involving human gametocytes, embryonic tissues, placenta, fetal hematocytes and stem cells were added. These are the first guidelines on modern biomedical ethics published in Thailand.

The Ethical Guidelines for Research on Human Subjects in Thailand, B.E. 2550 is designed to comprise of both Thai and English language in one book. It has been edited to present the contents of both languages correspondingly. Translation from Thai to English was accomplished by professional translator, Dr. Suchart Chongprasert, then edited by Mr. Thomas McManamon .

The Forum for Ethical Review Committee in Thailand (FERCIT) would like to thank the Working Group for Revising the Ethical Guidelines for Research on Human Subjects in Thailand, B.E. 2548-2550 for their hard work on the revision of the guidelines. Thanks and appreciation are dedicated to Ms. Bussara Sukpanichnant, Associate Director, Quality Assurance Unit, Armed Forces Research Institute of Medical Science (AFRIMS) for her help in applying for a grant to translate the guidelines from the Walter Reed Army Institute of Research.

The Forum for Ethical Review Committee in Thailand (FERCIT) wishes that this book "The Ethical Guidelines for Research on Human Subjects in Thailand, B.E. 2550" will be beneficial to ethics committee members, medical doctors, dentists, pharmacists, nurses and all researchers who do research on human subjects. The most ambitious purpose of writing these guidelines is to achieve the goal of best protection for all human volunteers as well as the accomplishment of advanced biomedical research.



(Professor Dr. Tada Sueblinong)

Chairperson, The Forum for Ethical Review Committee in Thailand (FERCIT)

25th December, 2007

CHAPTER 1

DEVELOPMENT OF THE ETHICAL GUIDELINES FOR RESEARCH ON 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 research on humans or animals. Developed countries also have attempted to stipulate regulations and guidelines for research on 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, or conduct a scientific research investigation involving human subjects, researchers are required to obtain ethical approval from a recognized ethics committee. In addition, seminars and 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 have been several declarations. The most prominent and widely accepted and most commonly 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, technology and social changes. The last amendment was formulated and adopted in Scotland in B.E. 2543. Later, several declarations concerning the conduct of a research on 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 are aware of the ethical issues of research on human subjects. As a result, an ethics committee is appointed whose responsibility it is to monitor that the research conducted within the institution adheres 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 have 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 aims to develop plans for promoting ethical research on human subjects. A Working Group was then appointed to draft ethical guidelines for research on human subjects, which are intended to serve as national guidelines. The national ethical guidelines were developed considering 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 Organizations 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 on Human Subjects

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

- 1.2.1 To generate a new body of knowledge and new understanding;
- 1.2.2 To enhance scientific advancement that benefits the research subjects.
- 1.2.3 Through research, the subjects may gain benefits from the development of new treatment, from new findings for higher living standard, from new discoveries, from writing, speech, and traditional culture, or from satisfaction in improving society;

- 1.2.4 Also, research provides benefits for the society at large or for certain groups of people or has 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 on Human Subjects in Thailand

Thailand has established three basic objectives regarding research on humans:

- 1.3.1 To ensure that the dignity, rights, safety and well-being of subjects participating in research are protected, and the results of the research 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 biomedical research conducted within each institution.

1.4 Related Terms and Definitions

- 1.4.1 **Research on human subjects** means a research study, inquiry, interviews in social science, environment 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 related to human or conducted in human. Also, such research includes research studies using information from patient 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 research projects are collectively called **biomedical research**.
- 1.4.2 **Ethics Committee** or **Research Ethics Committee** means a committee appointed by an institution, organization, or agency whose responsibility is to review the ethical aspects of research studies and experiments on 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 on Human Subjects.
- 1.4.3 **Ethical Guidelines for Research on Human Subjects** means ethical guidelines or criteria related to research studies or experiments on 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 on Human Subjects in Thailand

Thanks to rapid advances in science and technology, the first version of the Ethical Guidelines, published in B.E. 2545, could not cover or keep pace with contemporary issues. 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 on Human Subjects to be in charge of the revision. The process was completed by the Working Group for Revising the Ethical Guidelines, where 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 the Working Group for Revising the Ethical Guidelines, Annex 10).

