Content

I. Human Trial Subject Protection

Researches conducted on human are referred to as medical researches involving human subjects. The central competent health authority does not have an inclusive control over all medical researches involving human subjects but only those of the highest risk level including new medical technology, drug, medical devices and bioavailability and bioequivalence of generic drugs. The term used to describe these researches is human trial in the Medical Care Act and clinical trial in the Pharmaceutical Affairs Act. Currently there has not been any consistent terminology. In regard to other academic researches conducted on human subjects, the implementation facilities (hospitals) are responsible for supervising such researches. For those researches involving human subject which are other than mentioned, the "Human Research Ethic Policy Guideline" was announced as a reference for researchers. The definition for medical researches involving human subjects by the World Medical Association has been more generalized. In addition to researches conducted on human subjects, those involving identifiable human material and data can all be defined as medical researches involving human subjects. The scope of medical research involving human subjects can then be divided into the following categories based on the level of risks faced by the subjects:

A. Human trials that require prior approval from the central competent health authority

B. Human trials that do not require prior approval from the central competent health authority

C. Non-invasive academic researches conducted on human subjects.

D. Researches related to human subjects

The difference between type A and B is based on the regulation or announcement stipulated by the central competent health authority which are used to determine whether a human trial requires prior approval by the central competent health authority or can be supervised by the hospital under its own authority. In general, subjects of human trials requiring prior approval from the central competent health authority are faced with greater risks. Given that this type of human trials requires prior approval, the implementation is monitored more strictly. Hence the risks faced by the subjects are controlled more efficiently. Type B human trials are to be supervised by the hospital under its own authority. Risks faced by the subjects differ depending on whether the hospital takes on its

responsibility. The Department of Health has announced the "Healthcare Institution Institutional Review Board Organization and Operating (2003)" and "Good Clinical Practice" which stipulate in detail the procedures that hospitals should follow when supervising human trials.

Type C medical researches involving human subjects refer to questionnaires, interviews and other non-invasive researches. In general, risks faced by subjects of this type of research include psychological impacts and violation of rights. Whether to disclose personal privacy? Whether to participate voluntarily? Whether to sign the informed consent form? Does the content of the informed consent form include all relevant information? Another problem of this type of medical research is that the implementation facility might not necessarily be a hospital. This type of research is often conducted by academic researchers on campus. If students are the research subjects, it is worth discussing whether they participate in these researches voluntarily.

Article 22 of the Declaration of Helsinki states: In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The research subject should also be informed of the rights entitled to, including the rights to refuse to participate and to withdraw consent at any time without being retaliated. Once it has been confirmed that the subject has fully understood the above information, the doctor should take the procedure to have the research subject sign the informed consent form under his/her own free will. The informed consent form should be in a written form. In the event that the informed consent form cannot be prepared in a written form, the non-written consent must be officially documented and witnessed. According to paragraph 1 of article 3 of the "Human Research Ethic Policy Guideline": Human research shall, as much as possible, be performed only after notifying the subjects using clear and understandable methods concerning relevant aspects, and obtaining their written consent.

Researches related to human subjects defined in type D refer to those conducted without direct contact with the subjects, such as researches performed on human tissues already obtained and extracted from the human subject or analytical researches of patient's medical history. Given that this type of research does not necessitate a direct contact with the subject, the only problem involved is the violation of subject's rights. Under certain conditions, some researches are even conducted without

the signing of an informed consent form. The central competent health authority has announced a "Guidelines for Collection and Use of Human Specimens for Research" as a reference for researchers.

When discussing issues concerning medical researches involving human subjects, we should first clarify the scope of researches in question to avoid confusion among different definitions and scopes.

Declaration of Helsinki

The World Medical Association convened in 1964 at Helsinki to discuss the ethical principles for medical researches and announced the Declaration of Helsinki after the meeting. The Declaration of Helsinki has undergone several amendments but is still known as the Declaration of Helsinki. This document has been widely regarded as the cornerstone document of human research ethics in many countries. The vision of the Declaration of Helsinki lies in autonomy and beneficence. Autonomy refers to the voluntary participation of subjects after receiving complete information regarding the research. Beneficence refers to the trial objective that might generate benefits for the subject. The subject will not compromise his/her rights and shall still receive the best treatments proven effective after participating in the trial.

The Declaration of Helsinki is a set of ethical principles for human medical experiments and consists of 32 articles. It is divided into introduction, basic principles for all medical research and additional principles for medical research combined with professional care. The Declaration states that it is the duty of the physician to promote and safeguard the health of human. Medical process is based on research that ultimately must include studies involving human subjects. Therefore human trials are an inevitable procedure. All medical researches involving human trials must conform to the generally accepted scientific principles. All responsibilities arising from the human trials must be rest with a qualified medical person and never on the subject of the research, even though the subject has given his/her consent. The physician may combine medical research with medical care and should inform the patient to what extent the combined treatments are related to the trial. Patient's refusal to participate in the trial should not affect the doctor-patient relationship.

Institutional Review Board

Over the past decades, several unethical human trials that denied patient rights are disclosed. Apart from the notorious germ warfare and

human trial conducted by the Imperial Japan Army in "Unit 731" as well as the human trials conducted on Jewish by Germany, the U.S. has also conducted several unethical human trials. Of all unethical trials reported, the Tuskeegee syphilis study conducted in Alabama during 1932 and 1972 was of the greatest impact. This study received a long-term funding from the U.S. Public Health Services. In 1943, penicillin, an effective cure for syphilis, was discovered by the scientists. However, in order to observe the complete progression of syphilis, these scientists intentionally withheld treatments for these infected and impoverished African-American male patients. Research reports were published one after another ignoring the medical rights of these subjects. The trial was terminated after a leak to the press in 1972. In May 1997, U.S President Clinton publicly apologized for funding such unethical human trial on behave of the U.S. Government. This incident has also led to the questioning of self-discipline of the scientific community-for the purpose pursuing scientific achievements, physicians and scientists are tempted to conduct notorious actions that are against social values. Therefore, before the commencement of a human trial, a committee formed by non-institutional individuals should review whether the human trial project conforms to the social ethical principles. The committee set up to verify whether the medical research conforms to the ethical principles is known as the Human Subject Committee. In Europe, it is referred to as the Ethics Committee (EC), whereas in the U.S. it is referred to as the Institutional Review Board (IRB). Recently it has also been suggested that the correct title should be the Research Ethics Committee (ERC). The U.S. Government only provides funding for research projects approved by the Institutional Review Board.

The Department of Health stipulates in accordance with the Medical Care Act amended on 2009/5/20 and the "Healthcare Institution Institutional Review Board Organization and Operating " announced on 2003/11/12 that the composition of the Institutional Review Board should range from 7 to 21 and the ratio of one single sex should be no less than one-third. Apart from the medical science personnel, at least one-third of non-medical professional personnel including legal experts, social justice or local organization representatives. Therefore, the composition of the Institutional Review Board must consist of non-medical professionals in order to appropriately report the opinion of general public. The government further stipulates that to prevent internal administrative interference during operation, the Institutional Review Board should also recruit non-institutional individuals to reflect non-institutional opinions. Hospitals should consider whether to outsource the review to external

Institutional Review Board depending on the research development of the hospital. Some of the Institutional Review Board in Taiwan already have a mature operation and have been acknowledged by international certification

A human trial is a transitional stage to transform scientific research findings to important medical procedures for patient care. It is the most critical stage of medical advancement. Before commencement, the trial must be reviewed carefully by the Institutional Review Board under the consideration of patient's rights. A signed informed consent from the patient should also be obtained before the trial. Hence, a human trial is not an act to treat patients as test animals, but a highly stringent scientific research conducted with great care and great respect for human rights. It is our hope that with joint efforts, we will create a legal, ethical and convenient research.

II. Introduction of Good Clinical Practice (GCP)

Preface

The "Good Clinical Practice" (GCP) is a guideline stipulated to ensure the quality of drug clinical trials. After the announcement of the "New Drug Safety Surveillance Policy" in 1993, clinical trials in Taiwan have entered a new era. After the enforcement of the "Good Clinical Practice" in December, 1996 by the Department of Health, the quality control of clinical trials in Taiwan has achieved the same level of other developed countries. To be in a consistent format with the internationally adopted "Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance"(ICH E6), the Department of Health revised and announced the "Good Clinical Practice" in accordance with paragraph 2 of article 42 of the Pharmaceutical Affairs Act in December, 2001.

Objective

The objective of stipulating the "Good Clinical Practice" is to ensure the credibility of clinical trial results and to protect the subject's rights. In terms of ensuring the credibility of clinical trial results, the guideline reinforces that every step during the clinical trial must be documented. As for the protection of subject's rights, there are detail provisions in the guidelines that govern the composition and operation of the Institutional Review Board in order to prevent IRB reviews from becoming a mere formality.

Introduction of content

The content of the "Good Clinical Practice" is divided into 8 chapters and 123 articles.

The content introduces in detail the responsibilities of the medical institution, principle investigator, Institutional Review Board and trial sponsor during the clinical trial. The provisions within the guideline govern the implementation details and liability of the clinical trial. The chapter titles in the "Good Clinical Practice" are as follows:

Chapter 1 General Provisions

Chapter 2 Protection of Trial Subjects

Chapter 3 Institutional Review Board/ Independent Ethics Committee

Chapter 4 Trial Investigator

Chapter 5 Trial Sponsor

Chapter 6 Application and Review of Clinical Trial

Chapter 7 Implementation of Clinical Trial

Chapter 8 Attachments

The "Good Clinical Practice" states in article 4 that "the implementation of clinical trial should conform to the ethical principles of the Declaration of Helsinki". Other provisions also reflect the ethical principles of the Declaration of Helsinki in that the subject's rights, safety and welfare should take precedence over scientific and social interests and that each trial staff should receive education, training and possess experience qualified for the trial.

Provisions in chapter 2 Protection of Trial Subject and chapter 3 Institutional Review Board govern the composition and operation of the Institutional Review Board as well as the content of the informed consent form. In reference to the "Operational Guidelines for Ethics Committees That Review Biomedical Research" laid down by the World Health Organization, the Department of Health announced the "Healthcare Institution Institutional Review Board Organization and Operating" on 2003/11/12 as a reference for the establishment of medical Institutional Review Board. On 2009/5/20, paragraph 3 of article 78 of the "Medical Care Act" was amended: "The plan for human trial by a medical care institution referred to in the preceding two Paragraphs should be reviewed and approved by personnel in medical technologies, legal experts, social justice or local organization representatives and the ratio of one single sex

should be no less than one-third; the same applies to trial modification. Reviewer should avoid conflict of interests."

The operation of the Institutional Review Board consists of expedited review and general review. General reviews must undergo discussions and voting before a final verdict, including approval, rejection and revision comments before approval, is made. The meeting procedure must be documented. The Institutional Review Board must retain all relevant information (such as, written procedures, member list, member occupation/contact list, submitted documents, meeting minutes and correspondence) for at least 3 years after the clinical trial is terminated so that the competent health authority can request for review at any time. To ensure the operation standard of Institutional Review Board, a detailed written operation procedure, also known as the Standard Operation Procedures (SOP), should be in place.

The objective of an Institutional Review Board review is to protect the subject's rights, safety and welfare; therefore, the review should emphasize on trials involving venerable subjects. Apart from reviewing the trial protocol, qualification, education and experience of the trial investigator as well as other relevant information prior to the commencement of the project, the Institutional Review Board should also conduct routine assessment during the trial period based on the risks faced by the subjects.

Informed Consent Form

An informed consent form is an evidence to prove that the doctor has fulfilled his obligation to inform. It is an important tool to protect subject's rights and also one of the important review items for the Institutional Review Board. The informed consent form must be composed carefully and should not be treated as a simplified version of protocol. The reader of the informed consent form is the patient or his/her legal representative; therefore, its content should adopt a narrative writing method, be friendly and in the colloquial language, and avoid professional terms. The content should be prepared based on middle high school grade-3 (basic obligatory education level) language level and avoid mix of Chinese and English. It is advised that the informed consent form be proofread by a reader of middle high school grade-3 language level before finalizing the content. If the reader can comprehend the text without further explanation, the goal of narrative writing is achieved. Non-medical staff in the Institutional Review Board contributes significantly to whether the content of informed consent form is narrative. If the research is random and double-blinded, it can be described as follow:

This trial is a randomized and double-blinded research. The purpose of which is to ensure that the results cannot be distorted by human factors. Half of the subjects will be administered with study drugs while the other half with "placebo drug". The so-called "placebo drug" is an active drug with an identical appearance to the study drug. The decision of who will receive the study drug and who will receive the "placebo drug" will be determined by the ratio similar to flipping a coin. Neither you nor your study doctor will know which medication you receive.

The informed consent form should include:

1. Human trials are a type of research.
2. Trial objective, method and relevant tests
3. Subject responsibilities, including restrictions, limitations and instructions during the trial.
4. Experiment aspect of the human trial
5. Anticipated risks or inconvenience for the subject, fetus, infants or breastfed babies.
6. Reasonable clinical benefits that can be expected. If the trial does not involve any clinical benefit, the subjects should also be informed.
7. Other treatment methods or procedures as well as their potential benefits and risks.
8. Indemnification and/or treatments entitled to the subject in the event of trial-related injuries.
9. If there are foreseeable compensations, the subject participating in the trial should be informed.
10. If there are foreseeable extra costs, the subject participating in the trial should be informed.
11. Subject participation is of voluntary nature. The subject reserves the right to refuse to participate or withdraw from the trial at any time without being penalized or compromising the entitled interests.
12. By signing the informed consent form, the subject consents that the original medical records be reviewed by the monitor, auditor, Institutional Review Board/Independent Ethics Committee and competent health authority to ensure that the human trial procedure and/or data conform to the relevant laws and regulations without violating the confidentiality of subject's identification.

13. Subject identification records should be kept confidential and non-disclosed as required by relevant laws and regulations. The subject's identification should remain anonymous when publishing trial results.
14. If the new information might affect the subject's willingness to continue to participate in the clinical trial, the subject or his/her legal representative should be informed of such information immediately.
15. Acquire information relevant to the trial and find out ho the subject's contact personas and his/her contact method for subject's interests and rights and the contact person and his/her contact method in the event of injuries incurred during the trial.
16. Foreseeable situations and reasons for the subject to terminate his/her participation in the trial.
17. Estimated duration of subject's participation in the human trial.
18. Approximate number of subjects participating in the trial.

Other than the trial objective, method, relevant test and anticipated trial results for the research, the informed consent form should also include potential side effects, risks and other potential treatment methods. It should further state that the subject may withdraw his/her consent and terminate his/her participation at any time during the trial without having to provide any reason.

In the case that the subject or his/her legal representative is illiterate, an impartial witness should be present at all time during the discussion of the informed consent form. Once the inform procedure is complete and the subject or his/her legal representative is willing to participate in the trial, the subject should, within his/her capacity, sign and date the informed consent form in person.

Patient Safety

Adverse drug reactions (ADR) are poisonous responses of human to drugs. For new drug or new usage with unknown dosing regimen, there is no known relation between adverse reactions and trial. Therefore ADRs are referred to as adverse events (AE) to cover all adverse events in subjects during human trials, regardless the correlation with the trial which is confirmed during post hoc analysis. As a result, adverse events are used to merely describe the condition of subjects. In the event of serious adverse event, the Department of Health should be notified immediately to determine whether the research should be terminated prematurely. Serious

adverse events include death, fatal events, and events that may lead to hospitalization, prolong hospitalization or cause permanent disability or congenital deformation. Failure to inform the Department of Health of any serious adverse event is a punishable defense that will be penalized strictly by the health authorities worldwide. When serious adverse events are reported by subjects, other than notifying the competent health authority, the Independent Data Monitoring Committee (IDMC) established by the trial sponsor or the Institutional Review Board should investigate whether the research should be terminated prematurely. The Independent Data Monitoring Committee is established by the trial sponsor to routinely assess the trial progress, safety data, and important efficacy endpoints and to advise the trial sponsor whether to continue, revise or terminate the trial; therefore, it is a highly important in terms of protecting patients' safety.

Quality Assurance

To ensure that every step during the human trial can be validated post hoc, all corrections or backup made to or for the case report should not erase the original entry. All corrections should be made by crossing out the original entry and filling in the new information next to it. The person who made the correction should sign and date next to the correction, and record the reason if necessary. When a correction is made, the original entry should still be legible; therefore, it is forbidden to use a pencil or correction fluid. There are detail regulations governing the procedure for processing lab data and computer information.

Chapter 5 of the "Good Clinical Practice" specifies the responsibilities of trial sponsor including the selection of study investigator, provision of study drug and other relevant information as well as the establishment of a human trial quality assurance system. In the human trial assurance system, other than the written standard operation procedures, the pharmaceutical company should also assign an appropriate individual or committee to implement or monitor the trial, perform information processing, validation, statistic analysis and to compile reports. The management record of the study drug should include the quantity, transport condition, receipt, allocation and recycle of drugs as well as the destruction of remaining drugs. It should state specifically that the study drug should not be released to individuals other than trial subjects. The trial sponsor should preserve all relevant documents up to at least 2 years after the trial is officially completed or as requested by relevant regulations.

Since all documents are accessible to the trial sponsor and the central competent health authority for review, the central competent health authority reserves the right to inspect the trial location, medical institution, exam rooms, and all information (including original data) and documents. The inspection result will not only affect the approval of drug license application or the decision of whether the procedure can be used as a conventional medicine, it should also conform to the provisions of the Medical Care Act, Physicians Act, Guidelines for Medical Care Act and Pharmaceutical Affairs Act. For example, forgery of false data is punishable by law.

