I.Preface

Any research projects related to patients or require the participation of patients are referred to as human trials (also known as clinical trials or human researches). You may have heard of "human trials" or you are being invited to participate in one. This handbook is specially designed for patients, family and friends. It will help you understand the basic concept of human trials before considering whether or not you should participate in one.

II.What is a human trial?

Hospitals are where you seek medical attentions when you become sick. Other than providing medical treatments for patients, large-scaled hospitals and medical centers conduct teaching and researching activities concurrently. When a hospital conducts teaching and researching activities, it must carefully assess whether these activities will compromise patients' rights and interests.

Statutorily (Medical Care Act), a human trial is a method by which the effects of a new drug, new medical device, new treatment technique or generic drug on human are tested.

III.What is a research?

A "research" is an investigation conducted to answer questions. The objective of a research is to acquire knowledge previously unknown to us. The development of medical researches brings about fast-changing treatment methods to help us live better and longer. Researches can help us discover more new drugs to treat cancer, hypertension and other diseases, confirm whether new diagnosis methods are accurate and improve the medical services. Therefore doctors need to conduct researches in order to help improve the quality of medical services.

"Researches" are different from "treatments". A "treatment" has undergone complete researches and has a known potential treatment effect and incidence rate of side effects, whereas a "research" does not have a precise procedure and known effects. Hence, the participation in a research is not obligatory but rather voluntary.

Transforming the result of a scientific research into medical practices that are beneficial to human and can enhance human health and longevity can be defined as human trial. Therefore, human trials are an indispensable part of medical improvement. Despite the promising results generated in animals, many new treatments fail to demonstrate similar effects in human. Therefore before making these treatments conventional treatments, doctors must conduct human trials to collect relevant information and determine whether these treatments are effective in human and their potential side effects. In addition, the doctors should also identify the most appropriate treatment methods through the trials of human trials.

The completion of a new medical treatment must undergo safety and efficacy assessments. The development of a new medical technique or new medical device, on the contrarily, is simpler. The most complex development is the development of a new drug which can be a lengthy, difficult and expensive process before an official market approval is obtained. The process consists of three primary stages which include: physical and chemical analysis, animal studies and human trials. The fundamental principle is: make sure it is safe and harmless before it is effective!

1.Physical and chemical analysis stage

Use different physical and chemical approaches to purify, extract, modify and analyze chemical substances of different sources and pharmacological natures in order to identify new chemical substances with the greatest potential of becoming a new clinical trial candidate. Out of thousands or even tens of thousands of chemical substances tested, there might only be one or two new drugs that will make into the animal test stage.

2.Animal test stage

Apart from understanding the drug's effect on a particular disease, it is even more important to understand its negative effects of toxicity, mutagenesis and carcinogenesis. It usually takes about 2 to 3 years to complete this stage before the drug is allowed to enter the human trial stage.

3.Human trial phase. The human trial stage can be subdivided into 4 phases:

The study objective of phase 1 is to determine the magnitude of drug toxicity in human, what kind of organ damage and the degree of damage it will cause, and whether the damage is tolerable. Summarize all information to determine the safety dosage of the drug. Of course an animal study must be completed before the human trial can be performed. After all, human are different from animals; drugs that are safe to use in animals might be harmful to human. Therefore, phase 1 trials are usually conducted in a small number of healthy volunteers. The primary objective is to establish the safety data for the drug which falls into to the scope of clinical toxicology research.

The study objective of phase 2 is to determine whether the drug is effective, what is the appropriate dosage, what interactions does it have with other drugs, does it have clinical applications and is it worth developing. A phase 2 trial is a preliminary treatment observation on patients. The scale of the trial is usually small and involves approximately 100 patients. The primary purpose is to collect the basic information required for phase 3 clinical trial. Clinical trials of cancer drugs are highly toxic and are unethical to conduct in healthy volunteers in a phase 1 trial. Therefore, phase 1 and phase 2 trials are usually conducted on patients directly to determine the drug efficacy and tolerable dosage.

Once the drug completes the basic information assessment in phase 1 and 2 and is considered appropriate for clinical use, it will undergo a phase 3 clinical trial. A phase 3 clinical trial usually demands the greatest amount of manpower, materials and time. It involves fundamental principles of stringent placebo-control, random assignment, blinding and sometimes even several medical centers, for multi-centered researches, in order to perform a comprehensive treatment assessment. New drugs that pass the phase 3 clinical trial can then apply for market approval with the government authorities.

Clinical trials conducted on effective and safe drugs approved for launch in order to determine whether the drug has chronic side effects are called phase stage 4 trials. Since the phase 3 clinical trial involves a short observation period and a small number of patients, it is only possible to identify part of the acute side effects of the drug. Understanding of the drug's side effects is limited. Therefore it depends on the post-market surveillance to discover the presence of other side effects or chronic side effects. The primary objective of phase 4 clinical trial is to follow up on the side effects of chronic use of the drug which is different from the

phase 3 objective. A phase 4 trial is a follow-up study to determine the drug safety for long-term use.

IV.What should I know before participating in a trial?

Participation in a trial is not obligatory. You must know the followings before participating in a trial:

1.What is the objective of this trial?