CHAPTER 2

ETHICS FOR RESEARCH ON HUMAN SUBJECTS

2.1 General Ethical Principles

Three basic ethical principles consist of:

First, **respect for persons**;

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. 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 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 their consent any time without giving any reason. In practice, the informed consent may appear in a form of conversation.
- 2.2.2 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.
- 2.2.3 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 risks and benefits; An analysis of risks and benefits being exposed to the subjects is a key ethical issue of research on human subjects. Research ethics for 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 to 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 dignity always requires a proper and reliable research design, especially biomedical or health research, which needs 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 the 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 harm; Researchers are required to protect their subjects from all possible harm 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 research on human subjects. The subject sample size should then be as small as possible, but still maintaining 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 research on human subjects are to provide direct benefits to participating subjects and then to others or the society at large, or contribute to scientific progress. Currently, most research is primarily beneficial to society and the progress of science.

2.4 Principle of Justice

This principle covers the following aspects.

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

CHAPTER 3

CONDUCTING RESEARCH ACCORDING TO THE PRINCIPLE OF RESPECT FOR PERSONS

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. 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 without giving any 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. 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 persons, beneficence, and justice.

In providing the information or invitation for decision making, the investigator may separate the documents into two 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 consent granted.

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, the community, or 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 and 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 form 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 and 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 damage or death resulting 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 is normally entitled to;
- (20) that the study protocols have been reviewed and approved by the ethics committee for research in human subjects.

3.1.2 Practical guidelines that should be followed

The guidelines below clarify several relevant ethical considerations.

- (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 clear and complete information sufficient for the subjects to make their decisions. The investigator should pay attention to the 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 the subjects in advance of 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 subjects can make their own decisions;
- (5) Upon the completion of the study, whether the subjects are entitled to continuous access to the medicine, instruments, 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 that the 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 benefit. The subjects should make their own decisions, not be forced to do so, or induced unduly. The subjects can also withdraw from the study any time. Several aspects of inducement that should receive consideration include:

- 3.2.1 Payment or compensation either money or other benefits to be given to the subjects should not be too much to induce 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, and 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 opportunity to make their own decisions without any interference from the higher authority.
- 3.2.4 3.2.4 Payment given to investigators by pharmaceutical companies or sponsors in the form of money or other means that are excessive, or payment methods, such as the given payment is based on the number of subjects participating in the trial, may cause deviation in the case that the investigator attempts to recruit as many subjects 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 their rights to have their personal information protected strictly.
- (2) During the informed consent discussion, the investigator must inform the subjects in advance of the measures used to protect their confidentiality before signing the consent form.
- (3) The subjects must sign the informed consent form before the information is to be distributed in case the information can cause danger to them.
- (4) The possible leakage of the research results containing the subject's confidentiality should be minimized to the lowest level. 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 access to the data.
- (5) The subjects should be made aware of the investigator's limitations in keeping their confidentiality. An example is when, 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 a regulatory requirement exists 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 of the limitations for keeping confidentiality before the subjects participate in the study.
- (6) The subjects should be made aware of the social impact 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 receive social discrimination. Such risks should be carefully considered in the same manner as those for any treatment risk resulting from drug or vaccine studies.

- (7) In the case where the ethics committee decides that signing 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 right to receive strict protection of their own information." Any disclosure of the 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 gives 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 by having patients sign the form in advance and keeping it in the medical record or by calling for patients to sign later. In this case, therefore, the ethics committee may consider waiving the signing of the informed consent form. However, the evidence should be provided to prove that the subjects are informed about the methods for collecting the data. For example, the methods are to be included on 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 the social sciences, whatever conclusions are reached, may cause risks to community, society, races or minors such as stigmatization, injustice or discrimination.. An example is research results showing 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 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 ethnic and racial 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 decisions. These include hospitalized patients, prisoners, children, the mentally impaired, critically ill patients, psychotic patients, pregnant women, and the economically disadvantaged. They are easily taken advantage 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 study due to their economic or health constraints. However, if a valid need exists to conduct a study on these people, some recommendations should be followed.