Human trials are experimental researches conducted on human subjects with the purpose of proving the effectiveness of new treatment methods. They are the most fundamental and critical step in medical development. Since human trials are conducted on human subjects, they will inevitably attract the heat in a modern society with an upsurge in human rights. The enforcement of the "Good Clinical Practice" not only enhances the credibility of research results, but it also ensures the investment of sponsors in human trials and governs the implementation details to protect patients' rights. It also provides a regulatory reference for physicians participating in human trials of international collaborations. It is a regulation that creates a win-win situation for physicians, trial sponsors and trial subjects.

III. Legal responsibilities of human trials

Human trials are a mandatory and critical step to transform scientific research results into practical clinical applications. They are referred to as human trials in the Medical Care Act and clinical trials in the Pharmaceutical Affairs Act. There has not been a consistent terminology. From the perspective of trial subjects, human trials are not obligatory treatments and the participation may lead to unknown consequences. Therefore the informed consent form for human trials might look similar to those of regular medical procedures, the nature of which are entirely different.

The implementation of human trial involves scientifically unknown risks and therefore may not be beneficial to the subjects. In addition, subject welfare is not the primary objective for researchers when conducting human trials. Hence, there tends to be a conflict of interests between researchers and subjects during human trials. As a result, a subject's

consent for human trial is more important than a patient's consent for medical procedure. A subject's consent is not simply a signature on the informed consent form. It is a demonstration of consent after understanding the trial objective, meaning, risks and values by the subject. An effective communication between researchers and subjects is the key to subject consent. The informed consent form itself is a record of such communication process.

Indemnification or insurance terms entitled to the subjects in the event of injuries during human trials must be stated in the informed consent form in accordance with article 79 of the Medical Care Act. The content of this article aims to clarify the responsibilities of hospitals, physicians and trial sponsors to compensate and indemnify and to provide a template for the content of informed consent form referring to the compensation and indemnification.

Indemnification Obligor

Provision 1 of article 79 of the Medical Care Act states: "When conducting human trials, medical care institutions shall pay proper attention to the medical procedure, and shall first obtain a written letter of consent from the trial subject." Statutorily, the parties involved in a human trial include the medical institution and subject; therefore, the medical institution is the indemnification obligor in the case when injuries happen and compensation is to be paid to the subject. Even though several medical institutions request trial sponsors (such as pharmaceutical companies) to sign an affidavit which demands compensations to be paid by the sponsor on behalf of the hospital, according to article 268 of the Civil Law: "When one party of the contract had an agreement with a third party to pay to the other party and the third party refused to pay, the party is still held liable for the compensation." From the perspective of the subject, the medical institution remains liable to compensate the injuries attributable to the human trial.

Some medical institutions request trial sponsors to sign an affidavit to transfer the liability to compensate the subject. However according to the "Good Clinical Practice", such affidavit should exclude situations where the injuries are caused by medical malpractice. Article 47 of the Good Clinical Practice states: "The trial sponsor should be liable for the indemnification related to the trial caused by the trial investigator or trial institution or should be responsible for purchasing liability insurance. Indeminification attributed to medical malpractice are not included." That is, the individual

responsible for the medical malpractice (medical institution or trial personnel) is liable for providing indemnification for injuries resulted from such malpractice. Such liability cannot be transferred to the trial sponsor.

Some informed consent forms might have terms such as: exemption from liability to indemnify. According to article 18 of the Good Clinical Practice:" The informed consent form or any written documents relating to the subject shall not cause subjects, legal representatives, or authorized individuals to waive their legal rights or exempt trial investigator, trial institution, trial sponsor or any agents from any liabilities. Any provisions violating the above statement are rendered ineffective." Therefore, in a human trial, indemnification for injuries (misdemeanor) shall not be waived by citing article 222 of the Civil Law. Indemnification for injuries not attributable to medical malpractice can be transferred to the trial sponsor. The medical institution or individual responsible are, however, liable for indemnification resulted from medical malpractice. In addition, the medical institution is jointly and severally liable for all indemnification.

Differences between the responsibilities of human trial and conventional medical malpractice

Negligence refers to any action that should or could be prevented and yet is failed to be prevented by the individual. Regardless of human trials or conventional medical practices, individuals resulting in such negligence shall be solely liable. This is to follow out the principle of liability in order to govern the individuals in fulfilling their duties. As a result, article 47 of the Good Clinical Practice states: "Events attributable to medical malpractice by trial investigator or trial institution are not included."

In conventional medical practice, if there is no negligence involved in the medical practice; then the known risks (side-effects) of the medication should be the responsibility of the pharmaceutical company. In Taiwan, it is decompensate by the Drug Relief Fund to protect patient and reduce legal action. It also conforms to the principle of consumer protection law. However, if the injury was caused due to an unknown risk or was beyond the expected risk level, given that it was unknown or unexpected by the trial sponsor, the sponsor shall not be the liable such injury.

The repartition of risk is different in human trial and conventional medical care. Provided that the treatment method, effectiveness and safety level are uncertain in a human trail, uncertainty of the result is higher than that in conventional medical care. For subjects, it is not obligatory to accept the risk. In human trials, given that there is no medical malpractice involved,

the subjects are burdened with known risks, which demonstrates with the function of the informed consent system. Whereas if the unknown risk or injury was beyond the expected level, according the human trail ethic point of view, the trial sponsor is responsible. However, the trail sponsor could transfer the risk by purchasing human trail insurance. Therefore, in Taiwan, the insurance coverage for the human trail includes: "the insurer will be liable to indemnify, according to the terms of the informed consent form, in case of injuries caused by adverse drug reaction or death of subject during the human trail as insured by the medical insurance. The insurer should inform the insurance company during the trail period and request for compensation. The insurance company will be liable to compensate the insurer." The exclusion clause states: "The term covers the compensation liability for the expected side-effects of the insured drug but not those beyond. This is based on the same principle.

Table 1: Distraction of medical injury hazards

Medical practice	Negligence	No Negligence
Conventional medical practice	Perpetrator is responsible	Known risk: pharmaceutical company is liable (Drug Relief Fund)
		Unknown risk: no responsibility, no indemnification
Human trail	Perpetrator is responsible	Known risk: subject is liable for risk(Not covered in the insurance)
		Unknown risk: trial sponsor is liable(Within the insurance coverage of human trail compensation)

Note: The medical care facility is jointly and severally liable for all injury indemnification.

Recommended context for subject's informed consent form regarding injury indemnity and compensation.

In regard to the content concerning the indemnification, reimbursement and insurance in the informed consent form, it is recommended that the content specifies the compensation or treatment the subject is entitled to if injury related to the human trail occurs.

It should not, however, include any statement of exclusion or reduction of legal liability and should not mislead the subject to underestimate the risk by the offer of attractive compensation. Therefore, it should

inform who will be liable for the final indemnification, the reason of the indemnification and its coverage. It should also inform the subject of any compensation remedies beyond what is required by law. In addition, the content should specify who will provide the follow-up medical care, as the subject will not be responsible for the charges incurred by the follow-up medical care. Each Institutional Review Board will decide independently whether or not to inform the subject the existence of insurance.

Recommended context:

The trial sponsor will be liable to indemnify adverse events or injuries incurred during the proposed human trial as obliged by the law. Adverse events or expected injuries caused by adverse events listed on the informed consent form will not be compensated. (Note: if the trial is not sponsored by a pharmaceutical company, revise the trial sponsor as trial institution).

The purpose of the above paragraph is to inform the subject: the trail sponsor is liable for injury indemnification required by law. Only adverse events or injuries unpredicted by the human trail proposal will be indemnified. The subject will be solely responsible for the expected risks stated in the written informed consent form. This can be view as a demonstration of the function of the informed consent form.

- **Beside the compensation, indemnification and medical care required by law, this trail will not provide any other types of compensation. If you do not accept this risk, please do not participate in the trial.**

The purpose of the above paragraph is to remind the subject to be cautious when evaluating the risks and not to rash into participating in any trial. If the trail will offer other types of compensation other than medical care, the statement can be revised as: beside the compensation, indemnification and medical care required by law, this trail will offer compensation of XXX.

- **The hospitals will provide professional medical care and consultation for adverse events or injuries incurred during the proposed human trial. You will not be responsible for the medical charges accrued in the treatment for the adverse events or injuries.**

According to article 9 of the Medical Care Act, the National Health Insurance does not disburse the fee of human trial. Once the patient

participates in the human trail, all medical charges incurred during the trail period will be at the expense of the trail sponsor.

•You will not waive any legal rights by signing this consent form.

The above paragraph is meant to be declaratory. Its existence or absence will not affect the subject's rights. Nevertheless, adding such paragraph will provide a reminding function.

•(This trail has been insured for liability.)

Item 6 of paragraph 3 of article 79 of the Medical Law: "Indemnification or insurance mechanism related to the trial" indicates that there is no compulsory insurance provision for human trails in Taiwan. However, if the trial is insured, such information shall disclose in the informed consent form.

The indemnity and compensation of human trail is the last resort of the remedial measures. Nonetheless, the remarkable contribution of subjects participating in the trial to the advancement of the medical advances should not be denied. However, the goal that human trail development strives to achieve in Taiwan is to reach consensus between hospitals, doctors, human trail sponsors and other related parties on the compensation and indemnification in the subject informed consent form.

Reference

- The amendment of the Good Clinical Practice (GCP) on January 6th 2005.
- The amendment of the Medical Care Act of April 28th, 2004.
- National Health Insurance Act, amended on June 18th, 2003.
- Civil Law, amended on June 26th, 2002.
- The First Insurance Co. Ltd., clinical trail insurance policy

- Gratitude to Dr. Lin Chi Liao for valuable advice and assistance on finalization of the report

IV. Protection of vulnerable subjects

The concept of vulnerable subjects is very important from the research ethic and the degree of regulation compliance point of view. The U.S. HHS article 45CFR 46.111(b) and the FDA article 21 CFR 56.111(b) request that "when certain or all subjects might become vulnerable subjects due to

'forceful' or 'inappropriate impact', the research should include additional protection measures to ensure the subject's rights and welfare." The HHS and FDA regulation as well as the International Medical Law Association ICH guideline provide a list of candidates of vulnerable subjects, including children, prisoners, pregnant women, handicapped, mentally handicapped, or economically impoverished and under-educated population. It does not, however, provide a distinct definition of vulnerable subjects nor the reason that might cause them to be injured.

The definition of vulnerability

The ICH1.61 indicates "vulnerable subject" refers to an individual, due to personal expectation of "profiting by participating in a human trail" or "fear of retaliation by the senior members of the group if refuse to participate" thus results in inappropriate impact on the subject's voluntarity to participate in the human trail. Therefore, for people within the hierarchy system, such as students (medical, dentistry, pharmaceutical, nurse), or lower level personnel (hospital/laboratory), pharmaceutical companies employees, military service personnel, detainees, are all considered vulnerable subjects. In addition, vulnerable subjects also include patients with incurable disease, dependants of nursing home, unemployed or extremely deprived people, patients in critical condition, ethnic minority, homeless people, vagrants, refuges, minors, and other non autonomous people.

Autonomy

Concerning one's autonomy, there are two factors to be considered: mental capacity and voluntariness. The so-called mental capacity is the ability to understand and process information, it is called the capacity of autonomy here. The so-called voluntariness is to think without the control or impact from other people. Therefore, the subject's total autonomy must possess the ability to understand and process information, and the liberty to "voluntarily participate in researches in a condition without external control or under inappropriate influence. Therefore, vulnerable subjects are subjects whose autonomy can be easily manipulated by inappropriate influence or exploitation.

Analyzing the constituent factors of autonomy can help to understand whether or not subject's autonomy is inappropriately exploited. Of course, children and mentally handicapped people lacking autonomy are susceptible to injuries. Subjects who are under critical condition, of lower-class level, economically or educationally deprived, or socially marginalized,

suffering fatal or incurable disease are vulnerable subjects who are vulnerable due to a restricted autonomy. However, not all the cases are the same in the vulnerable subjects group. The level of vulnerability of each individual subject varies, thus it is necessary to consider the level of vulnerability of each individual subject. The level of vulnerability of each individual subject varies according to his/her autonomy or the conditions that influence his autonomy.

Types of vulnerability

Vulnerable subjects are vulnerable when their body is being controlled, highly pressured, under inappropriate influence or manipulated. Sometimes vulnerable subjects are forced to participate in researches when their body is controlled by others, which means the loss of complete autonomy. The classical example is the "low body temperature research" that the Nazi concentration camp conducted on their prisoners with a final objective of death of the subject – subjects have no choice over their participation and their bodies were completely under the control of the researchers. Recently there is another case where a surgeon in California conducted a clinical trail on a patient who refused to participate by continuing the anesthesia after the surgery to proceed with the trial. "Highly pressured" refers to the approach of using threats that can cause injuries or forcefully controlling someone. For example, the dependents of the nursing homes are forced to make a choice between "participating in the research" or "leaving the nursing home". The so-called "inappropriate influence" means to inappropriately use "trust" and "authority" to influence the subject into making a choice he/she would not have made otherwise. For example, when the patient asks himself whether or not to participate in a research, even when knowing that participating in this research does not correspond to the patient's best interest, the doctor still encourage the patient to participate. "Manipulation" means to deliberately handle certain conditions or information, so to cause someone make decision that he would not have made otherwise. For example, lying, withholding information, or exaggerating the facts, and so on.

The project investigator may not want to harm the vulnerable groups intentionally; yet, it is easy to overlook the situation of the vulnerable group. Regardless of the importance of the research to the medicine or science discipline, human trials that may sacrifice the subjects' interests should not be executed.

V. Introduction of group harm

There has been incident where researchers conducted human trails on aboriginal groups in Taiwan that caused controversy. The reason is due to the fact that researchers were unclear or ignored the "group harm" of subject protection. Here we introduce the "group harm" concept, which includes the introduction of potentially vulnerable groups and the types of measures that researchers can undertake to reduce the risk of such vulnerability, as a reference.

The so-called "group" or "communities" implies a group of people with a specific characteristic. Sometimes it can be categorized by national or racial groups (such as African American, Spanish, Bantu), religious groups (Islam, Taoism, Christian), geographical groups (New Yorker, Parisian, New Zealander), professional groups (farmers, doctors, teachers), or disease group (diabetes, low vision, cancer patients). An individual can belong to more than one group. Some people might consider themselves as a member of certain group or might be placed in a group by others.

Due to their particular status in the society, some groups might be under the risk of endangerment due to the participation of its members in the research. In general, these groups include those used to be discriminated or are still being discriminated (such as African American, American Indians, Alaskan aboriginals), those with limited access to educational opportunities, social assistance or medical care (such as people of lower socio-economic status), and people who are behaviorally or politically blamed (such as sex workers, drug addicts, religious fanatics). Although sometimes only members who participate in the research might be endangered, but when the majority or all members are endangered, the whole group is endangered, including those who did not agree to participate.

These endangerment might include humiliation, loss of social status, genetic decision-making rights, and violation of cultural or community order and values.

The precedents of group harms in other countries

Although some researches endanger certain groups due to the lack of careful design, yet, even with careful design, members of certain groups might still be inevitably affected by the result. The following cases illustrate that the recipient of negative impacts is not the subject himself but rather the group:

Phillips, Warner, Meschino et al. conducted a study based on the Jewish family of the Central Europe. The result was published in the Journal of Clinical Trial in 2000 (Phillips KA, Warner E, Meschino WS, Hunter J, Abdolell M, Glendon G, Andrulis IL, Goodwin PJ., "Perceptions of Ashkenazi Jewish breast cancer patients on genetic testing for mutations in BRCA1 and BRCA2," Clin Genet. 2000 May;57(5):376-83). This report led to the misconception of Jewish being susceptible to gene defects and genetic diseases thus might result in unfair health and medical insurance in the society for all Jewish in central Europe.

Klausner and Foulks published a report in 1982, entitled "The Eskimo Capitalist: oil, alcohol, and social change." (Klausner, S. and Foulks, E. (1982). Eskimo Capitalists: Oil, alcohol and social change. Montclair, NJ: Allenheld and Osmun). The content of this report is about the drinking problems of the Alaskan aboriginals living in Barrow, hence stigmatized the Alaskan aboriginals. This is an example where the group was stigmatized and the city was censured for its economic status as the result of a research report.

In 1994, Hernstien and Murray indicated many researches trying to understand the intelligence of different ethnic groups. For example the result of a research entitled: "Bell-shaped distribution: the intelligence and hierarchical structure of the United States" gave negative reputation to some ethnic groups investigated in the research. There are many similar types of researches that caused damages to members of particular ethnic groups due to the lack of careful design and narration.

Reduce group harm.

There are many ways to reduce the risk of group harms:

- Community consultation: researchers should understand the intended groups of study better, in order to ensure that the participating groups comprehend the potential harms, and that the research is designed for the benefit the group.
- The Collaborative IRB review: certain groups, such as tribal groups, retired groups, and academics, have their own research ethnic review procedures. The researchers should discuss with the local ethic review groups, to obtain the consent from such groups.
- Plan on-going consultation: researchers should maintain close contact with the group to ensure that during the implementation or modification of research project, the group leader can provide accurate information related to the research. Researchers should

understand that in order to reduce inevitable harms, the content of the original protocol might be modified or terminated.

- Plan disclosure of research results ahead of time: most group harms are caused by improper publication of research result. Before publishing or announcing the results, researchers should discuss with each group to inform the members who participated in the research how the research results will be published and the implication of such publication. This will substantially reduce the possibility of group harms.

Researchers should carefully evaluate and assess whether the research will result in group harm, and when necessary, take proper measures to reduce as much risk as possible.

VI. Important References

Good Clinical Practice
(Amended on 6 January 2005)

Provisions

Chapter I General

Article 1 These rules are established in accordance with Section 2, Article 42 of the Pharmaceutical Affairs Law.

Article 2 The regulatory authority for these rules is the Department of Health, the Executive Yuan.

Article 3 The terminologies in these rules are defined as follows:

1. Clinical Trial/Study: An investigation in human subjects intended to discover or prove the clinical, pharmacological or other pharmacodynamic effects of a drug.
2. Nonclinical Study: Biomedical studies not performed on human subjects.
3. Subject: An individual who participates in a clinical trial, either as a recipient of the investigational drug or the comparator drug.
4. Informed Consent Form: A document voluntarily signed by a subject confirming a willingness to participate in the trial after having been informed and understood the information related to the clinical trial and after consideration of all elements for determining whether or not to participate in the trial.
5. Institutional Review Board (IRB): A committee composed of professionals with medical backgrounds and fair persons from the society with non-medical backgrounds with the responsibility to protect the rights, safety and well being of the subjects.
6. Institution: A medical institution that performs the clinical trial.
7. Investigator: A person responsible for the conduct of the clinical trial in the Institution.
8. Sponsor: An entity that initiates and manages the clinical trial.

9.Contract Research Organization (CRO): A person or an organization contracted by the sponsor to perform one or more of a sponsor's trial-related duties.

10.Investigational Drug: A drug subject to trial or active components or placebos used as reference in a clinical trial, including any application of any commercialized drug in any purpose, prescription, package, indication other than those which have been approved or for the purpose of obtaining further information with regard to the approved purposes.

11.Protocol: A document that describes the objective, design, methodology, statistical considerations and organization of a clinical trial, which may also provide the background and rational related to the trial.

12.Investigator's Brochure: A compilation of the clinical and nonclinical data of the investigational drug.

13.Adverse Drug Reaction: A response that is harmful and unintended following use of the drug. There should be a reasonable causal relationship between the reaction and the investigational drug.

14.Adverse Event: Any undesirable occurrence in a subject following participation in a trial, which does not necessarily have a causal relationship with the investigational drug.

15.Blinding/Masking: A procedure in which one or more parties to the trial are kept unaware of the treatment assignments. Single blind refers to subjects being unaware and double blind refers to the subjects, the investigator, the monitor and, in some cases, the data analyst being unaware of the treatment assignments.

Article 4 Clinical trials should be conducted in accordance with the ethical principles of the Declaration of Helsinki.

Before a Clinical trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual subject and society. A trial should be initiated only if the anticipated benefits exceed the potential risks and inconveniences.

The rights, safety and well being of the subjects are the most important considerations and should prevail over interest of science and society.

The IRB should safeguard the rights, safety and well being of the subjects. Special attention should be paid to trials that may include vulnerable subjects.

Article 5 The Investigator should obtain the Informed consent forms voluntarily given by the subjects prior to conducting the clinical trial.

The investigator or a person designated by the investigator should fully inform the subjects of the information of the proceedings of the clinical trial, the provisions of the informed consent form and all written opinions related to the clinical trial which are approved by the IRB, have the form personally signed and dated by the subject following their full understanding.

With regard to actions to be taken in the previous two paragraphs, if the subject is a person with no legal capacity, his/her legal representative shall act on his/her behalf. If the subject is a person with limited legal capacity, the consent from his/her legal representative shall be obtained. If the person is not a person of none or limited legal capacity, but cannot act on his/her own due to unconsciousness or mental disorder, a representative with authority to give consent shall act on his/her behalf.

The person with authority to give consent referred to in the previous paragraph shall be a spouse or a family member who cohabits with the subject.

Article 6 During subjects' participation in a trial and the subsequent follow-up period, the Investigator and the Institution should ensure that adequate medical care is provided to a Subject for any adverse event. The investigator should inform a subject when medical care is needed for any illness of which the investigator becomes aware.

Article 7 The investigator should inform the subject's referring physician if the subject has a referring physician and if the subject agrees to the referring physician being informed.

Article 8 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate in a trial.

During the performance of the clinical trial, neither the investigator nor the trial staff should coerce or unduly influence a subject to continue in a trial.

Article 9 The subject may withdraw from a clinical trial at any time without giving any reason.

The investigator should make a reasonable effort to ascertain the reason for a subject's withdrawal from a clinical trial, while fully respecting the subject's rights and wiliness.

Article 10 The Sponsor should not coerce or unduly influence the subjects about the amount and the method of payment to the subjects

Payments to a subject should be prorated in accordance with the progress of the clinical trial and not made only after completion of the trial, except small amounts.

The method of payment to subjects, the amount and the prorated schedule should be specified in the informed consent form and other written information provided to the subjects. The method in which payment will be prorated should be specified.

Article 11 The identifies of the subjects and their records related to the clinical trial should be kept confidential.

Article 12 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

Article 13 No clinical trial shall be performed without approval from the IRB.

The IRB may give approval for an institution to perform a clinical trial after review of the informed consent form, the protocol and other relevant documents.

Article 14 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

Article 15 All clinical trial information should be recorded and stored.

Chapter II Protection for Subjects

Article 16 Prior to the beginning of the trial, the investigator should have the IRB's approval of the informed consent form and any other written information to be provided to subjects.

The approval referred to in the previous paragraph should be in writing.

Article 17 The informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent and the subject or the subject's legal representative or a person with authority to give consent should be informed in a timely manner.

Any revised informed consent form and any other written information to be provided to subjects should receive the IRB's approval. The approval by the regulatory authority should also be obtained if the clinical trial is performed under the approval of the regulatory authority.

The information referred to in the first paragraph and the approval referred to in the second paragraph of this article should both be done in writing.

Article 18 Neither the informed consent form nor any other written information to be provided to subjects should contain any language that causes the subject, the subject's legal representative or the person with the authority to give consent to waive any legal rights, or that releases the investigator, the institution, the sponsor, or their agents from liability.

Any language in violation of the previous paragraph shall be null.

Article 19 The language used in the oral and written information about the trial, including the informed consent form, should be as colloquial and non-technical as practical and should be understandable to the subject, the subject's legal representative or the person with authority to give consent.

Article 20 Prior to a subject's participation in the trial, the informed consent form should be signed and personally dated by the subject, the subject's legal representative or the person with authority to give consent.

Before informed consent form may be obtained, the investigator, or a person designated by the investigator, should provide the subject, the subject's legal representative or the person with authority to give consent ample time and opportunity to inquire about details of the trial.

All questions about the trial should be answered to the satisfaction of the subject, the subject's legal representative or the person with the authority to give consent.

The persons referred to in the second paragraph of this article should sign the informed consent form.

In emergency situations where it cannot be expected to obtain prior consent of the subject, the subject's legal representative or the person with authority to give consent, the trial may be performed prior to obtaining the written consent from the subject, the subject's legal representative or the person with authority to give consent if the protocol specifies the procedure for handling emergency cases. However, if the written consent may be obtained from the subject, the subject's legal representative or the person with authority to give consent, it should be obtained immediately.

Article 21 If a subject, the subject's legal representative or the person with authority to give consent is unable to read, an impartial witness should be present during the entire informed consent discussion.

The witness should read the informed consent form and any other written information to be provided to the subjects to attest that the information was accurately explained to, and apparently understood by, the subject, the subject's legal representative or the person with authority to give consent.

Under the circumstances referred to in the first paragraph, the subject, the subject's legal representative or the person with authority to give consent should still personally sign and date the informed consent form. However, the signature may be replaced by a fingerprint.

After the tasks referred to in the second paragraph are completed and after confirmation that the informed consent was freely given by the subject, the subject's legal representative or the person with authority to give consent, the witness should sign and personally date the informed consent form.

The trial staff may not serve as a witness.

Article 22 The informed consent form or other written information to be provided to the subjects should include explanations of the following:

1.That the trial involves research.
2.The purpose of the trial.
3.The trial treatment(s) and the probability for random assignment to each treatment.
4.The trial procedures to be followed, including all invasive procedures.
5.The subject's responsibilities.
6.Those aspects of the trial that are experimental.
7.The reasonably foreseeable risks or inconveniences to the subject or to an embryo, fetus, or nursing infant.
8.The reasonably expected benefits.
9.The alternative procedures or courses of treatment and their important potential benefits and risks.
10.The compensation or treatment available to the subject in the event of trial-related injury.
11.The anticipated remuneration, if any, to the subject for participating in the trial.
12.The anticipated expenses, if any, to the subject for participating in the trial.
13.That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
14.That by signing the informed consent form, the subject agrees that the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records to verify that the clinical trial procedures and data are in compliance with relevant laws and regulations, with the undertaking from such persons not to violate the confidentiality of the subjects' identifies.
15.That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

16. That the subject, the subject's legal representative or the person with authority to give consent will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
17. The person to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
18. The foreseeable circumstances and reasons under which the subject's participation in the trial may be terminated.
19. The expected duration of the subject's participation in the trial.
20. The approximate number of subjects involved in the trial.

Article 23 Prior to participation in the trial, the subject, the subject's legal representative or the person with authority to give consent should receive a copy of the signed and dated informed consent form and any other written information provided to the subjects, except if the clinical trial is used for the treatment or handling of emergency illness and it is expected that the consent from the subject or the person with authority to give consent cannot be obtained in advance.

During a subject's participation in the trial, the subject, the subject's legal representative or the person with authority to give consent should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

Article 24 Non-therapeutic trials may not be conducted in subjects with consent of a legal representative or a person with authority to give consent, unless all of the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can sign the informed consent form personally.
(b) The foreseeable risks to the subjects are low.

(c)The negative impact on the subject's well being is low.
(d)The trial is not prohibited by law.
(e)The written approval of the IRB is obtained.

The trials conducted in accordance with the previous paragraph should be conducted in patients having a disease or condition for which the investigational drug is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

Chapter III Institutional Review Board (IRB)

Article 25 The institution should have an IRB to review the clinical trial. Members of the IRB should have the scientific, medical or ethical qualifications and experience to review and evaluate the clinical trial.

The IRB should include at least five members, among whom at least one member whose primary area of interest is in a nonscientific area and at least one member who is independent from the institution.

The IRB should establish and follow written operating procedures and should maintain written records of its activities and minutes of its meetings.

The composition and operation of the IRB should comply with the rules publicly announced by the regulatory authorities.

Article 26 The resolutions of the IRB should be in compliance with the fourth paragraph of the previous article.

Article 27 Only members who participate in the IRB review and discussion should vote in a resolution or provide their opinion.

Article 28 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations or resolutions of the IRB provide opinions.

An IRB may invite nonmembers with expertise in special areas for assistance.

Article 29 The IRB should retain written procedures, list of members, vocations of members, contact lists, submitted documents, minutes of meetings, letters and other information related to clinical trials for a period of three years following completion of the trials and make them available upon request from the regulatory authorities.

The IRB may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and full list of members and the IRB may not refuse to provide them.

Chapter IV Investigator

Article 30 The investigator should meet the qualifications and abilities specified by the regulatory authority and the experience for the proper conduct of the trial.

Article 31 The investigator should be thoroughly familiar with the appropriate use of the investigational drug as described in the protocol, in the current investigator's brochure, in the drug information and in other information sources provided by the sponsor.

Article 32 The investigator should be aware of and should comply with these rules and the applicable regulatory requirements.

Article 33 The investigator and the institution should permit monitoring and auditing by the sponsor and inspection by the appropriate regulatory authorities and their designated authorities.

Article 34 The investigator should maintain a list of trial related staff to whom the investigator has delegated relevant trial-related duties.

Article 35 The investigator should be able to demonstrate a potential for recruiting the required number of subjects within the period specified in the protocol.

Article 36 The investigator should have sufficient time to conduct and complete the trial within the trial period.

Article 37 The investigator should have available an adequate number of qualified staff and adequate facilities to conduct the trial properly and safely.

Article 38 The investigator should ensure that all trial related staff are adequately informed about the protocol, the investigational drug, and their trial-related duties and functions.

Article 39 If the protocol and the investigator's brochure is updated during the clinical trial period, the investigator and the institution should supply a copy of the updated versions to the IRB

Chapter V Sponsor

Section I General

Article 40 The Sponsor is responsible for selecting the investigator.

Article 41 Before entering an agreement with an investigator and an institution to conduct a trial, the sponsor should provide the investigator and the institution with the protocol and an up-to-date investigator's brochure, and should provide sufficient time for the investigator and the institution to review the protocol and the relevant information.

Article 42 The sponsor should obtain the investigator's and the institution's agreement:

(a)to conduct the trial in compliance with these rules, with the applicable regulatory requirements, and with the protocol agreed to by the sponsor and approved by the IRB;

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

(c)to permit monitoring, auditing and inspection; and

(d)to retain the essential documents which should be filed by the investigator and the institution as designated by the sponsor.

The sponsor, the investigator and the institution should sign the protocol or other documents to confirm this agreement.

Article 43 A sponsor may transfer any or all of the sponsor's trial-related rights and obligations to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

The transfer referred to in the previous paragraph should be done in writing.

Within the scope of rights and obligations transferred in accordance with the first paragraph, the provisions for sponsors under these rules should apply mutatis mutandis to the CRO.

Article 44 The sponsor may establish 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.

The IDMC may recommend to the sponsor whether to continue, modify, or stop a trial.

The IDMC should have written standard operating procedures and maintain written records of all its meetings.

Article 45 The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions. If necessary, outside consultants may be appointed for this purpose.

Article 46 Prior to initiating a trial, the sponsor should define and allocate all trial-related duties and functions.

Article 47 The sponsor should indemnify the investigator and the institution against claims arising from the trial or should provide insurance, except for claims that arise from medical negligence by the investigator or the institution.

Article 48 Noncompliance with the protocol or these rules by the investigator, by the institution, or by members of the sponsor's trial-related staff should lead to prompt action by the sponsor to secure compliance.

If the sponsor or the institution does not comply with the action taken by the sponsor in accordance with the previous paragraph, the sponsor should proceed in accordance with Article 116.

Section II Quality Assurance and Quality Control

Article 49 The sponsor is responsible for the establishment of written standard operating procedures and the continuous implementation of quality assurance and quality control systems to ensure that trials are conducted and data are generated, recorded, and reported in compliance with the protocol and these rules.

Article 50 The sponsor is responsible for securing the agreement from the institution to ensure direct monitoring and auditing on the trial related sites, source data, documents and reports, and inspection by regulatory authorities.

Article 51 Agreements made by the sponsor with the investigator, the institution and any other parties involved with the clinical trial should be in writing, and may be part of the protocol.

Article 52 The sponsor should utilize qualified individuals for designing the protocol, preparing the case report form, planning the analyses, and preparing interim and final clinical trial reports.

Section III Data Handling and Keeping

Article 53 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Article 54 The sponsor should utilize appropriately qualified individuals to perform the following tasks:

1.supervise the conduct of the trial;
2.handle the data and verify the data; and
3.conduct the statistical analyses.

Article 55 When using electronic trial data handling or remote electronic trial data systems, the sponsor should:

1.Ensure that the electronic data processing systems conform to the sponsor's requirements for completeness, accuracy, reliability, and consistency.
2.Comply and maintain standard operating procedures for using these systems.
3.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, maintaining an audit trial, data trial and edit trial.
4.Maintain a security system that prevents unauthorized access to the system or the data.
5.Maintain a list of the individuals who are authorized to make trial data changes.
6.Maintain adequate backup of the data.
7.Safeguard the blinding design.

Article 56 If data are transformed during processing, it should be possible to compare the original data and observations with the processed data.

Article 57 The sponsor should use an unambiguous subject identification code that allows identification of all the data reported for each subject.

Article 58 The sponsor, or other owners of the data, should retain all of the essential documents pertaining to the trial that the sponsor is responsible for keeping for at least 2 years after the approval of a marketing application of the investigational drug in the R.O.C. These documents should be retained for a longer period if required by the other regulations.

Article 59 If the sponsor discontinues the clinical development of an investigational drug, the sponsor should inform all investigators, institutions and regulatory authorities.

Under the circumstances referred to in the previous paragraph, the sponsor should maintain all essential documents referred to in Article 58 for at least 2 years after formal discontinuation. These documents should be retained for a longer period however if required by the other regulations.

Article 60 Any transfer of rights of the data should be reported to the regulatory authorities.

Article 61 The sponsor should inform the investigator and the institution in writing of the need for record retention.

The sponsor should notify the investigator and the institution in writing when the trial related records are no longer needed.

Section IV Management of Investigational Drugs

Article 62 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical or clinical trials are available to support the methods and dosages of the drugs which the subjects can endure during the trial period.

Article 63 The sponsor should immediately update the Investigator's Brochure as significant new information becomes available.

Article 64 The sponsor should ensure that the investigational drugs, comparators and placeboes are characterized as appropriate to the stage of development of the drugs, are manufactured, handled and stored in accordance with the Good Manufacturing Practice, and are coded and labeled in a manner that protects the blinding.

Article 65 The sponsor should determine, for the investigational drugs, the storage temperatures, storage conditions, storage times, reconstitution fluids devices for product infusion. The sponsor should inform the monitors, investigators, pharmacists, storage managers and other relevant staff of these determinations.

Article 66 The investigational drugs should be properly packaged to prevent contamination and deterioration during transport and storage periods.

Article 67 In blind trials, the coding system for the investigational drugs should include a mechanism that permits rapid identification of the drugs in case of an emergency, but does not permit breaks of the blind design.

Article 68 If significant formulation changes are made in the investigational or comparator drugs during the course of clinical development, additional study should be conducted to evaluated whether the formulated drugs would significantly alter the stability, dissolution rate, bioavailability and other pharmacokinetic profile of the drug prior to the use of the new formulation in clinical trials.

Article 69 The sponsor should not supply an investigator or institution with the investigational drugs until approval is obtained for the trial.

Article 70 The sponsor should ensure that written procedures it establishes include the following:

1. Instructions that the investigator and the institution should follow for the handling and storage of investigational drugs for the trial, and
2. Procedures for the handling, storage and dispensing of drugs, retrieval of unused drugs from subjects, and return of unused drugs to the sponsor.