- 3.4.1 An irrefutable rationale for conducting research in these population groups should be clearly explained in the protocols.
- 3.4.2 Precautions against possible physical and mental harm should be exercised especially when the study is conducted on 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 provided.
- 3.4.5 In a study involving minors, psychiatric patients, or the incompetent, the informed consent should be obtained from their parents, or guardians or legal representatives.
- 3.4.6 It should be ensured that parents, guardians, or legally acceptable representatives are fully informed about the study.
- 3.4.7 The rights of the minors and the economically disadvantaged should be respected for making their voluntary decisions.
- 3.4.8 It should be shown that the research participants have freedom in voluntarily participating in a research study, including for example a research study conducted on prisoners, inmates, and refugees.
- 3.4.9 Precautions against harm 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 the case where a study is conducted on the vulnerable people without direct health benefit to them, the possible risks should not be greater than the 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 study be justified to conduct on humans by an assessment of a favorable risk and benefit ratio. In the context of research involving human subjects, the term "risk" means the possibility to receive harm, whereas the term "benefit" denotes that which gives a positive value to health or well being.

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

The common types of harm that occur to subjects include physical harm or injuries or psychological harm. In addition, other harm may be overlooked such as legal, social, and economic impacts. Moreover, the types of the expected benefits may be consistent with the types of potential harm 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 to science and society.

4.2 Systematic Assessment of Risks and Benefits

In most cases 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 practical as possible. This can be done in practice by collecting and evaluating the data covering all aspects of the research. 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 Containing the Minimum Elements:

- 4.3.1 A demonstrated real need exists to conduct a study in human subjects
- 4.3.2 Brutal or cruel treatments to subjects are completely unjustified.
- 4.3.3 Risks are minimized as much as possible, but research objective(s) are still achieved
- 4.3.4 When research involves a significant risk capable of serious damage, special confirmation is needed in justifying the risk.
- 4.3.5 When a research is conducted in vulnerable people, the rationale and need should be clearly explained and any and all harm avoided.
- 4.3.6 The relevant risks and benefits are 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 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 for potential risks is required.

- 4.4.4. For research conducted in a community, a private sponsor should provide 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. 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, 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 involved in research on 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 ACCORDING TO THE PRINCIPLE OF JUSTICE

The selection of groups of people of communities for 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 research on human subjects, however, the term "justice" is referred to as distributive justice, which requires that both burdens and benefits entitled to the subject participating in the research be distributed equally. Therefore, the key questions of this principle are 1) who bears the burdens and 2) 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 bear 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 research on 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 societal.

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 a favorite group of people or recruiting 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. 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 the community bears the burdens, or which the community takes the benefits must be in accordance with the principle of distributive justice as well. A common problem of injustice occurring at the community level is exemplified in the case of 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 the lack of 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 justice to all levels from the individual to the society.

However, please be aware that in reviewing research on 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 careful and appropriate consideration. This is to serve as criteria for decision making in the case that different treatments are given to individuals, and this consideration should be made on an individual basis.

CHAPTER 6

ETHICS COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS

A research protocol involving human subjects must be subject to review and approval by an ethics committee for research on human subject before initiating a study. Thus, institutions or organizations with established research protocols or investigators have to appoint and authorize the ethics committee to decide about the research protocol. The institution or organization should establish 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 with 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 a member's term of holding office should be established.

6.1.3 The institution or organization should provide for the ethics committee adequate resources, including stationery supplies, facilities, clerical 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 members and share legal and other liabilities, as appropriate.

6.1.6 The institution or organization should appoint the ethics committee by its highest authority. However, 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 protocols provide 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 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, and case report form, 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 five members, both male and female, and with the following qualifications:

(1) At least one member should have knowledge and experience 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 should be a lawyer or endowed with knowledge of law.

(3) At least one member should be 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 experience in the current practices of patient 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 undergone training about human research ethics.

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

6.3 Appointment of a Member of an 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 duty as an ethics committee member.

6.4 Ethical Review Process

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

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

6.4.3 In case the ethics committee cannot reach a definite decision on any scientific aspects, the committee may seek for other expert's opinions. However, it must ensure that the experts have no conflicts of interest with the research protocols, and that the experts can maintain the confidentiality of the protocols. Otherwise, the ethics committee may forward the protocols to a scientific committee or an epidemiology committee or to 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 four 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 temporarily;

(4) disapproval/negative opinion.