Article 71 The sponsor should carry out the following matters with regard to the handling of the investigational drugs:

1. Ensure timely delivery of investigational drugs to the investigators.
2. Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational drugs.

3.Follow and maintain a system for retrieving investigational drugs and documenting this retrieval.
4.Follow and maintain a system for the disposition of unused drugs and for the justification documentation of this disposition.
5.Ensure that the investigational drugs are stable over the period of use.
6.Maintain sufficient quantities of the investigational drugs used in the trials to reconfirm specifications, should this become necessary.
7.Maintain records of batch sample analyses and characteristics.

If the samples under items 6 and 7 of the previous paragraph are retained in order to obtain approval for the extension of drug storage time, samples should be retained until the analyses of the trial data are completed, or any other longer period as required by the regulatory requirements.

Article 72 The sponsor should continuously conduct a safety assessment of the investigational drugs.

Section V Monitoring

Article 73 The sponsor should ensure that the trial is conducted under proper monitoring.

Article 74 The purposes of monitoring are as follows:
1.To ensure that the rights and well being of the subjects are protected.
2.To ensure that the reported trial data are accurate, complete, and verifiable from source documents.
3.To ensure that the conduct of the trial is in compliance with the approved protocol and its amendments, with these rules, and with the applicable regulatory requirements.

Article 75 The selection and qualifications of monitors should comply with the following:
1.Monitors should be appointed by the sponsor.
2.Monitors should be appropriately trained, and should have the scientific and clinical knowledge needed to monitor the trial adequately

3.A monitor's qualifications should be documented.
4.Monitors should be thoroughly familiar with the investigational drugs, the protocol, informed consent form and any other written information to be provided to subjects, the sponsor's standard operating procedures, these rules, and the applicable regulatory requirements.

Article 76 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.

There is a need for on-site monitoring, before, during, and after the trial. However, the sponsor may add monitoring procedures such as investigators' training and meetings.

Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

Article 77 The monitor, in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities:

1.The monitor should act as the main line of communication between the sponsor and the investigator.
2.The monitor should ensure that the investigator has adequate qualifications and resources and remain adequate throughout the trial period.
3.The monitor should ensure that the trial related staff and relevant facilities, including laboratories and instruments are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
4.The monitor should ensure that the investigational drugs comply with the following:
(1)That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
(2)That the investigational drugs are supplied only to subjects who are eligible to receive them and at the protocol specified doses.

(3)That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational drugs.

(4)That the receipt, use, and return of the investigational drugs at the trial sites are controlled and documented adequately.

(5)That the disposition of unused investigational drugs at the trial sites complies with applicable regulatory requirements and is in accordance with the steps authorized by the sponsor.

5.Ensure that investigator follows the approved protocol and its amendments.

6.Ensure that informed consent forms are signed before each subject's participation in the trial.

7.Ensure that the investigator receives the most updated investigator's brochure and the trial information and trial supplies needed to conduct the trial properly.

8.Ensure that the investigator and the trial related staff are adequately informed about various details of the trial.

9.Ensure that the investigator and the trial related staff are performing the specified trial functions in accordance with the protocol and any other written agreement between the sponsor and the investigator and the institution and have not delegated these functions to unauthorized individuals.

10.Ensure that the investigator is enrolling only eligible subjects.

11.Report the subject recruitment rate.

12.Ensure that source documents, files and other trial records are accurately and completely maintained.

13.Ensure 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.

14.Check the accuracy and completeness of the care report form entries, source documents, files and other trial-related records against each other. The monitor should verify the following:

(1)The data required by the protocol are reported accurately on the care report forms and are consistent with the source documents.
(2)Any dose or therapy modifications are well documented for each of the trial subjects.
(3)Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the case report forms.
(4)Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported on the case report forms.
(5)All withdrawals of subjects from the trial are reported and explained on the case report forms.

15.Inform the investigator of any case report form entry error, omission, or illegibility and ensure that appropriate corrections, additions, or deletions are made, dated, explained and signed by the investigator or by a member of the investigator's trial staff who is authorized to sign case report form changes for the investigator. A file should be established for a list of such authorized persons.
16.Verify whether all adverse events are reported in accordance with Article 106.
17.Verify that the investigator keeps the essential trial information.
18.Communicate deviations from the protocol, standard operating procedures, these rules, and the applicable regulatory requirements to the investigator and take appropriate action to prevent recurrence of the detected deviations.

Article 78 The monitors should follow the sponsor's established written standard operating procedures as well as those procedures that are specified by the sponsor for monitoring a specific trial.

Article 79 The monitoring report should comply with the following:
(1)The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(2)Reports should include the date, site, name of the monitor, and name of the investigator or other individuals contacted.

(3)Reports should include a summary of what the monitor reviewed and the significant findings, deviations and deficiencies, conclusions, actions taken or to be taken and actions recommended to secure compliance.

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

Section VI Audit

Article 80 The purpose of a sponsor's audit, which is independent of monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, standard operating procedures, these rules, and the applicable regulatory requirements.

Article 81 The selection of auditors should comply with the following:

1.The sponsor should appoint individuals who are independent of the clinical trials and data collection systems to conduct audits.

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

Article 82 The auditing procedures should comply with the following:

1.The auditing should be conducted in accordance with the sponsor's standard operating procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

2.The sponsor's audit plan and procedures should be guided by the importance of the trial, the number of subjects, the type and complexity of the trial, the level of risks to the subjects, and any identified problems.

3.The observations and findings of the auditors should be documented.

4.To preserve the independence and value of the audit function, the regulatory authorities should not routinely request the audit reports. However, the regulatory authorities may request audit report on a case-by-case basis when evidence of serious non-compliance to these rules exists in the course of legal proceedings.
5.The sponsor should provide an audit certificate.

Chapter VI Application and Review of Clinical Trials

Article 83 Applications should be filed for clinical trials and the following documents should be submitted:
1.The protocol.
2.The informed consent form.
3.Subject recruitment advertisement or documents of other recruitment steps.
4.Written information provided to the subjects.
5.Investigator's brochure.
6.Current safety information on the investigational drugs.
7.Descriptions about the subjects' payments and compensations.
8.Latest credentials or other information to prove the qualifications of the investigator.
9.Other documents designated as necessary by the IRB.

Article 84 The IRB should complete the review of the clinical trial within one month and reach a review decision based on the following four review results:
1.Approval.
2.Modifications required prior to approval.
3.Disapproval.
4.Suspension or termination of prior approval.

Article 85 The review decision should be in writing and should include the following:
1.Name of the trial.
2.Trial institution and investigator.
3.Information and numbers of versions reviewed.
4.Review results and reasons.
5.Date, month and year.

Article 86 The IRB should review the qualifications, credentials and other related information of the trial investigator.

Article 87 The IRB/IEC should conduct a review of each ongoing trial at intervals appropriate to the degree of risk to the subjects, but at least once per year.

Article 88 When a clinical trial is to be carried out with the consent of the subject's representative with the authority to give consent, the IRB should ensure that the protocol and other documents adequately addresses relevant ethical concerns.

Chapter VII Conduct of Clinical Trial

Section I Protocol

Article 89 The investigator and the institution should conduct the clinical trial in accordance with the protocol agreed by the sponsor, the IRB and the regulatory authorities.

The investigator and the institution should sign the protocol together with the sponsor or sign other written agreements to confirm both parties' agreements.

Article 90 The investigator may not deviate or change the conduct of the protocol prior to obtaining consent from the sponsor and approval from the IRB, unless the change is for the purpose of avoiding injury to the subjects or solely for administrative purposes.

In case of any deviation or change made for the purpose of avoiding injury to the subjects, the investigator should submit the deviations or changes, their reasons or the proposed amendment to the protocol to the IRB, the sponsor and also the regulatory authorities if the conduct of the clinical trial was approved by the regulatory authorities.

Article 91 The investigator and the staff designated by the investigator should record and explain the deviations from the protocol.

Section II Investigational Drug

Article 92 The investigator or the institution should be responsible for the counting and keeping of the investigational drugs.

The investigator or the institution may designate a dedicated pharmacist or another appropriate individual to be responsible for all or part of the counting and keeping of the investigational drugs.

Article 93 The investigator, the institution, the designated dedicated pharmacist or appropriate individual should keep the following records:

1.Counting and acceptance of investigational drugs delivered to the trial site.

2.Inventory of investigational drugs.

3.Investigational drugs used by subjects.

4.Unused investigational drugs that are returned to the sponsor or disposed of in other manners.

The records referred to in the previous paragraph should include dates, quantities, batch numbers, expiration dates, and the code numbers assigned to the investigational drugs and trial subjects.

The Investigator should maintain records that document that the subjects were provided the doses specified by the protocol and reconcile the quantity of investigational drugs used and the quantity received from the sponsor.

Article 94 The investigational drugs should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.

Article 95 Investigational drugs should only be used for approved clinical trial protocols.

Article 96 The investigator, or a person designated by the investigator should explain the correct use of the investigational drugs to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

Article 97 The investigator should follow the trial's randomization procedures.

If the randomization procedures referred to in the previous paragraph can be decoded, the code should be broken only in accordance with the protocol.

If the clinical trial is blind, the investigator should promptly document and explain to the sponsor any premature unblinding of the investigational drugs.

Section III Records and Reports

Article 98 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the case report forms and in all required reports.

Article 99 Data reported on the case report forms should be consistent with the source documents or the discrepancies should be explained.

Article 100 Any correction to a case report form should be dated, and explained and should not obscure the original entry.

The previous paragraph applies to both written and electronic corrections.

The investigator should designate a representative to record corrections to case report forms and the corrections should be agreed by the investigator.

The investigator should maintain a record of corrections.

Article 101 The investigator and the institution should exercise due case as a good administrator to property keep all essential documents related to the clinical trial in order to avoid accidental damage or premature destruction.

Documents referred to in the previous paragraph should be kept for at least 2 years after the approval of a marketing application of the investigational drug in the R.O.C. These documents should be retained for a longer period if required by the other regulations

Article 102 The financial plan of the clinical trial should be documented in a written agreement between the sponsor and the institution or the investigator.

Article 103 The monitor, auditor, IRB or regulatory authority may request to review any trial related information. However, before reviewing any personal identification information of any subject, it should be confirmed that a written consent from the subject has been obtained.

Article 104 The regulatory authority may request the investigator to file written report to its affiliated institution to explain about the progress of the clinical trial.

The investigator and the institution should file annual regular summary reports on the progress of the clinical trial to the IRB. If necessary, the IRB may request to shorten the intervals between each regular summary report.

Article 105 The investigator should promptly provide written reports to the sponsor, the IRB and the regulatory authority on any changes significantly affecting the conduct of the trial or increasing the risk to subjects.

Article 106 In case of any serious adverse event by any subject, the investigator should immediately inform the sponsor and should provide detailed written report as soon as possible. In case of any unexpected serious adverse event, the investigator should immediately inform the IRB and the regulatory authority.

The sponsor should inform the regulatory authority or its sponsoring institution within 7 days from learning about any death or life threatening serious adverse event and should provide detailed written information within 15 days from such learning.

The sponsor should inform the regulatory authority or its sponsoring institution within 15 days from learning about any serious adverse event other than death or life threatening events and should provide detailed written information.

The verbal and written reports referred to in the fist paragraph of this article should use subject codes to represent the identities of the subjects and should not show the names, identification numbers, addresses or other identifiable information of the subjects.

The items categorized as serious adverse events are those publicly announced by the regulatory authority.

Article 107 Adverse events or laboratory abnormalities related to safety evaluations of the investigational drugs should be reported to the sponsor by the investigator within the time periods specified in the protocol.

Article 108 In the case of death, the sponsor, the IRB and the regulatory authority may request the investigator to provide autopsy report, terminal medical report or other additional information.

Article 109 The sponsor should immediately notify the instigator, the institution and the regulatory authority in case of the following:

1.New discovery that may endanger the safety of the subjects.

2.New discovery that may impact the conduct of the trial.

3.New discovery that may impact the agreement by the IRB for continuous conduct of the trial.

Article 110 The sponsor should submit the latest safety report to the regulatory authority.

Article 111 Upon completion or early termination of the trial, the investigator and the institution should provide the sponsor and the regulatory authority with any reports required and should provide a summary of the trial results to the IRB.

Under the circumstances referred to in the previous paragraph, the sponsor should submit a complete and detailed clinical trial report to the regulatory authority.

The format of the above-mentioned reports should be publicly announced by the regulatory authority.

Section IV Suspension and Termination of Trial

Article 112 If the trial is suspended or terminated for any reason, the investigator and the institution should promptly inform the trial subjects and should assure appropriate therapy and follow-up for the subjects.

Under the circumstances referred to in the previous paragraph, the investigator and the institution should inform the regulatory authority in writing about the reasons for the suspension or termination.

Article 113 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator and the institution should promptly inform the sponsor and the IRB and should provide a detailed written report.

Article 114 If the sponsor terminates or suspends a trial, the sponsor should promptly inform the investigator, the institution, the IRB and the regulatory authority and should provide a detailed written report.

Article 115 If the IRB terminates or suspends a trial, the investigator and the institution should promptly notify the sponsor and provide a detailed written report.

Article 116 If the investigator or the institution significantly or continuously violates the protocol, the sponsor should terminate their continuous participation in the clinical trial and should immediately inform the regulatory authority.

Section V Multicenter Trials

Article 117 For multicenter trials, the investigators should conduct the trial in compliance with the protocol agreed to by the sponsor and approved by the IRB and the regulatory authority.

Article 118 In multicenter trials, for those investigators who are collecting additional data in accordance with the protocol and other participating investigators, the sponsor should provide supplemental case report forms that are designed to capture the additional data.

Article 119 The responsibilities of and coordination between the investigator and the other participating investigators should be documented prior to the conduct of a multicenter trial.

Article 120 In a multicenter trial, all investigators should follow comply with a uniform set of standards for the assessment of clinical and laboratory findings and should complete the case report forms.

Article 121 In a multicenter trial, the sponsor should reinforce the communications among the investigators.

Chapter VIII Miscellaneous

Article 122 Clinical trials that started in accordance with the Good Clinical Practice prior to the implementation of these rules should be conducted in accordance with the provisions of these rules after implementation of these rules.

Article 123 These rules are implemented starting from the date of publication.

DECLARATION OF HELSINKI 2008 English version

A. INTRODUCTION

1.The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2.Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3.It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4.The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5.Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6.In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7.The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8.In medical practice and in medical research, most interventions involve risks and burdens.

9.Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research

populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected..

13. Appropriate caution must be exercised in the conduct of medical research that mayharm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate

any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in theresearch should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Human Research Ethics Policy Guidelines

Wei-Shu-Yi-Tzu No. 0960223088 Announced by Department of Health on July 17, 2007

1. Human rsearch shall be conducted for the purpose of improving the welfare of human beings, and shall be conducted under the principles of respecting the voluntary wishes of the subjects under study, and protecting their privacy and right to health.

2. Unless otherwise prescribed in laws and regulations, human research shall include all processes seeking to acquire, analyze, and investigate human tissue or information concerning individual behavior, thinking, physiology, psychology, sociology, genetics, and medicine for the purpose of research.

3. Human research shall, as much as possible, be performed only after notifying the subjects using clear and understandable methods concerning relevant aspects, and obtaining their written consent.

   The content of notification in the preceding paragraph shall include at least the research goal and timetable, name of the investigator, name of the research institution, source of research funding, a summary of the research content, subjects' rights and the duties of research personnel, mechanisms for safeguarding subjects' personal privacy, foreseeable risks within a reasonable score, remedial measures that can be applied for in the event of damages, and name of and method of contacting liaison person in the event of relevant problems.

4. Human research shall be planned on the basis of the best scientific evidence and assumptions. With regard to the acquisition and analysis of data and use of results, subjects' private personal information shall not be disclosed without their consent under any circumstances. Risks shall be controlled as much as possible. There shall be a proper response plan including remedial measures addressing any damages possibly caused during the research process.

5. Materials acquired during research shall not be used for purposes other than original notices and written consent. When it is necessary to use such materials for other research purposes, the subjects' consent must be obtained again in accordance with the regulations of Point 3.

6. Human research shall not be conducted on minors or on underprivileged persons. However, this restriction shall not apply when such research is clearly beneficial to the subjects' collective or individual interests, and when the subjects' legal guardians or most appropriate relations have been notified, and their written consent obtained.

7. Research organization shall establish ethics committees or commission the ethics committees of other organizations to perform review of human research ethics matters. At least one-third of the members of the ethics committee shall be legal specialists or other impartial public figures; each ethics committee shall contain at least two persons from outside the organization in question.

   Ethics committee shall review and approve human research, and shall bear responsibility for the supervision of project implementation and handling of research results.

8. Subjects shall be informed of any commercial benefit possibly derived from human research; any necessary agreements shall be made in writing.

Principle for Clinical Trial Subject Recruitment

Wei-Shu-Yao No. 0960317637 Announced by Department of Health on June 6 2007

I. As stipulated according to Article 83 of Good Clinical Practice

II. The advertisement for the clinical trial subject recruitment (recruitment advertisement below) shall not be posted in the campus of the junior high school or lower.

III. The recruitment advertisement shall be approved by the Human Subject Committee prior to being posted.

IV. The recruitment advertisement shall provide the following information:

1. Name and address of the Principle Investigator
2. Name and address of the trial institution
3. Trial objective or trial overview
4. Major inclusion and exclusion criteria
5. Anticipated benefits of the trial
6. Cooperation matters for the subject
7. Trial contact person and contact manner

V. The recruitment advertisement shall not contain the following or words of similar meanings

1. Declaration or implication that the investigational drug is safe, efficacious, or able to cure disease
2. Declaration or implication that the investigational drug is superior or similar to the currently available drug or treatment
3. Declaration or implication that the subject will receive a new treatment or drug but not that the study is experimental in nature
4. Emphasis on that the subject will receive free medical treatment or expense subsidy
5. Emphasis that the clinical trial has been approved by the competent health authority or human study committee
6. Use of words such as “registration is limited”, “application ends soon”, or “contact us immediately or be left out”.
7. Use of graphs, pictures, or signs of compelling, seductive, or encouraging nature.
8. Any other content prohibited by the central competent health authority’s announcement

Guidelines for Collection and Use of Human Specimens for Research

Wei-Shu-Yao No. 0950206912Announced by Department of Health on August 18 2006

1.To ensure the proper collection and use of specimens for research purposes, to safeguard the rights and interests of those providing specimens and to promote proper scientific development, these guidelines have been formulated.

The collection of specimens for research purposes, unless otherwise stipulated by laws and regulations, shall be carried out in accordance with these guidelines.

2.Terms used in these guidelines are defined as follows:

(1)specimen(s): cells, tissue, organs, body fluids or derivatives thereof (containing genetic material) taken from the human body, to include remnant specimens and specimens taken from an embryo, fetus or cadaver.

(2)specimen donor: a person from whom a specimen is collected.

(3)specimen user: a person or institution who/that directly uses the specimen, directs another person to use the specimen or who/that may use the specimen in accordance with a specific relationship, such as a contract, with the specimen provider.

(4)specimen custodian: a person or institution who/that keeps a specimen.

(5)ID encoding: a process of using a code composed of numbers or English letters used to take the place of information, like name, national ID card number and case number, that could serve to identify the specimen donor.

(6) De-linking: a process where, after the specimen ID encoding is done, the code and corresponding data that serve to identify the specimen donor are completely and permanently destroyed.

(7)Remnant specimen(s): specimen(s) that remain following pathology examinations, medical lab tests or research.

3.Prior to the collection or use of specimens, a research plan shall be presented and approved by the Committee on Human Trials or similar committee dealing with ethical matters (hereinafter, ethics committee) before work may proceed.

For research involving remnant specimens, a research plan shall be sent to an ethics committee for approval prior to use.

4.The collection and/or use of specimens may not violate medical ethics, and care should be taken to prevent harm to people, a specific ethnic group or the environment.

5.For the collection of specimens for use in research, the specimen donor shall be informed of the following, and his/her consent obtained, unless otherwise regulated by law:

(1)Purpose and possible scope and dates of use.
(2)Method, type, amount and area of collection.
(3)Possible complications and dangers.
(4)The rights and interests of the donor and the obligations of the user and the custodian.
(5)The significance of the research.
(6)The reasons for selecting the donor.
(7)Anticipated research results.
(8)Reasonable extent of foreseen risks and negatives.
(9)The mechanism for safeguarding the privacy of the specimen donor.
(10)The fact that a potential specimen donor may refuse to participate in the research or, after participation, may withdraw from the research at anytime, as well as the procedures for doing so. A refusal to participate in, or a withdrawal from, the research will not affect the medical care the patient is due.
(11)The impact of information obtained from the research could have on the specimen donor and the donor's family or ethnic groups.
(12)The identity of the specimen custodian and specimen user.
(13)Whether or not the specimen will be supplied to, turned over to or authorized for use by a domestic or foreign third party.
(14)Handling of remnant specimens.
(15)Source of research funding and those institutions participating in the research.
(16)Other important information relative to specimen collection, medical case review, follow-up exams and tests or information related to the patient's condition as required by the research plan.

With regard to remnant specimens used for research, except for the items indicated in Sub-paragraphs 2 and 3 of the preceding paragraph, the donor shall be notified of the remaining items and his/her consent obtained.

The notification and consent referred to in the preceding two paragraphs shall be done in writing and accompanied by an oral notification to make certain that the specimen donor has a clear understand of the contents.

6.Collection of a specimen from an embryo or fetus requires the consent of the mother.

If a specimen donor is a minor under seven years of age, consent shall be given by a legal representative of the child; if the donor is a minor seven years or older, consent shall be given by both the legal representative and the donor; if the donor is decisionally impaired, then consent shall be given by the legal representative, but if there is no legal representative, consent shall be given by the closest relative; for a specimen provided from a cadaver, consent may be obtained from the closest relative or be in the form of a written consent agreement signed by the deceased prior to death.

The "closest relative" referred to in the preceding paragraph refers to the following:
(1)spouse
(2)an adult inferior lineal relative by blood
(3)parents
(4)brothers and sisters
(5)grandparents
(6)great-grandparents or third-degree collateral relative by blood
(7)first-degree direct relation by marriage

A written consent agreement of the closest relative may be done by one person; if there is no unanimity among several closest relatives, a priority list in accordance with the listing of the preceding sub-paragraphs shall be set up. In the case of relatives with the same priority, the degree of relationship shall take precedence; in the case of an identical degree of relationship, the co-habiting relative shall have precedence; if there is no co-habiting relative, age shall take precedence.

7.When the collection and use of a specimen may possibly give rise to rights and interests, such as commercial profits, the specimen user shall notify the donor and complete the necessary written contract.

When the specimen collection referred to in the previous paragraph is done from an embryo or fetus, a cadaver, a minor or a person with dicisionally impairness, the specimen user shall notify the designated consent-giver as stipulated in the preceding section and shall complete the necessary written contract.

8. When research results can reasonably be anticipated to have a significant impact on the personal health of an identifiable donor, the specimen user will obtain approval from the ethics committee and, if the donor chooses to be informed, the specimen user shall notify and assist the donor with the relevant and necessary counseling.

   The review by the ethics committee as referred to in the preceding paragraph, shall take into consideration the degree to which the health of the donor is endangered as well as the cost efficiency related to prevention and treatment.

9. The specimen user shall use the specimen within the parameters as agreed by the donor or as prescribed by law.

   If use of the specimen is to exceed the parameters outlined in the previous paragraph, the notification and review procedures shall be carried out as stipulated in Sections 3, 5 and 7.

10. Unless otherwise provided by law, the potential specimen donor may refuse permission to collect a specimen, may terminate the specimen use agreement or may change the agreed parameters for use. However, cases where personal information has been de-linked from the specimen shall not be subject to this decision.

    The specimen custodian and/or specimen user shall keep and manage the specimen in an appropriate manner.

    When use of the specimen is completed, or when the donor terminates the specimen use agreement, the destruction of the specimen shall be certified; without prior written agreement on the part of the donor, the specimen may not continue to be kept. However, cases of specimens that have undergone de-linking shall not be subject to this decision.

11. The specimen custodian and the specimen user shall respect and safeguard the publicity rights of the specimen donors

    All confidential, private or personal information regarding the specimen donor that becomes known as a result of collection, retention or use of the specimen may not be disclosed without cause.

    The specimen collection and management procedure shall be carried out using an ID encoding, de-linking or any other method that provides anonymity for the donor.

    When a specimen user provides information obtained from a specimen to a third party or makes the information public, the specimen user shall do so in a manner that prevents identification of the donor's personal information.

12. Without an ethics committee review or the safeguarding of the rights, interests and safety of the specimen donor and the public, no specimen shall be turned over or authorized for use in a foreign country.

13. For any one of the following circumstances, the restrictions stipulated in Section 5 and 7 may be waived; however, the stipulations of Section 3 with regard to an ethics committee review and approval shall still be followed before action may be taken:
    (1) It is difficult to determine the identity of the specimen donor.
    (2) Because it is impossible to trace or establish contact with the donor, it is difficult to obtain a renewed consent agreement.
    (3) Specimens that could be publicly obtained prior to the issuance of these revised guidelines.

14. When specimens collected in accordance with these guidelines are used for teaching purposes, the stipulations of Section 12 may be use.

Medical Care Act

provisions pertain to human trials

Amended on May 20, 2009, by President Order Hua Chung(1) Yi Tze No. 098001525131

Article 8 The term — "human trial" as used in the Act shall refer to experimentation research conducted by medical institutions on humans according to medical theory by use of Newmedical technologies, medicaments, or medical implements and bioavailability and bioequivalence of generic drugs.

Under the implementation of the human clinical trial, a subject's independent willingness should be respected, and the health rights and interests and privacy thereof should be protected.

Article 22 Receipts shall be made by medical care institutions for medical fees charged, which shall clearly state the item(s)and fee(s).

Medical fees charged by medical care institutions shall not violate or exceed the standard for the fees, nor shall medical institutions charge for items without authorization.

Article 78 For the purpose of improving the standard of domestic medical technology or the prevention of disease, teaching hospitals may conduct human trials after formulating a plan and approval from the central competent authority, or upon entrustment of the central competent authority. However, bioavailability and bioequivalence of generic drugs could be conducted without approval of central competent authority.

Non-teaching hospitals may not conduct human trials. However, the preceding Paragraph may apply mutatis mutandis to specify hospitals with the approval of the central competent authority.

The plan for human trial by a medical care institution referred to in the preceding two Paragraphs should be reviewed and approved by personnel in medical technologies, legal experts, social justice or civil organization representatives and the ratio of one single sex should be no less than one-third; the same applies to trial modification. Reviewer should avoid conflict of interests.

Article 79 When conducting human trials, medical care institutions shall pay proper attention to the medical procedure, and shall first obtain a written letter of consent from the experiment subject.

Trial subject should be limited in adult who has capacity. However, the trial that could be beneficial to the specific group or specific disease patients is an exception.

The trial subject of aforementioned exception is a person of limited capacity to make juridical acts, consent shall be obtained from oneself and legal agent. If the trial subject has no capacity, consent shall be obtained from legal agent.

The medical care institution shall clearly state the following on the written letter of consent referred to in the preceding Paragraph, and shall inform the experiment subject of the following before obtaining his/her consent:

1.Purpose and method of trial;
2.Possible side-effects and risks;
3.Expected trial results;
4.Explanation of other possible treatment methods;
5.Retraction of consent at anytime by experiment subject.
6.Trial related damage indemnification or insurance mechanism.
7.Confidentiality of the subject's personal information.
8.Storage and reuse of the subject's biological specimens, personal information or the derivatives thereof.

In respect of the information and the written consent set forth in the previous paragraph, the medical institution should give sufficient time for consideration, and cannot act by duress or other improper means.

Article 79-1 Expect for the regulations otherwise provided, the human clinical trial related matters set forth in the previous two articles, including application procedures, guidelines of inspection procedure and principles of avoiding conflicts of interests, information disclosure, supervision and management, audit, and other informed contents are established by the central competent authority.

Article 79-2 In respect of the subject who does not agree to participate in the human clinical trial or withdraw the consent, the medical institution should perform the routine treatment, and cannot prejudice the legitimate rights and interests on medical care thereof.

Article 80 Medical care institutions shall submit trial report in accordance with notification by the central competent authority during human trial period. If the central competent authority feels there is concern for safety, the medical care institutions shall cease trial immediately.

Medical care institutions shall submit trial report to the central competent authority at the completion of the human trial.

Article 98 The central competent authority shall establish a medical review committee, which shall set up different working groups in accordance with the different missions, which are as follows:

1.Improvement of the medical care system;
2.Review of medical technologies;
3.Review of human trials;
4.Assessment commissioned by the judiciary or procuratorial authority;
5.Improvement of the specialist system;
6.Promotion of medical ethics;
7.Review of establishment or expansion of large hospitals exceeding a certain scale;
8.Review of other medical affairs.

The organization, meeting, and other regulations of the medical care committee referred to in the preceding Paragraph shall be established by the central competent authority.

Article 100 Members of the medical review committee referred to in the preceding two Articles shall include medical experts, legal experts, scholars, and social personages, excluding legislators/councilors and representatives of medical juridical persons, of which legal experts and social personages shall account for at least one-third of the number of members.

Article 102 The institutions with following situations would be subject to a fine of no less than NT$10,000 but no more than NT$50,000, and have to correct it within a given time. If matters don't get improved by time, the institutions would receive consecutive punishment.

(1)The one who has violated Paragraph 1 of Articles 25; Articles 26; Paragraph 1 of Articles 27; Articles 59; Paragraph 1 of Articles 60; Articles 65; Articles 66; Paragraph 1 and 3 of Articles 67; Articles 68; Articles 70; Articles 71; Articles 73; Articles 74; Articles 76 or Paragraph 2 of Articles 80.

(2)The one who has violated the Establishment Standards of the central competent authority authorized by the Paragraph 3 of Article12.

(3)The one who has violated the Governing Regulations of the central competent authority authorized by the Article13.

(4)The one who has violated the regulations of the central competent authority authorized by the Article 69.

The institutions with following situations would be punished by preceding regulations and have to correct it within a given time. If matters don't get improved by time, the institutions would get a determination of suspension for no less than one month and no more than one year.

(1)The one who has violated Paragraph 1 of Articles 25 or Articles 66.

(2)The one who has violated the Establishment Standards of the central competent authority authorized by the Paragraph 3 of Article12.

(3)The one who has violated the Governing Regulations of the central competent authority authorized by the Article13.

(4)The one who has violated the regulations of the central competent authority authorized by the Article 69.

Article 105 Persons who violate any of the provisions of Paragraphs1 of Article 78 shall be subject to a fine of no less than NT$100,000 but no more than NT$500,000 by the central competent authority. Serious violations shall be subject to cessation of practice for no less than one month but no more than one year.

Persons who violate the provisions of Paragraph2 of Article 78 shall be subject to a fine of no less than NT$200,000 but no more than NT$1,000,000 by the central competent authority. Serious violations shall be subject to suspension of practice for no less than one month but no more than one year, or revocation of practice license.

The one who has violated Paragraph 3 of Article 78 or the regulations related to the guidelines of inspection procedures stipulated by the central competent authority by the authorization under Article 79-1, is punished by the central competent authority with a fine no less than NT$100,000 and no more than NT$500,000, and the human clinical trial or the inspection set forth in Paragraph 3 of Article 78 may be ordered to be discontinued.

The one who has violated Articles 79, 79-2, Paragraph 1 of Article 80, or the regulations related to the matters of supervision and management or audit and stipulated by the central competent authority by the authorization under Article 79-1, is punished by the central competent authority with a fine no less than NT$100,000 and no more than NT$500,000, and the human clinical trial may be further ordered to be discontinued when there are concerns of safety or prejudice to the subject's rights and interests; under significant circumstances, in respect of the whole or part of involved business or the divisions and services violating provisions, a determination of suspension for no less than one month and no more than one year may be made.

VII. Application Form Format

1.New Medical Technology (New Medical Technology Combined with New Medical Device) Human Study Protocol Application Data Check List

2.Human Cell Therapy and Gene Therapy Human Study Protocol Application Data Check List

3.New Medical Technology (including New Medical Technology Combined with New Medical Device)Human Study Adverse Reaction Report Form

4.Clinical Trial Application Form

5.Protocol Amendment Application Form

6.Interim Report

7.Closure Report

8.Clinical Trial Informed Consent Form Sample

9.Informed Consent Form Content Guidelines

10.Guidelines for the Informed Consent of Pharmacogenomical Research

11.Post-Marketing Surveillance Study, PMS study

Attachment 1

New Medical Technology (New Medical Technology Combined with New Medical Device) Human Trial Protocol

Application Data Check List

The submission of the human study protocol data shall include the following items:

☐Human Trial Protocol with the content meeting the following requirements:

- ☐The content shall be written in Chinese with the abstract in both Chinese and English included
- ☐The citation and reference shall be noted.
- ☐The content shall be in detail and substantial.
- ☐Trial subject
- ☐Trial objective
- ☐Trial method
- ☐Principle Investigator's and Associate Investigator's background information such as education, experiences, and training
- ☐Relevant literature reports supporting documents
- ☐All required drugs including the names and numbers of drugs which must be imported
- ☐All required equipments, including the names and numbers of equipments which must be imported (please list the brand name and model number)
  - ☐Those who have been approved for registration by the Department of Health, please present the registration approval permit from the Department
  - ☐For new medical device, the manufacturing and marketing approval or the proof of approval for conducting the clinical trial from the highest competent health authority from the country of origin.
  - ☐The original instruction and user's manual of the product – including its function, application, use method, and working principle

- ☐The relevant training certificate of the physician operating the new medical instrument
- ☐Anticipated study outcome
- ☐Potential injury and treatment

☐The content of the Informed Consent Form shall be substantial and written in the wording easily understandable by the physicians about the inadequacy of the traditional treatment for the disease, the current efficacy of the new treatment (citing the domestic or international literature reports), and the advantage and potential side effects of the new treatment to replace the traditional one. The study process, method, required examinations, and the contact telephone number in case of problems. The following items shall be stated:

- ☐Study objective and method
- ☐Potential side effects and risks
- ☐Anticipated study outcome
- ☐Other alternative treatments and instructions
- ☐Subject may withdraw the consent at any time
- ☐Prior to the human study, the routine medical service to confirm the diagnosis may require the collection of fees. Other than that, all medical fees for the conduct of the human study and the related follow-up diagnosis and treatment before the restraint of the human study is lifted shall all be exempted.