The ethics committee is required to provide an explanation for its disapproval decisions 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 procedures for an expedited review of the research protocols that imposes a minimal risk, or of 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 protocols that can be conducted with no ethical review submission.

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

6.4.8 The ethics committee should implement an efficient system for recording minutes and archiving to allow for an audit upon request and receive 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 three 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 protocols under 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 protocols. The committee should respect 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 research protocol with high risks, the investigator should report the progress more frequently than a low risk protocol. The applicant should propose to 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 collaborating organizations, and as a trial conducted by investigators who later change their original affiliated institution or organization to a new affiliation.

6.7.2 The multi-center protocols 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 that the practices are the same 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 protocols, the outcome of which may not necessarily be the same as those of the committees in the other institutions. The research protocols 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 with one another in case of any possible

different opinions about the main principle so as to reach a clearly agreed upon decision. The investigator should amend the protocols' 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 request minor amendment for the ethical aspect. This is to facilitate an efficient review and approval of the multi-center protocols.

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 to ensure that the research complies 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 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. This includes when serious adverse effects are reported, or when the conduct of the research does not comply with the protocols 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 ON HUMAN SUBJECTS

7.1 CLINICAL DRUG TRIAL

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

In general, an investigational drug used in clinical trial falls into one of four 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 required efficacy testing.

Phases of Clinical Drug Trials

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

A Clinical Drug Trail Can Be Classified in Four 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 on children, the elderly, or women with childbearing potential. Anesthesia or anticancer drugs should not be used in the healthy volunteers as a result of its high toxicity. In general, the number of the subjects should not exceed 30 subjects. Every subject should give 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 phase I also involve 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, the 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 on 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 on 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 be 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 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 Phase II. The primary and secondary objectives are to evaluate the pharmacological effectiveness and to study short-term toxicity, respectively. The number of the subjects in Phase II trials may be considerably increased 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 survival or to improve

patient 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 comparative 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 numbers 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 population groups 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 an 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 the risks and 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 in the control group. Placebos should not be used in a control group if standard treatments are available because the subjects will lose medical benefits from participating in the trial. In addition to a focus on the freely informed consent process, ethical considerations in a placebo-controlled trial should pay 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 the number of patients 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 clinical drug trials in four phases, in particular the medical device that is to be inserted into the body. In such a case, a specific consideration is required depending on the types of devices. For example, the conduct of a trial using a cardiac pace maker, which is a very expensive device, requires 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 the research procedures and/or the use of the device may impose extremely high risks and harm, 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, allows 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 ethical justification if the use of that device is the only opportunity for the subject to obtain benefit from the treatment, such as surgery to insert the artificial joint to replace irreversibly impaired joints.

In general, a sham surgery in the comparator group is regarded as ethically inappropriate as it can greatly impose risks and harm to the subjects, while it provides no benefits. 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 much 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. In addition a device available on the market may be altered or further developed and used in the treatment for patients unable to access other available treatments. The investigator or the sponsor of this type of trial may get less financial support than that from drug companies in the case of a clinical drug trial. Hence, the design of a clinical study of a medical device to prove its effectiveness, efficiency and safety may be an observational study instead of a randomized controlled trial, which is the standard for a clinical trial of new drugs. The observational study allows for collecting the data completely and completing the follow-up for all patients for a sufficiently long time. This is demonstrated by the study of artificial joints and cardiac valves that are widely recognized.

Systematic consideration of 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 devices that

- risk death upon usage;
- risk permanent disability upon usage;
- require a surgery or certain drugs to prevent 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 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 contains 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 which type of risk the trial of a medical device or the device itself falls into is the responsibility of the 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 is 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 the specific characteristics of the trial of medical devices explained earlier.

Finally, the investigator and the subject should always realize that devices inserted into the human body undergo failure both in short and long term. The failure of the device may result in damage, even death. When such a risk exists, 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 the research budget to ensure that the issue of benefits has been taken into account. In general, the sponsor will pay the investigator based on the number of subjects. Payment calculated based on the number of recruited subjects is an ethical issue, because it is possible that the investigator has conflicting thoughts between the payment to be received and the beneficial 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.