☐Approval letter from the Institutional Ethics Committee

☐Related certificate to prove that the human study has been conducted abroad

☐Non-clinical related study data and information

Attachment 2

Human Cell Therapy and Gene Therapy Human Trial Protocol

Application Data Check List

The submission of the human trial protocol data shall include the following items:

☐Human Trial Protocol with the content meeting the following requirements:

- ☐The content shall be written in Chinese with the abstract in both Chinese and English included
- ☐The citation and reference shall be noted.
- ☐The content shall be in detail and substantial.
- ☐Study subject
- ☐Study objective
- ☐Study method
- ☐Principle Investigator's and Associate Investigator's background information such as education, experiences, and training
- ☐Relevant literature reports supporting documents
- ☐All required drugs including the names and numbers of drugs which must be imported
- ☐All required equipments, including the names and numbers of equipments which must be imported (please list the brand name and model number)
  - ☐Those who have been approved for registration by the Department of Health, please present the registration approval permit from the Department
  - ☐For new medical device, the manufacturing and marketing approval or the proof of approval for conducting the clinical trial from the highest competent health authority from the country of origin.
  - ☐The original instruction and user's manual of the product – including its function, application, use method, and working principle

- ☐Product property information (product's physical and chemical properties, toxicology data, and clinical and non-clinical data) or Investigator's Brochure
- ☐Major component and finished product analytical specification report, finished product stability test results, master files, and batch records
- ☐The relevant training certificate of the physician operating the new medical instrument
- ☐Anticipated study outcome
- ☐Potential injury and treatment

☐The content of the Informed Consent Form shall be substantial and written in the wording easily understandable by the physicians about the inadequacy of the traditional treatment for the disease, the current efficacy of the new treatment (citing the domestic or international literature reports), and the advantage and potential side effects of the new treatment to replace the traditional one. The study process, method, required examinations, and the contact telephone number in case of problems. The Informed Consent Form shall include the following items:

- ☐Study objective and method
- ☐Potential side effects and risks
- ☐Anticipated study outcome
- ☐Other alternative treatments and instructions
- ☐Subject may withdraw the consent at any time
- ☐Prior to the human study, the routine medical service to confirm the diagnosis may require the collection of fees. Other than that, all medical fees for the conduct of the human study and the related follow-up diagnosis and treatment before the restraint of the human study is lifted shall all be exempted.

☐Good Tissue Practice Self-evaluation Form

☐Good Tissue Practice Basic Information Form

☐Approval letter from the Institutional Ethics Committee

☐Related certificate to prove that the human study has been conducted abroad

☐Non-clinical related study data and information

Attachment 3

Case No. (by Bureau of Medical Affairs):

New Medical Technology Human Study Adverse Reaction Report Form

New Medical Technology (including New Medical Technology Combined with New Medical Device) Human Trial Adverse Reaction Report Form Bureau of Medical Affairs, Department of Health **Tel**: (02) 8590-6666 ext. 6664 or 8590-6664 **Fax**: (02) 8590-6061, 8590-6062 **Address**: 6 F, No.36, Tacheng St., Datong District, Taipei **Email**: md0985@doh.gov.tw	1.Event Date: _____ year _____ month _____ day	2.Report Date: _____ year _____ month _____ day
	3.Report to Bureau of Medical Affairs: _____year _____month _____day (filled out by Bureau of Medical Affairs)	
	4.Reporter Name: Tel: Employer: Occupation: ☐medical staff, title: _____ _____ ☐Industry	5.Case Origin: ☐Overseas,(country) _____ ☐Domestic, trial center : _____ trial physician : _____ 6.Report Category: ☐initial report ☐follow-up report, # _____
	7.Title: 8.DOH Approval Document No.:	
I.Patient Information		
9.ID No.(for reporter):	10.Gender: ☐ male ☐ female 11.Date of Birth: _____ year _____ month _____ day or age: _____	12.Weight: _____ kg 13.Height: _____ cm

14.Health Condition Prior to Study:

II. Potential Factors to Adverse Reactions

☐Caused by new medical technology alone,
☐Caused by combined medical product (including medical device) alone,
☐Caused by new medical technology plus combined medical product (including medical device),
☐Indistinguishable

III. Predictability of Adverse Reactions

☐Predictable, ☐Unpredictable

IV. Severe Adverse Reactions and Consequences

15.Adverse reaction consequence
☐A.Death, Date:
_____year_____month_____day,
Cause of death:
☐B.Life-threatening
☐C.Patient hospitalization
☐D.Permanent Disability
☐E.Prolongation of patient hospitalization
☐F.Treatment required to avoid permanent injury
☐G.Congenial deformity
☐H.Others (please describe)

17.Related examinations and test data (please include date and relevant information)

16.Description of reported incidence or problem (please describe in the order of event occurrence time and date, including the study initiation date, adverse reaction date, region, symptom, severity, and treatment. If ADR is suspected to be cause by Chinese herbal medicine, please describe the diagnosis of the prescription by the doctor of Chinese Medicine)

18.Other related information (for example, diagnosis, allergy, pregnancy, drinking or smoking habit, other disease, liver/kidney function impairment, etc.) (please include relevant information)

<table>
<tr><th colspan="2">V. Combined medical product (including medical device) suspected to cause adverse reaction -- Not required for unsuspected or uncombined medical product (including medical device)</th></tr>
<tr><td>19.Study medical device name (including the DOH registration number)</td><td>23.Start date:
____ year ____ month ____ day</td></tr>
<tr><td>20.Brand name and supplier:</td><td>24.End date:
____ year ____ month ____ day</td></tr>
<tr><td>21.Model# _____
Serial# _____
Batch# _____
Manufacturing date:
____ year ____ month ____ day</td><td>25.Reason:</td></tr>
<tr><td>22.Medical device operator
☐Medical personnel
☐Patient or family member
☐Others</td><td>26.Can medical device be provided for evaluation?
☐Yes
☐No
☐Returned to the manufacturer on
____ year ____ month ____ day</td></tr>
<tr><td>27.Combined medical</td><td>deviceRelated Setup and Use Environment Instruction
#1

#2</td></tr>
</table>

28.Combined drug	Generic name/ Brand name (including DOH registration number) Amount /Dosage Administration route Dose / Frequency Initiation date Reason for clinical use #1 #2

29.Experience of use of similar medical device
☐Yes Medical device: _____ Adverse reaction: _____
☐No ☐Not sure

30.Alleviation of adverse reaction after the use is halted
☐Yes ☐No ☐Not sure

34.Same reaction after the use is resumed
☐Yes ☐No ☐Not sure

31.Concomitant use of ☐Chinese herbal medicine* ☐Western medicine*
☐Health food ☐Others:

*If used at the same time, please enter it in the combined drug field

VI.Principle investigator's evaluation of this new medical technology (including new medical technology combined with new medical device) Relationship between human study and adverse reaction

32.☐Certain (certain),
☐Probably (probable/likely),
☐Possible (possible),
☐Unlikely (unlikely),
☐Unrelated (unrelated)

VII. Principle Investigator's Evaluation Comment
33.Principle investigator's evaluation comment: ☐Continue the study ☐Suspend the study ☐Study closed for reference ☐Others (please describe)
VIII. Institutional Review Board's Evaluation Comment
34.Institutional Review Board's review opinion and evaluation comment: Institutional Review Board member's signature on evaluation of adverse event: Date:

Note:

1.In the event of fatal or life-threatening severe adverse reaction (items 15A and 15B in this Table), the medical institution shall report within 7 days and submit the complete written information within 14 days.

2.In the event of other severe adverse reaction (items 15C~H in this Table), the medical institution shall report within 15 days and submit the complete written information within 30 days.

Attachment 4

(pages including the Principle Investigator's signature page in this application form)

Institutional Review Board
Clinical Trial Application Form

Except for people's names in Chinese only, other information may be in Chinese or English. The font size shall not be less than 14.

Application Date: yyyy/mm/dd

1.Title of protocol:

2.Protocol No.:

3.Principal investigator :

Name:

Institution / company:

Position:

Tel: Fax:

E-mail:

Obtain the certificate of GCP related training ☐yes ☐not yet

4.Investigator list (include sub-investigator):
<How many sites (hospitals) are involved ?>

Name	Institution	Obtain the certificate of GCP related training
		☐yes ☐not yet
		☐yes ☐not yet
		☐yes ☐not yet

5.Is this protocol substantially similar to a study previously reviewed by JIRB?
☐No
☐Yes, you may indicated the similar protocols:
JIRB No.: _____ Protocol No.: _____

6.Has another IRB reviewed this protocol prior to submission to JIRB?
☐No
☐Yes, please provide the IRB correspondence.
IRB No.: _____ Protocol No.: _____

7.Study Type:

☐Clinical trial
- ☐Phase I safety research— for the purpose of drug toxicity understanding.
- ☐Phase II to realize the prime efficacy
- ☐Phase III to evaluate the entire treatment efficacy
- ☐Phase IV to follow up the side-effects of long-term use

☐Gene related clinical trial
☐PMS
☐Add on study
☐Extended research
☐Observation research
☐Others (please specify: _____)

8.Identifier on ClinicalTrials.gov:
or other websites / Identifier:

9.Regulatory parties that are in charge of reviewing the result
☐DOH, Executive Yuan, ROC
☐FDA, USA
☐EMEA
☐Ministry of Health, Labor & Welfare, Japan
☐For academy purpose
☐Others (please specify: _____)

10.Contents of the Trial:
a.Study Design: ☐parallel design ☐cross-over design ☐others
b.No. of groups: ☐single ☐double ☐if more than two: _____ groups
c.Total sample size: _____
subjects(target enrolment in Taiwan: _____);
the ratio of effective treatment: _____ %
d.Period of follow-up: _____ weeks (or, _____ days)
e.Is there any of the followings included:
☐randomization ☐comparison groups ☐interim analysis
☐DSMB, Data Safety Monitoring Board
f.Period of the Study: from 20yy / mm / dd to 20yy / mm / dd

11.Trial material:
☐Drug (Please reference and fill-in Appendix I)
☐Vaccine (Please reference and fill-in Appendix II)
☐Gene transfer (Please reference and fill-in Appendix III)
☐Device (Please reference and fill-in Appendix IV)
☐Iatrotechniques (Please reference and fill-in Appendix V)
☐Observation research (Please reference and fill-in Appendix VI)

12.Method for Recruitment:
☐Recommended by the investigators (include subinvestigators)
☐By other medical workers
☐Poster (enclosed or not?:□yes □not)
☐Internet (enclosed or not:□yes □not)
☐Others (please describe)

13.Informed Consent Form: For application for the exemption of Informed Consent Form, please refer to 14.
a.Who explained the entire study to the subject or subjects' legal representatives?

b.When will the subject or subjects' legal representatives be initially approached for consent?
☐before screening stage
☐between screening and randomization stage

c.Where will the consent process occur and over what time period?

d.In addition to the consent form, what else do you do to confirm the subject or subjects' legal representatives understand the research?
☐Provide Brochure
☐Conference with patient and family member
☐Conference with an interpreter
☐Arrange time for follow-up discussion
☐Others (please describe)

14.Will the following minors involve in this Trial?
●Children (who need the legal representatives to sign the consents)
●Pregnant Women, Human Fetuses and Neonates
●Prisoners
☐no ☐yes. if yes, please check a proper answer as below:
☐Research not involving greater than minimal risk.
☐Research involving greater than minimal risk, but presenting the prospect of direct benefit to individual subjects.
☐Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

15.Principle Investigator will receive monetary subsidy?
☐not receive any subsidy
☐receive subsidy, detail: in order to avoid confusion, the subsidized items (such as referral fee) and the amount of subsidy must be described.

16.Any monetary subsidy provided to the subject?

☐no subsidy provided

☐subsidy provided, detail: in order to avoid confusion, the time of subsidy provided (such as in which return visit) and the amount of subsidy must be described.

17.Sponsor:

Contact person for this research:

Title / position:

Tel. (O): (Cell Phone):

Fax: E-mail:

Address:

18. Checking the attachments:

a.Application form b.Synopsis of protocol (Chinese version)	☐yes ☐not applicable ☐yes ☐not applicable
c.Synopsis of protocol (English version)	☐yes ☐not applicable
d.Protocol (code/version/date)	☐yes ☐not applicable
e.Informed Consent form (code/version/date)	☐yes ☐not applicable
f.Application form g.Synopsis of protocol (Chinese version)	☐yes ☐not applicable ☐yes ☐not applicable
h.Synopsis of protocol (English version)	☐yes ☐not applicable
i.Protocol (code/version/date)	☐yes ☐not applicable
j.Informed Consent form (code/version/date)	☐yes ☐not applicable
k.Case Report form (code/version/date)	☐yes ☐not applicable
l.Adverse Events Report form	☐yes ☐not applicable
m.Investigator's C.V. & the Certificate of GCP	☐yes ☐not applicable
n.Investigator's Brochure (code/version/date)	☐yes ☐not applicable
o.Reference data for Pre clinical research	☐yes ☐not applicable
p.Others (please list in sequence)	☐yes ☐not applicable

- Statement of Consignee:I declare that the above information are written as concord as possible by myself. If any unreal or deceiving, I am willing to take the legal responsibility.

Your Name (printed): Institution:

_____ _____

Signature: Date:

_____ _____

Investigator's Signature

The principal investigators and co-investigators are required to sign on this page

●Investigator's Statement:

1.I, who am executing this clinical trial, have read this protocol carefully. In order to ensure the subjects' lives, health, privacy and dignity, I am willing to carry out the procedure according to the principles of Declaration of Helsinki and the domestic regulation.

2.To ensure the subjects' benefits, I promise to conduct the trial according to the protocol, and inform the Serious Adverse Events, pass on the annual report, the final report, and submit all relative information to JIRB conforming to the local regulation.

3.No amendments will be put into effect without JIRB approval except where necessary to eliminate apparent immediate hazards to trial subjects. I authorize Chief Principal Investigators to submit amendment of protocol and ICF to JIRB for my site after I was well explained on all changes in amendment.

4.I authorized Chief Principal Investigator to submit annual report and final report for my site after I confirm the content of reports.

Investigator's Printed Name: _____ Affiliation: _____

Signature: _____ Date: _____

Principle Investigator's Declaration

The principle principal investigator is required to sign on this page

●Principle Investigator's Statement:

1.I bear the responsibility to conduct this clinical trial and have carefully read the protocol. I will abide by the principles of the Declaration of Helsinki and the related regulations of the country to ensure the life, health, personal privacy, and dignity of the trial subjects.

2.I hereby assure to conduct the study according to the trial protocol, report the severe adverse events in accordance with the relevant laws of the country, submit the interim and final reports, and provide all required related information to XX Human Study Committee for the review to ensure that the subjects' rights and interests are protected.

3.I hereby assure to follow the original protocol or the content of the Informed Consent Form to conduct this study unless there is any immediate danger to avoid prior to being approved by the XX Human Subject Committee in writing, if the approved protocol or Informed Consent Form needs to be amended. I understand that the application for the approval of the amendment of the protocol or Informed Consent form described above shall follow that the Co-investigator, Associate Investigator or other investigator of this study have received my full notification of the content to be amended and be confirmed without any errors. I will then be authorized to submit the application on my behalf alone.

4.I understand that the submission of the interim and final reports shall follow that the Co-investigator, Associate Investigator, or other investigator have received my full notification of the content of the reports to be submitted and are confirmed to be without error. I will then be authorized to submit the reports on my own behalf alone.

Appendix I Information of the Test Drug

1.Name of the Drug (Generic name, brand name, dosage):

2.Country of the manufacturer:

3.Country of the origin:

4.Country of the developing manufacturer:

5.Domestic permission: ☐yes (No. _____) ☐no

6.Global research: (if FDA IND No. is available, please provide: _____)

7.In which country is the drug permitted on market? Which year is the permit issued?

8.Record in pharmacopoeia: (version/page)

U.S.P.: / PDR: /

BP.: / Extra Pharmacopoeia: /

JP.: / others:

9.Chemical structure:

10.Information on pharmacokinetics:

11.Mechanism of action:

12.Indication and usage:

13.Routine dosage and route of administration:

14.Adverse events:

15.Contraindications and cautions:

16.Protocol number / title (either the completed or ongoing)

Appendix II Information of Test Vaccine

1.Name of the Vaccine (Generic name, brand name, dosage):

2.Country of the manufacturer:

3.Country of the origin:

4.Country of the developing manufacturer:

5.Domestic permission: ☐yes (No. _____) ☐no

6.Global research: (if FDA IND No. is available, please provide: _____)

7.In which country is the drug permitted on market? Which year is the permit issued?

8.Protocol number / title (either the completed or ongoing)

Appendix III Gene Transduction Introduction

Appendix IV Tested Device

1.Name of the Device (Generic name, brand name, specifications):

2.Country of the manufacturer:

3.Country of the origin:

4.Country of the developing manufacturer:

5.Domestic permission: ☐yes (No. _____) ☐no

6.Global research: (if FDA IND No. is available, please provide: _____)

7.In which country is the drug permitted on market? Which year is the permit issued?

8.Degree of risk: ☐significant ☐non-significant

Appendix V Information of medical technology

1.Name of the medical technology:

2.Global research status:

3.In which country is the drug permitted to practice? Which year is the permit issued?

4.References: (no more than 10 issues)

Appendix VI Summary of Observation Research (within 250 words)

Attachment 5

XX Institutional Review Board

Protocol Amendment Application Form

Except the people's names in Chinese only, the other information may be in Chinese or English. The font size shall not be less than 14.

Inapplicable items may be deleted by oneself.

Application Date: yyyy/mm/dd

1.No.:

2.Trial Title:

3.Trial No.:

4.Principle Investigator:

Employer:

Job Title:

Tel: Fax:

e-mail:

5.Approval Expiration Date: yyyy/mm/dd

6.Amended Items:

The comparison table for the data before and after the amendment shall be submitted. The revised parts must be in bold face and underlined. The inapplicable items may be deleted.

Amended Item	Original Version/Date	Revised Version/Date
☐Trial Protocol		
☐Informed Consent Form		
☐Individual Case Report		
☐Addition/Change of Principle Investigator	NA	NA
☐Addition/Change of Associate Investigator	NA	NA
☐Other		

7.Reason for Amendment

☐Request by the Department of Health (submission of official document required)

☐Administrative change (such as the address and telephone number of trial contact person)
☐Study design change (including dose/frequency of examination)
☐Patient inclusion or exclusion criteria change
☐Sentence fluency improvement or more detailed instruction
☐Safety data change
☐Assurance content change
☐Other, please describe:

8.This amendment requires re-signing the Informed Consent Form:
☐No ☐Yes, Informed Consent Form version/date:

9.Dose change:
☐No ☐Yes, please include the table to briefly describe the dose change

10.Enrollment of new subjects before XX Human Study Committee approves this amendment
☐No
☐Yes, the Principle Investigator bears the responsibility to assure that the previously approved protocol be used before the approval for the amendment.