Research conducted in public hospitals or public health care facilities involve expenditures to cover such as laboratory tests, and lump sum fees determined by the institution. The disclosure of the payment and the other budget items helps the ethics committee to evaluate any 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 in a control group in a trial where standard treatments or medically proven medicines are available, because patients will lose medical benefits entitled to from participating in the clinical trial. However, the use of a placebo in 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 managed by itself due to a placebo effect;

- (5) the disease to be studied is a minor condition and treating with a placebo causes the only discomfort or the illness is alleviated slowly or negligibly, and causes no serious or irreversible harm to the subjects;
- (6) compelling scientific and methodological reasons 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 focus on an appropriate design to maximize benefits and minimize harm to patients.

7.1.7 Analysis and Distribution of Research Results

In most clinical trials, the sponsor has rights as agreed upon for the analysis and 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 rules, there must be an independent interim analysis. However, prior to implementing the termination rules, it should be identified 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

Epidemiological research is an integral part of public health or health service research, which is 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 research 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 populations. Then, an ethical consideration is needed 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 research involves 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 details as a zip code that may be used as an identifier;
- b. potentially identifiable, coded, re-identifiable data, which are referred to as the data of the identifier, 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 from 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 research 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 many records are searched.

7.2.2 The ethics committee may approve 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 benefit 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 does not involve any abnormality of the genetics;
- (3) the public benefit 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, the relatives or the involved communities do not gain any benefits or the informed consent cannot practically be obtained because of too many or outdated 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 guaranteed that the conduct complies completely with the requirements on the research in the community.

7.2.5 When identified or the re-identifiable data are used in research, the ethics committee should ensure that the collection, handling, and storage of the data comply 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 the use of the identifier to assure 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 epidemiological research 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 concluding, 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 culture or other sensitivities.

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 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 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 much 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 medical records consisting of the confidentiality of patients, only the authorized medical personnel are allowed to access 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 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 routes 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 a trial using a recombinant DNA vaccine, the adverse effects of which are not yet clear, the investigator has to strictly follow the regulations 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, secretions, and excretions from all organ systems. The objective of using the tissue samples is for the diagnosis of a disease or for other purposes.

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

- a. taken directly from the body of the subject for research use where the donors of the tissues give their informed consent;
- b. taken from the body for treatment, diagnosis, or other objectives (e.g., learning and teaching, organ donation for transplantation);
- c. taken from either of the aforementioned sources above, and kept under the applicable regulatory requirements, 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 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 follow the guidelines below.

- (1) obtain the written informed consent to use the samples from the donor, giver of the tissue samples or from the legal owner of the corpse;
- (2) provide detailed information to the donor, 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 techniques and systems for the storage of the tissue samples that are appropriate and secured from access by unauthorized persons;
- (5) use the appropriate data recording, storing, and retrieving systems that ensure protection of the confidentiality of the owner of the tissue samples;
- (6) appoint a personnel staff responsible for the handling 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 research using the tissue samples and for the ethical review and approval of the research protocols. 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 protocols taking into

consideration international ethical principles, i.e., respect for persons, beneficence, and justice;

- (8) A material transfer agreement should be made in case the tissue samples are transferred to other institutions to ensure consistency with the principle of respect for persons.

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 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 the best attempt to maintain the confidentiality of the patient. When research is conducted using stored tissue samples, searching for the patients or the patients' information should be done as little as possible and only as necessary 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:
 - 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 protocols and the new protocols;
 - 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 consistency with the principle of respect for persons.

7.6 HUMAN GENETIC RESEARCH

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

Regarding the ethics in human genetic research, some additional elements are needed to be considered apart from those applied for other research involving human subjects because of the specific nature of this type of research. For example, the co-operation of the subjects and their families is very much needed for 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 are the relatives of the subjects involved 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 research may directly impact the subjects, e.g., causing social stigma or discrimination. Therefore, the investigator should be aware of these potential impacts, and should have measures for solving problems that may arise. The procedures for strictly protecting the subject's privacy and the confidentiality of the data should be implemented.

Generally, researchers should be aware of the following important considerations when conducting human genetic research.

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 free of charge (appropriate persons mean the research participants who inform in advance that they need to know the results).
- (3) Human genetic researches is often conducted in groups of families or in communities that are related to 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 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 Risks

- (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 impact 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 protocols provide 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 a violation of research ethics. The research study on gene alteration then must not be approved, except for gene therapy that may need to be considered on a case by case basis to receive ethical approval for the research.

7.6.5 Eugenic Concern

The objectives of the human genetic research are related to improved knowledge and understanding of genetic diseases that may affect human health only, including health care, and not for eugenic purposes. Additionally, attention must be paid to 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 informed about a risk imposed upon 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 be of benefit in the future, it may impose risks to individuals who are the owners of the genetic materials and their families. Therefore, the following guidelines are recommended.

- (1) The investigator involved the storage of the genetic materials in the bank should demonstrate to the ethics committee and to the subjects the operating procedures used for keeping confidentiality, privacy, and 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 the 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 the destruction of the materials upon completing storage time. Uses of the materials for purposes other than those specified in the approved protocol should receive informed consent from the research participants or their heirs. Furthermore, 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 research protocols to create further awareness in the ethics committee and the subjects.

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

Research using advanced reproductive health technology influence the practices of research ethics, researcher's ethics, and people at large. The regulations issued by the Medical Council, by the advice of the Royal College of Obstetrics and Gynecology of Thailand, have already laid down the medical practice guidelines on the standards of services concerning reproduction technology. In addition, in conducting research involving human gametes, embryos, and the 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 are recommended.

7.7.1 Research involving human gametes

- (1) Obtaining the informed consent from the owners of the gametes is required in research using human gametes, which follows the principles and practices applied in other research 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. Any research conducted using commercialized gametes, or inducing artificial cross-fertilization between the human gamete and an animal gamete, is considered unethical.

7.7.2 Research on human embryos and embryonic stem cells

- (1) The fertilization of human gamete results in an embryo, and it is unethical to create 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) Research on the 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, and 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 the intrauterine fetus

Research 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

Research that uses fetal tissues must be conducted in accordance with the ethical principles as applied in other human experimentation. 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 research using 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 research and experiments.

“Ethical Guidelines for Research Studies and Experiments in Human Subjects” refer to ethical guidelines or ethical principles for research 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 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 damage that happen to the subjects in the experiment and such dangers or damage 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) (๓) 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 experience 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 four but not more than five representatives from institutes experienced in bone marrow transplantation with one representative being from each institute, and two members from 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 ten 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) being able to provide laboratory testing and radiology for 24 hours
 - (d) being 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 suitable for donating blood stem cells

(2) inform and explain to the donors the possible risks to 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 the case a married couple would like to have a baby by having the 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 the case a married couple who wishes to have a baby by having another woman who is not the 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 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 a written informed consent shall be obtained 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 moral responsibility in both science and management.
2. Researchers must be aware of the obligation for the conduct of 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 bias throughout all stages of research.
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.

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.

* 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.

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 two 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 two 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 until at least two 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 protocols, 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 the protocols, 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, 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 comparative 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 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 protocols, 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, and 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 protocols 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 protocols, 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 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.

* 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.

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 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 and evaluable 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.....
(.....)

Name.....
(.....)

Position:

Position:

Date.....

Date.....

Signature of Witness

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

Signature of Witness

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

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
Institute.....

/ Address:

Date:

Date:

Explanatory Note:

[1] Fill the name, address of the Faculty/Institution that provides the materials, for example,
Faculty of Medicine, Chiang Mai University 110 Intavaroros Road, Sripum District,
Muang, Chiang Mai 50200, Thailand

[2] Fill the brief name of the Faculty/Institution, for example, Faculty of Medicine

[3] Fill the name, address of the Faculty/Institution that receives the materials

Attachment B is the protocol.