11.Anticipated Risks after Amendment
☐Similar risks to the original protocol after amendment
☐Higher risks than the original protocol after amendment, with subjects' welfare significantly improved.
☐Higher risks than the original protocol after amendment, no significant improvement of subjects' welfare but with valuable outcome on the study

●Declaration: The above data is filled out personally to assure the accuracy of the information with no effort spared. If there is any false information or deliberate concealment, I shall be held responsible by law.

Chinese Name in Block Letters: Employer:

Signature: _____ Date: _____

Cell Phone: Work Telephone:

Fax: e-mail:

Express Delivery Address:

Principle Investigator's Signature Page

The application of this amendment is authorized on the Principle Investigator's behalf. Prior to the submission of the application, the Principle Investigator is responsible for informing the Co-investigator, Associate Investigator, or other investigator of the information related to the study. If the trial-related personnel is not informed, the Principle Investigator is responsible for any subsequent condition and applicable legal liability.

●Declaration of Principle Investigator

1.I assure that, except under the circumstance of immediate danger, I shall abide by the originally approved protocol but not the amended one to conduct this study.

2.I assure that the information related to the amendment application has been provided to the Co-investigator, Associate Investigator, or other investigator of this trial. In addition, I have been authorized to submit the application on my own behalf.

3.I shall provide the full related information required by the XX Human Study Committee for the review.

Principle Investigator's Name: Employer:

Signature: _____ Date: _____

Other Investigator's Signature Page

The Additional Investigator or Associate Investigator of

This Study Must Sign this Declaration

●Declaration of Investigator:

1.I bear the responsibility to conduct this clinical trial and have carefully read the protocol. I will abide by the principles of the Declaration of Helsinki and the related regulations of the country to ensure the life, health, personal privacy, and dignity of the trial subjects.

2.I hereby assure to conduct the study according to the trial protocol, report the severe adverse events in accordance with the relevant laws of the country, submit the interim and final reports, and provide all required related information to XX Human Study Committee for the review to ensure that the subjects' rights and interests are protected.

3.I hereby assure to follow the original protocol or the content of the Informed Consent Form to conduct this study unless there is any immediate danger to avoid prior to being approved by the XX Human Subject Committee in writing, if the approved protocol or Informed Consent Form needs to be amended. I understand that the application for the approval of the amendment of the protocol or Informed Consent form described above shall follow that the Co-investigator, Associate Investigator or other investigator of this study have received my full notification of the content to be amended and is confirmed without any errors. I will then be authorized to submit the application on my behalf alone.

4.I understand that the submission of the interim and final reports shall follow that the Co-investigator, Associate Investigator, or other investigator have received my full notification of the content of the reports to be submitted and are confirmed to be without error. I will then be authorized to submit the reports on my own behalf alone.

Investigator's Name: Employer:

Signature: _____ Date: _____

Attachment 6

Institutional Review Board
Interim Report

This Form Includes the Trial Situation since the Previous Interim Report

Application Date: yyyy/mm/dd

1.XX IRB No.

2.Trial Title

3.Trial No.

4.Principle Investigator:

Employer:

Job Title:

Tel: Fax:

e-mail:

5.Approval Expiration Date: yyyy/mm/dd
Interim Report Period: year month day to year month day
Condition

6.First Patient Enrollment Date: yyyy/mm/dd

7.Enrollment During This Report Period

Hospital Name	Subject Screening Number	Subject Enrollment Number	Subject Completion Number	AE (person-time)	SAE (person-time)
Total					

If no enrollment during this report period, please check the following best describing the real situation:

☐There is no new subject enrolled during this report period. The recruitment is on-going.

☐The study no longer recruits new subjects. The existing subjects have not completed the related study.

☐The study no longer recruits new subjects. All subjects have completed all related study and are required for long-term follow-up study.

☐There has been no subject enrolled and no new danger has been discovered. Please skip to 12.

☐The remaining study is restricted for data analysis only.

8.Enrollment Up to Now:

Hospital Name	Subject Screening Number	Subject Enrollment Number	Subject Completion Number	AE (person-time)	SAE (person-time)
Total					

9.Description of Individual Enrollment (please indicate the hospital name of the individual):

Status Codes:
1. in screening 2. in treatment 3. completion 4. withdrawal
Withdrawal Reason Codes:
1.adverse event/intercurrent illness
2.death
3.insufficient therapeutic response
4.failure to return
5.violation of selection criteria at entry *please specify
6.other protocol violation * please specify
7.refused treatment/withdraw consent
8.early improvement
9.administrative/other * please specify

Hospital Name	Subject No.	Patient's Initial	Administered Drug NA for Double-blind Study	Status Code	Withdrawal Reason Code	Signed Informed Consent Form Version	Informed Consent Form Signing Date

10.Description of Individual SAE Current Condition please specify hospital name, anticipated/unanticipated, related/unrelated

11.Decoding
☐No
☐Yes, please describe reason and decoding date (yyyy/mm/dd)

12.If new scientific information discovered, the risk of the subject enrolled in the study will rise
☐Yes ☐No

13.Data Safety Monitoring Board (DSMB) for This Study

☐ No ☐ Yes

i.How frequent is the review? Is it consistent with the protocol?

ii.During this interim report period, will DSMB review the data of this study?

☐Yes, please submit the review report

☐No, please indicate the next review date

☐Others, please specify

14.Previous application of amendment to the Board

☐No

☐Yes, please list the amendment dates of the submissions during this interim report period in the sequential order.

15.Submitted Data Table

i.Copy of Signature Page of Informed Consent Form (each trial hospital separated)	☐Yes ☐Not applicable
ii.DSMB Review Report	☐Yes ☐Not applicable
iii.Others (please list in the sequential order)	☐Yes ☐Not applicable

●Declaration: The above data is filled out personally to assure the accuracy of the information with no effort spared. If there is any false information or deliberate concealment, I shall be held responsible by law.

Chinese Name in Block Letters: Employer:

Signature: _____ Date: _____

Cell Phone: Work Telephone:

Fax: e-mail:

Express Delivery Address:

Principle Investigator's Signature Page

The application of this interim report is authorized on the Principle Investigator's behalf. Prior to the submission of the application, the Principle Investigator is responsible for informing the Co-investigator, Associate Investigator, or other investigator of the information related to the study. If the trial-related personnel is not informed, the Principle Investigator is responsible for any subsequent condition and applicable legal liability.

- Declaration of Principle Investigator

  - I bear the responsibility to conduct this clinical trial. I will abide by the principles of the Declaration of Helsinki and the related regulations of the country to ensure the life, health, personal privacy, and dignity of the trial subjects.
  - The content of this interim report has been verified by me to be accurate. If necessary, I shall provide all required related information to XX Human Study Committee for the review to ensure that the subjects' rights and interests are protected.

Principle Investigator's Name: Employer:

Signature: _____ Date: _____

Attachment 7

Closure Report

This Form Includes the Trial Situation since the Previous Interim Report

Application Date: yyyy/mm/dd

1.XX IRB No.

2.Trial Title

3.Trial No.

4.Principle Investigator:

Employer:

Job Title:

Tel: Fax:

e-mail:

5.Approval Expiration Date: yyyy/mm/dd
Interim Report Period: year month day to year month day
Condition

6.First Patient Enrollment Date: yyyy/mm/dd

7.Case Conclusion Reason (Choose More Than One If Applicable)

☐All subjects have completed all related studies (only data analysis remaining)
☐Superior therapeutic effect, early termination
☐Unsatisfactory subject recruitment, early termination
☐Insufficient therapeutic effect, not suitable to continue
☐Extremely high risk for enrolled subjects, not suitable to continue
☐Others, please specify

8.Enrollment During This Report Period

Hospital Name	Subject Screening Number	Subject Enrollment Number	Subject Completion Number	AE (person-time)	SAE (person-time)
Total					

9.Enrollment Up to Now:

Hospital Name	Subject Screening Number	Subject Enrollment Number	Subject Completion Number	AE (person-time)	SAE (person-time)
Total					

10.Description of Individual Enrollment (please indicate the hospital name of the individual):

Status Codes:
1. in screening 2. in treatment 3. completion 4. withdrawal
Withdrawal Reason Codes:
1.adverse event/intercurrent illness
2.death
3.insufficient therapeutic response
4.failure to return
5.violation of selection criteria at entry *please specify
6.other protocol violation * please specify
7.refused treatment/withdraw consent
8.early improvement
9.administrative/other * please specify

Hospital Name	Subject No.	Patient's Initial	Administered Drug NA for Double-blind Study	Status Code	Withdrawal Reason Code	Signed Informed Consent Form Version	Informed Consent Form Signing Date

11.Description of Individual SAE Current Condition please specify hospital name, anticipated/unanticipated, related/unrelated

12.Decoding
☐No
☐Yes, please describe reason and decoding date (yyyy/mm/dd)

13.Data Safety Monitoring Board (DSMB) for This Study

☐No ☐Yes

i.How frequent is the review? Is it consistent with the protocol?

ii.During this interim report period, will DSMB review the data of this study?

☐Yes, please submit the review report

☐No, please indicate the next review date

☐Others, please specify

14.Previous application of amendment to the Board

☐No

☐Yes, please list the amendment dates of the submissions during this interim report period in the sequential order.

15.Submitted Data Table

i.Copy of Signature Page of Informed Consent Form (each trial hospital separated)	☐Yes ☐Not applicable
ii.DSMB Review Report	☐Yes ☐Not applicable
iii.Others (please list in the sequential order)	☐Yes ☐Not applicable

●Declaration: The above data is filled out personally to assure the accuracy of the information with no effort spared. If there is any false information or deliberate concealing, I shall be held responsible by law.

Chinese Name in Block Letters: Employer:

Signature: _____ Date: _____

Cell Phone: Work Telephone:

Fax: e-mail:

Express Delivery Address:

Principle Investigator's Signature Page

The application of this interim report is authorized on the Principle Investigator's behalf. Prior to the submission of the application, the Principle Investigator is responsible for informing the Co-investigator, Associate Investigator, or other investigator of the information related to the study. If the trial-related personnel is not informed, the Principle Investigator is responsible for any subsequent condition and applicable legal liability.

●Declaration of Principle Investigator

■I bear the responsibility to conduct this clinical trial. I will abide by the principles of the Declaration of Helsinki and the related regulations of the country to ensure the life, health, personal privacy, and dignity of the trial subjects.

■The content of this interim report has been verified by me to be accurate. If necessary, I shall provide all required related information to XX Human Study Committee for the review to ensure that the subjects' rights and interests are protected.

Principle Investigator's Name: Employer:

Signature: _____ Date: _____

Attachment 8

Clinical Trial Informed Consent Form Sample

The Highlighted Black on White Varies with the Trial Center

Trial Protocol:
Trial Center: Sponsor/Drug Company: Principle Investigator: Title: Telephone: Associate Investigator: Title: Telephone: 24 Hr Emergency Contact Telephone:
Subject's Name: Gender: Date of Birth: Medical Record No.: Mailing Address: Telephone: Legal Representative/Attorney's Name: Relationship with Subject: Gender: Date of Birth: ID Number: Mailing Address: Telephone:
1.Overview of Drug in Global Market:
2.Trial Objective: Instruction:The description in this paragraph shall express the implication of Article 22 of Good Clinical Practice, i.e., it shall be clearly stated that the clinical trial is a study. The objective shall be included.
3.Major Inclusion and Exclusion Criteria:

4.Trial Method and Related Examinations:

Instruction:The description of this paragraph shall be able to fully convey Items 3, 4, 6, 19, and 20 in Article 22 of Good Clinical Practice as illustrated below:

(3)Trial treatment and randomized distribution probability of each treatment

(4)Treatment procedure including all invasive actions

(6)On-going part of the clinical trial

(19)Estimated duration of the subjects in the clinical trial

(20)Approximate subject number

5.Potential Side Effects, Incidence Rates, and Countermeasures:

Instruction:The description of this paragraph shall be able to fully convey Item 18 in Article 22 of Good Clinical Practice to properly illustrate the anticipated conditions and reasons for the subject to terminate the participation in the study.

6.Other Alternative Treatments:

Instruction:The description of this paragraph shall be able to fully convey Item 9 in Article 22 of Good Clinical Practice to properly illustrate the other potential treatment methods or courses and their benefits.

7.Anticipated Trial Benefits:

Instruction:The description of this paragraph shall be able to fully convey Item 8 in Article 22 of Good Clinical Practice to properly illustrate the reasonably anticipated clinical benefits of the participation in the study.

8.Contraindications, Prohibitions, and Cooperations during The Trial Progression:

Instruction: The description of this paragraph shall be able to fully convey Items 5 and 7 in Article 22 of Good Clinical Practice to properly illustrate the subject's responsibility and the anticipated risks and inconvenience to the subjects, embryos, infants, or breast-fed babies.

9.Confidentiality:

Instruction:The description of this paragraph shall be able to fully convey Items 14 and 15 in Article 22 of Good Clinical Practice.

Item 14: After signing the Informed Consent Form, the subject then agrees that the original medical record may be directly viewed by the monitor, auditor, Human Subject Committee, and competent authority to assure that the clinical trial process and data meet the requirements of applicable laws and regulation and guarantee that the confidentiality of the subject shall not be violated.

Item 15: The record which can identify the subject shall be kept confidential and not be disclosed as required by the applicable laws and regulations. If the trial results are published, the identity of the subject will still be kept confidential.

10.Damage Indemnification and Insurance:

- As the clinical trial protocol stipulated for this study, the damage caused by the occurrence of adverse reaction shall be OOO company's (or together with OOO hospital) responsibility for the indemnification (please refer to the indemnification instruction in the Appendix such as insurance policy and/or indemnifications by the hospital). However, the anticipated adverse reactions indicated in the Informed Consent Form shall not be indemnified.
- In the event of the occurrence of adverse reaction or damage following the clinical trial protocol of this study, the hospital is willing to provide professional medical care and consultation. You will not be held responsible for the medical expenses for treating the adverse reaction or damage.
- Except the above 2 indemnifications and medical care, this study does not offer the indemnification in any other form. If you are unwilling to accept such risks, please do not participate in the study.
- You will not lose any legal right by signing this Informed Consent Form.
- (This study is insured for liability. This study is not insured for liability.)

(Note: Whether to state the insurance related matters or not will be up to the trial sponsor and the trial center.)

Instruction: The description of this paragraph shall be able to fully convey Items 10, 11, and 12 in Article 22 of Good Clinical Practice.

Item 10: In the event of trial-related damage, the subject shall receive indemnifications or treatments.

Item 11: If there is any receivable subsidy, the subjects participating in the clinical trial shall be informed.

Item 12: If there is any payment to make, the subjects participating in the clinical trial shall be informed.

11.Subject's Rights:

A.During the course of the trial, any significant discovery related to your health or illness which may affect your intention to continue the participation in the clinical trial will be made available to you immediately.

B.If you have any question regarding the nature of the study, comment on the rights as a subject, or suspect harm due to the participation in the study during the course of the trial, you can contact the clinical trial review committee of the hospital for further consultation. The telephone number is : _____ .

C.In order to conduct the study, you must receive the care of Dr. _____. If you have any question or experience any condition now or during the trial period, please do not hesitate to contact the _____Division of the _____ Department in the _____Hospital (24 hr contact telephone: _____).

This Informed Consent Form is prepared in duplicate. The physician has given a copy to you and thoroughly explained the nature and objective of this study. Dr. _____ has answered your questions regarding the drug and the study.

Instruction: The description of this paragraph shall be able to fully convey Items 16 and 17 in Article 22 of Good Clinical Practice.

Item 16: As the new information which may affect the subject's intention to continue the participation in the clinical trial becomes available, the subject, legal representative, or power of attorney shall be informed immediately.

Item 17: The contact person to further inquire the trial-related information and the rights of the subject and the contact person as the trial-related injury occurs

12.Withdrawal and Termination:

You are entitled to freely choose to participate in this study or not; You may cancel the concent at any time during the trial without any reason and this will not cause any discomfort or affect the following medical care by the physician. The Principle Investigator or the sponsor may halt the progression of the study if necessary.

Instruction:The description of this paragraph shall be able to fully convey Article 22 of Good Clinical Practice to properly illustrate that the subject voluntarily participates in the study, can withdraw from the trial if he or she does not agree to without any penalty or loss of the benefits deserved.

13.Signature

A.The Principle Investigator or Associate Investigator has thoroughly explained the nature and objective in the protocol of the study described above and the potential risks and benefits.

Principle Investigator/Associate Investigator's Signature:

Date: month day year

B.The subject has fully understood the study method and the potential risks and benefits described above. The questions regarding this study have been explained in detail by the Principle Investigator.

Subject's Signature:

Legal Representative's Signature

Date: month day year

Power of Attorney's Signature:

Date: month day year

C.Witness:

Name:

ID No.: Telephone:

Mailng Address:

Signature: Date: month day year

Attachment 9

Informed Consent Form Content Guidelines

June 2007

The Informed Consent is the most important document to ensure the doctor has fulfilled the informing obligation and to protect the rights of the participant. This is also one of the most important audit items in the review of the protocol by the institutional review board. The rights of the participant will not be reduced by signing the Informed Consent, which should be written with care and should not be considered as the simplified protocol. The Informed Consent should be written with the spoken language and suitability in mind.

Using the Spoken Language

The reader of the Informed Consent is the patient or their legal representative. This is why the content should be written in the descriptive form with friendly and spoken language. **The content should be prepared based on middle high school grade-3 (basic obligatory education level) language level** and avoid mix of Chinese and English. It is advised that the informed consent form be proofread by a reader of middle high school grade-3 language level before finalizing the content. If the reader can comprehend the text without further explanation, the goal of narrative writing is achieved. Non-medical staff in the Institutional Review Board contributes significantly to whether the content of informed consent from is narrative.

Content Suitability

The Informed Consent should not be too long but those parts of the content which might negatively affect the willingness of the participant to take part in the trial must be included. The Informed Consent can be deemed as part of the participation contract of the clinical trial, but it should **not contain the whole contract**. The reason is the clinical trial is highly technical, and it will complicate the Informed Consent and hinder understanding if all the content is included. The professional details can be included in the protocol or the investigator's manual, and it will be equally legally binding. The participant will not know and it will not affect their rights. **Not all items related to the clinical trial are necessary to be included in the Informed Consent**, for example, the include and exclude conditions do not need to be added. However, **those parts of the content**

which might negatively affect the willingness of the participant to take part in the trial must be included. Those parts which might positively affect the willingness of the participant to join do not have to be included. For example, the insurance for the trial is meant for the transfer of liabilities in case of compensation. This might increase the willingness of the participant to take part in the trial, therefore, it does not have to be included in the Informed Consent. The protocol and principle investigator's manual are legally binding. **Any breach on the part of the principle investigator will have to bear the responsibility**. This is the reason why the protocol or principle investigator's manual has to be signed by the principle investigator, as their commitment to follow the protocol.

As specified in Article 52 of the Enforcement Regulation of the Medical Act, the Informed Consent should include "purpose of the Research", "potential side effects and risks", "expected effects", "alternative treatments" and "the right of withdrawal for the participant anytime". For studies other than new medical techniques, drugs or equipment, such as questionnaires, the Informed Consent should describe "purpose and method of the Research", "effects on the respondents" (e.g., the time involved), and the contact information of the researcher. The Informed Consent can also be designed into a form which can be completed by filling-in the fields. Due to the different backgrounds of the participant in a trial, the Informed Consents can varies according to individual hospital, but they have to be reviewed and approved by the individual institutional review board.

ICH-GCP recommended that the Informed Consent should include the following 20 items, which should be checked one by one and make sure they have all been explained before the Informed Consent is finalized.

(1)The clinical trial is a research

(2)The purpose of the Research

(3)The treatment in the trial and the randomized possibility of each treatment

(4)Procedures and all types of intervention that will be undertaken.

(5)The responsibility of the participant

(6)The trial in the Research

(7)The expected risk or inconvenience for participants, embryos, babies or breastfed infants

(8)Reasonably expected clinical benefits. The participant should be informed in case there is none.

(9)Alternative treatments and their potential main benefits and risks

(10)Compensation and / or treatment for the participant should trial-related damage occurred.

(11)The participant should be informed if there is any expected reward.

(12)The participant should be informed if there is any fee expected to be paid.

(13)The participant should join the trial in a voluntary basis. They can decline to participant or withdraw from the trial any time without any punishment or harm on their rights.

(14)By signing the Informed Consent, the participant is deemed to have agreed that his medical history can be reviewed directly by the supervisors, examiners, institutional review boards/ ethics committees and health authorities, in order to ensure the compliance of the trial procedures and / or data with related laws and regulations. The identity of the participant will be kept confidential in all cases.

(15)The identity information of the participant should be kept confidential and should not be made public according to related laws and regulations. Should the result of the trial be published, the identity of the participant will still be kept confidential.

(16)Should there be any new information which might affect the willingness of the participant to stay in the trial, the participant or their legal representatives should be informed immediately.

(17)Provide further information of the trial, the contact person on participants' rights and the contact person for trial-related damages.

(18)The expected conditions and reasons for the participant to withdraw from the trial

(19)The expected duration of the trial for the participant

(20)The estimated number of participants

Guidelines for Each Paragraphs of Informed Consent

1.Background Information

The **introductory part** of the Informed Consent should be **short and explained** the importance of the trial. Global launching status can be described for trials of new drugs. It can be followed by the purpose of the trial. All these should be completed in a few simple sentences. It is not the supportive information of the protocol but an introduction for the participant on the trial.

2.Methods

The methods of the trial should be explained in this paragraph. You should explain what you will do and what are the responsibilities of the participant, which should include: the randomized possibility of different treatments for each group, duration of the trial, estimated number of participants, the responsibilities of the participant (e.g., contraception should be adopted and driving should be avoided), and the inconvenience for the participant (e.g., number of return visit, the amount of blood (in cc) to be drawn and the tests to be done). **Information which might negatively affect the willingness of the participant to participate must be included,** especially for interventional examination which must be clearly stated. Jargon should be prevented. For randomized double-blinded research, the following description is recommended:

> **The study is a randomized double-blinded trial. In order to ensure the trial results will not be distorted, half of the participant will be taking the trial drug and the other half will be taking the "placebo". "Placebo" is a drug with the same appearance with the trial drug but without the effective ingredients. As to who are going to take the trial drug and who are going to take the "placebo", it will be decided randomly just as the same as tossing a coin. Neither you nor your trial doctor knows which type of drug you take.**

3.Potential Side Effects, Risks and the Handling

The focus of this paragraph is to explain on the risk of participation to the subject. **The historical incident rate of the side effects should be clearly stated, and preferably, in figures.** This should not be hided from participants as it might reduce their willingness of participation. The result will be extremely undesirable if the participant discovered any hiding of facts or any deception by the trial doctor, after they entered into the trial. For side effects with low incident rates, they do not need to be completed listed out, and can be summarized by "from the past experience, the incident rates of other side effects are all less than 1%". **Any potential fatality and infertility must be clearly stated.** Contact and handling information for any dangerous condition or emergency should also be included, with conforming words such as "the doctors will try their best in saving the participant's life". The expected conditions and reasons for the participant to withdraw from the trial should also be stated.

4.Alternative Treatments and Explanation

The main point of this paragraph is to let the participant know that they **do not have to take part** in the trial and, in case that they don't, the alternative treatments that they can go through.

5.Expected Effects and Benefits

The focus of this paragraph is to explain to the participant the benefits for taking part in the trial. The expected effects basing on historical information should be clearly stated, **preferably, with figures.** This is to enhance the willingness of the subject to participate. For example, x% of the patients can be cured and the condition of x% of patients can be under control. **The content should be based on facts** and should not be exaggerated.

6.Banned or Restricted Activities during the Trial

This paragraph stated the activities that the subject should not participate or should limit their participation during the trial. For example, certain drugs or food should be avoided, contraception should be adopted and driving should be avoided.

7.Confidentiality

Although the privacy of the participant will be protected in the trial, the issue on responsibility should be stated in case of information leakage. The following explanation is recommended:

Your examination result and diagnosis will be kept confidential and will only be identified by a research number instead of your name, which will not be released except when requested by legal investigation. We will protect your privacy and your identity will stay anonymous even if the result of the study is published.

8.Compensation

The following write-up is recommended in accordance with the template of informed consent issued by the Department of Health:

- **In case of any damage created by adverse effects when the trial is conducted according to the protocol, it will be compensated by xxx Company (or with xxx Hospital). Please refer to the Appendix for compensation details such as insurance policy and / or compensation guidelines of the Hospital. No compensation will**

be paid for the expected adverse effects stated on the Informed Consent.

- **In case of any damage created by adverse effects when the trial is conducted according to the protocol, the Hospital will provide professional medical care and consultation. You will not have to pay for the necessary medical fee for the treatment of adverse effects or damages.**
- **Apart from the compensation and the medical care stated above, the Research does not provide any other forms of compensation. If you are not willing to take the risk, please do not participate.**
- **You will not lose any of your legal rights by signing the Informed Consent.**
- **(The Research has purchased liability insurance. The Research has not purchased liability insurance.) (Remarks: The trial assigner and organizer should design on whether to mention the insurance or not.)**

9.Rights and Obligations

The rights and obligations of the participant should be protected during the trial. The following write-up is recommended:

- **The organizer of the Research will protect the legal rights of the participant during the trial.**
- **The participant is free to revoke their consent and withdraw from the trial anytime and it will not create any issue nor will it affect their medical care in the future.**
- **Should there be any new information which might affect the willingness of the participant to stay in the trial, the participant or their legal representatives should be informed immediately.**
- **No extra fee is needed for participating in the trial.**
- **The Informed Consent has one original copy and one duplicated copy. The doctor has already given the duplicated copy to you and they have thoroughly explained the nature and purpose of the Research. Doctor xxx has replied your questions on the drug and the Research.**

Lastly, the contact information of the Institutional Review Board should be added, in case if the participant would like to contact the Institutional

Review Board directly to double check the information. For protocols to be submitted for review under the Joint Institutional Review Board, the contact persons of the institutional review boards of all individual hospitals should be included. The following write-up is recommended:

You have decided to participate in this trial on your own accord. You have the right not to participate. If you have any question on the rights of participating in the Research, please contact Mr / Ms xxx of the Institutional Review Board at Tel. No. xxxxxxxx, Fax. No. xxxxxxxx or email: xxxxx.

10.Declaration

The Informed Consent can be ended with a declaration summarizing the details of the Consent. According to the applicable law, apart from the participant or their legal representative, the trial doctor and assigner must also sign the Informed Consent. The witness is to confirm that the Informed Consent and all other written information provided to the participant have already been clearly explained to and being understood by the participant or their legal representative, and the consent is given on the participant's or their legal representative's own accord. Having the Informed Consent signed by a witness is desirable. The principle investigator should only sign on the Informed Consent after the informed process has been full completed. The following write-up is recommended:

Participant's Declaration:

The above information has been explained to me and I have had the opportunity to ask questions about the Research and any questions that I have asked have been answered to my satisfaction. I agreed to participate in this Research. If I have any question in the future, I can contact Doctor xxx from xxx Hospital.

Name of Participant: _____

Signature of Participant / Legal Representative / Person with the Right of Consent: _____

Date: _____

Name of Legal Representative
(If it is signed by a legal representative): _____

Legal Representative / Person with the Right of Consent:

_____

Informed Consent Explainer: (explains and describes the person referred to in the informed consent form)

Name:_____ **Signature:**_____ **Date:**_____

Name of Witness:_____ **Signature:**_____

Date:_____

Principle Investigator's Declaration:

I guarantee that I myself or one of the members in my research team, who has been authorized to conduct the procedure, have / has already explained the Research, including the purposes, procedures, current alternative treatments, and the potential risks and benefits of participating in the Research, to the above person. All the questions raised have been satisfactorily answered.

Name of the Principle Investigator:_____

Signature:_____ **Date:**_____

Attachment 10

Guidelines for the Informed Consent of Pharmacogenomical Research

Wei-Shu-Yao No. 0940338555 Announced by Department of Health on 13 October 2005

1.Name of the Protocol

For supplementary trial of clinical trial of drug, it is recommended to retain the original name of the trial, instead of creating a new name to include "pharmacogenomical research".

2.Duration of the Trial

The duration of joint participation in the trial.

3.Contact Information of Principle Investigator / Vice Principle Investigator

Please state the department, organization, contact phone number and fax number of the Principle Investigator / Vice Principle Investigator.

4.Purpose of Research

Explain: (1) The acedmeic values, rational and purposes of the Research; (2) The source of funding; (3) Planned Number of Participants; (4) Description of the genes to be studied, e.g. N-acetyltransferase controlled genes. The specific scope of Research should be described in case the genes to be studied cannot be identified under the current scientific level and development. For example, in order to study the effects and side effects of a certain drug, we will study the genetic information of "genes related with drug metabolism" in you. This information, however, is not the only base for understanding the effects and side effects of that drug.

5.Tests and Procedures Required on the Participant

For example: Types of testing sample, frequency and amount of blood extraction (in cc), body parts involved in the extraction of testing sample, the size of the tissue to be extracted, intervals between extractions and frequency of extractions, etc.

6.Participants of the Research might experience physical, psychological or social side effects.

A.Physical Aspect

Potential physical effects after the extraction of tissue testing sample should be stated. (e.g. short-term discomfort, blue, bleeding, swelling

or infection at the point of blood extraction. The incurrence rates should also be stated if possible.)

B.Psychological Aspect

The impact on the participant and their social relationship after getting their genetic information from the Research should be stated.

C.Social Aspect

The participant should be informed that the impact on their social rights, such as education, employment, medical and care, in case of leakage of genetic information cannot be predicted under the current circumstances. The Principle Investigator should, however, protect the genetic information of the participant from being leaked. Please see Item 15 for the ways to protect the confidentiality of the genetic information of the participant.

7.Compensation

In case of any personal damage caused by the implementation of the protocol, the assigner of the trial xxx Company (or xxxx Hospital) shall bear the liabilities of compensation and medical care according to the law.

8.The Handling and Storage of the Testing Sample

The handling of the extracted testing sample should be explained. For example, extracted DNA, made into cell line, and laboratory, department, organization, city and country of storage, and the name of person in-charge of the storage (include overseas organization) and the expiry date of the testing sample.

9.The Personnel who Might Use the Testing Sample and Related Information

According to legal requirements, the personnel who might use the testing sample should be stated. Apart from that, it should also be stated that whether other related academic researchers would be legally authorized to use the testing sample, if yes, the name of the researchers should be stated, or will the testing sample be legally transferred to another organization overseas, if yes, the name of the country, organization and the researcher should be stated.

10.The Handling of the Testing Sample after the Research

The possible handlings of the testing sample after the end of the Research should be listed out. The handling methods should be executed with the participant's approval.

For example:

☐I am willing to provide the testing sample to xxx Hospital for other

genetic researches. We will need to ask you to sign another Informed Content at that time, which will be reviewed and approved by the Institutional Review Board of xx Hospital beforehand.

☐The testing sample will be destroyed by xxx Hospital or xxx organization

☐The testing sample will be returned. As the remaining testing sample might contain diseases, its storage and transfer might carry the risk of infection. It is recommended to be destroyed by xxx Hospital if there is no need for retaining or if there is no storage facilities.

11.Assistance for the Participant

The potential assistance for the participant should be stated, such as whether the participant will be informed of the testing result, provided with consultation services on the testing result, and provided with related medical information.

12.Personal Reimbursements for the Participant

Whether or not the participant of the trial will be rewarded with any kinds of reimbursement or other subsidy, if yes, the amount should be stated.

13.The Fee to be borne by the Participant

Whether or not the participant needs to pay extra fee, if yes, the fee descriptions and amounts should be stated.

14.Derivative Benefits of the Trial

The legal rights and ownerships derived from the result of the trial for the trial assigner / organizer / principle investigator. For example, academic, patent or commercial usage.

15.Protection for the Confidentiality of the Participant's Genetic Information

The participant should be informed that the principle investigator must keep the test result and diagnosis of the participant confidential. The name of the participant should be replaced by a research number. The principle investigator shall protect the privacy of the participant except disclosure is required in legal investigation by the authority.

16.The Handling of the Personal Test Sample in case of Withdrawal during the Trial

The possible handlings of the testing sample after the end of the Research should be listed out by the principle investigator. The handling methods should be executed with the participant's approval. Please refer to the examples in Item 10.

17.Other Important Issues Related with the Collection or the Use of Test Sample

For example: A second test sample can be requested if the original test sample has been lost or damaged. The approval of the participant should be seek again, if the test sample has been used out of the original scope.

After the explanation by the principle investigator, you have fully understood all the above information and agree to participate in the Research. You will be given the duplicated copy of the Informed Consent and you fully understand that:

1.You will be provided with all the related and important discovery during the trial.

2.If you experience any discomfort or if you have any question related to the trial, please contact Doctor xxx from xxx Branch of xxx Department at Tel. No. xxxxx, or supervisor Mr / Ms xxxx at Tel. No. xxxxx. If you have any question on the rights related with the participation in the Research, you can contact Mr / Ms xxxx of the Institutional Review Board of xxx Hospital at Tel. No. xxxx.

3.You have the right to decline or withdraw from the Research (please state the withdrawal deadline) and it will not affect your rights of receiving medical care.

Signature of Participant: _____ Date: _____

Signature of Legal Representative: _____ Date: _____

Signature of Principle Investigator: _____ Date: _____

Witness for Verbal Consent

(A witness is required if the participant is not able to read the above content, which has been read to him instead)

This is to confirm that the principle investigator has already thoroughly explained the content of the Research to the participant.

Signature of the Witness: _____ Date: _____

Signature of the Principle Investigator: _____ Date: _____

(For participant below 20 years old or unable to move, the Informed Consent shall be signed by their legal representative, spouse or family member.)

Attachment 11

Post-Marketing Surveillance Study, PMS study

The objective of PMS study is to collect patient information and to explore the treatment experience in Taiwan. It involved the treatment of indication stated in the approved user guide of drugs. Basing on the Benchmarks of Marketing Practices announced by IRPMA, all the post-marketing drug trials must be approved by the Institutional Review Board, and PMS study is no exception. As the drug is already in the market, the treatment is available for the patients. The emphasize of the Institutional Review Board is not to safeguard the safety of the patients going through the treatment, but to protect the privacy of the patients, and whether or not the patients agree to enable the drug manufacturer to access their medical records. The acceptable Informed Consent should include the purpose of the Research, the methods of the Research, the handling of information and the explanation of related rights. Each parts are explained as follows:

- Purpose of Research: Explain the objectives of collecting the information. Who will be using the information? It should also be explained that it is the post-marketing survey study on patients' information. For detailed drug related information, please refer to the user guide of the drug.
- Methods: Explain what is the information to be collected? Will the collection be only limited to disease-related information (e.g. back pain) or all medical information? Will the demographical information (e.g. age and gender) be collected? The collection of information can be explained in terms of which are those information that will not be collected (e.g. social and economical information such as occupation and income).
- Handling of Information: Explain how the information will be handled and who will be in-charge. It is especially important to explain how privacy can be protected (e.g. replacing names with numbers and password protected database).
- Rights: For example, no fee is involved, withdrawal during the trial, and whether or not the result will be disclosed.
- Principle investigator and their contact information.

MEMO