ANNEX 9

LIST OF MEMBERS, THE WORKING GROUP FOR THE DEVELOPMENT OF NATIONAL ETHICAL GUIDELINES FOR RESEARCH IN HUMAN SUBJECTS B.E. 2545-2547

- | | |
|--|--------------------|
| 1. Vichai Chokevivat, M.D.
Food and Drug Administration, Ministry of Public Health | Advisor |
| 2. Professor Anek Areebhak, M.D.
Faculty of Medicine, Chulalongkorn University | Advisor |
| 3. Somboon Kiatinun, M.D.
Faculty of Medicine, Thammasart University | Chairlady |
| 4. Professor Manit Sritpramote, M.D.
Bangkok Medical College, Bangkok Metropolitan Administration | Member |
| 5. Assoc. Prof. Nimit Morakote, Ph.D.
Associate Dean for Research Affairs,
Faculty of Medicine, Chiangmai University | Member |
| 6. Assoc. Prof. Col. Aphornpirom Ketpanya, M.D
Phramonkutklao Medical College, the Royal Thai Army | Member |
| 7. Assoc. Prof. Rojana Sirisriro, M.D.
Faculty of Medicine, Ramathibodi Hospital, Mahidol University | Member |
| 8. Suchart Chongprasert, Ph.D.
Food and Drug Administration, Ministry of Public Health | Member |
| 9. Korakot Juthasmith, M.D.
Department of Medical Services, Ministry of Public Health | Member |
| 10. Wiwat Rojanapityakorn, M.D.
Office for International Development of Health Policies | Member |
| 11. Assoc. Prof. Sopit Thammaree
Faculty of Medicine, Chulalongkorn University | Member & Secretary |

ANNEX 10

LIST OF MEMBERS, THE WORKING GROUP FOR REVISING THE ETHICAL GUIDELINES FOR RESEARCH IN HUAMN SUBJECTS IN THAILAND B.E. 2548-2550

- | | |
|---|--------------------|
| 1. Somboon Kiatinun, M.D.
Faculty of Medicine, Thammasart University | Chairperson |
| 2. Vichai Chokevivat, M.D.
Director General,
Department for the Development of Thai and Alternative Medicines,
Ministry of Public Health | Member |
| 3. Assoc. Prof. Nimit Morakote, Ph.D.
Faculty of Medicine, Chiangmai University | Member |
| 4. Assoc. Prof. Major. Gen. Aphornpirom Ketpunya, M.D.
Department of the Royal Thai Army | Member |
| 5. Assist. Prof. Phanuwat Lertsitthichai, M.D.
Faculty of Medicine, Ramathibodi Hospital,
Mahidol University | Member |
| 6. Assoc. Prof. Sopit Thammaree
Faculty of Medicine, Chulalongkorn University | Member & Secretary |
| 7. Assist. Prof. Col. Suthee Panichkul, M.D.
Phramongkutklao College of Medicine | Editorial Team |
| 8. Prof. Pankhae Mahaisawariya, M.D.
Faculty of Medicine, Siriraj Hospital, Mahidol University | Editorial Team |
| 9. Prof. Tada Sueblinvong, M.D.
Faculty of Medicine, Chulalongkorn University | Editorial Team |

ANNEX 11**LIST OF MEMBERS,
THE MEDICAL COUNCIL'S SUB-COMMITTEE FOR THE PROMOTION OF RESEARCHES
IN HUMAN SUBJECTS
B.E. 2548-2550**

1. Anek Areebhak, M.D.	Chairman
2. Vichai Chokevivat, M.D.	Member
3. Jomjug Juntarasakul, M.D.	Member
4. Somboon Kiatinun, M.D.	Member
5. Banharn Koranantakul, M.D.	Member
6. Pinit Kulawanit, M.D.	Member
7. Sumalee Nimmannit, M.D.	Member
8. Tada Sueblinvong, M.D.	Member
9. Piyatat Tasanawiwat, M.D.	Member
10. Hatern Thintara, M.D.	Member
11. Pakorn Siriyong, M.D.	Member
12. Yotee Thongpenyai, M.D.	Member
13. Phanuwat Lertsitthichai, M.D.	Member
14. Suwat Lertsukprasert, M.D.	Member
15. Nimit Morakote, Ph.D.	Member
16. Aphornpirom Ketpunya, M.D.	Member
17. Sopit Thammaree, MSc (Pharm.).	Member & Secretary

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