The objective of a research is to increase knowledge. Therefore you should know what kind of information this trial is exploring. Research personnel should use a narrative and simple language to explain the objective of this trial and whether your participation is obligatory. If you are not willing to participate, what other treatment options are available.

2.What will happen during the trial?

You need to know what will be performed on you during the trial, how you should cooperate (such as: What is the frequency of return visits? How much blood will be drawn each time? What kind of tests will be performed?), and what kind of inconvenience it will cause (such as: no driving and needs to use birth control).

3.What are the potential adverse reactions?

All trials come with risks; therefore, you need to know the extent of risks involved in participating in this trial. Make sure to ask from the existing information what the potential side effects and their incidence rates are, preferably the exact figure of incidence rate. In the event of dangerous or emergence conditions, make sure you know what to do, who to contact, how to contact them, who will provide subsequent medical treatments and who will be responsible for the costs. You should be clarified all the details before participating in the trial.

4.What are the benefits and anticipated effects for me?

Participation in the trial is not obligatory; therefore, you should think about it carefully before you participate. You should understand that the "research" might not be beneficial to you. A "treatment" is a proven procedure that is beneficial to patients whereas a "trial" has unknown effects. Therefore a trial will not necessarily help the participants. The result of the trial might, however, help people with similar health problems. Overall, you should take a moment to think about whether you would like to participate in the trial and also be aware of the anticipated effect that you should expect without holding an over-optimistic expectation.

5.Are there any other treatment options available besides participating in the research?

Participation in the trial is not obligatory; therefore, you should know if there are other treatment options available and whether the participation in the trial is the only way to receive new treatments.

V.How do I know for sure that I have understood this trial well enough to make a decision?

After listening to the instructions given by the research personnel and asking all the questions, please try to answer the following questions. If you can answer the following questions correctly, that means you have known the trial well enough to make

the decision of whether you should participate.

1.What is the objective of this trial?

2.What are the benefits of participating in this trial?

3.What are the potential risks for participating in this trial?

4.There are no other treatments available if I do not participate in this trial: right/wrong (What is the treatment method?)

5.I need to pay to participate in this trial: right/wrong

6.I can change my mind and withdraw from the trial at any time after enrolling in the trial: right/wrong

7.My participation in this trial is voluntary: right/wrong

8.Trial personnel and government authorities will review the information I provided during the trial: right/wrong

The trial result can enhance human health. However, you must make sure that you know what type of trial you are about to participate in, the benefits and shortcomings of your participation, attain all information you need and ask all your questions.

VI. Responsibilities of medical personnel

The doctor in charge of the human trial has the obligation to be familiar and comply with the relevant ethical and legal principles for obtaining informed consent:

1.Patient's consent must be a decision made under a pressure-free environment and with decision-making capabilities.

2.Unless under an emergency condition or otherwise stipulated by the law, the doctor must obtain the patient's consent before conducting examinations, treatments or any other medical interventions. The consent for human trial must be in the form of a written informed consent form signed by the subjects.

3.Doctors should take proper steps and approaches to provide the following information to the subjects in order to allow the subjects understand their own condition as well as the information concerning the treatment in the human trial.

(1)Trial objective, method and relevant tests.
(2)Subject responsibilities including restrictions, limitations and instructions during the trial.
(3)Foreseeable risks and inconveniences for subjects, fetuses, infants, or breastfed babies.
(4)Reasonable clinical benefits that can be expected. If the trial does not involve any clinical benefit, the subjects should also be informed.
(5)Other treatment methods or procedures as well as their potential benefits and risks.
(6)Indemnification and/or treatments entitled to the subjects in the event of trial-related injuries.
(7)Participation from the subject is of voluntary nature. Subjects reserve the right to refuse to participate or withdraw from the trial at any time without being penalized or compromising the entitled interests.
(8)Subject identification records should be kept confidential and remain undisclosed under the relevant laws and regulations. Subjects will also remain anonymous when the trial results are published.
(9)If the new information might affect subject's willingness to participate in the trial, he/she or his/her legal representative should be informed of such information immediately.
(10)Acquire information relevant to the trial and find out

who the subject's contact person is 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.

(11)Foreseeable situations and reasons for subjects to terminate their participation in the trial.

(12)Estimated duration of subject's participation in the human trial.

(13)Approximate number of subjects participating in the trial.

4.Subjects with decision-making capabilities reserve the right to refuse to participate in the trial.

5.For subjects rendered incompetent or declared interdicted, the doctor should obtain their signatures on the written consent form according to the Medical Care Act. The legal representative is authorized to give the consent on behave of the incompetent subject. In the event that the subject is declared interdicted, his/her consent should be validated by the legal representative.

VII.The role and function of medical personnel in a human trial

1.Case manager for patients participating in the trial: provide direct healthcare and physiological assessment for the subjects; evaluate the safety and side effect of the trial for the subjects during each return visit to identify the occurrence of side effect timely and provide proper health education and treatment.

2.Information provider: provide information concerning the human trial such as the procedure, frequency, effect, side effect, drug toxicity, intervention, and complication of the treatment to help the subjects make the decision. Help the subjects learn about the progression of his/her disease as well as other available treatments; ensure that the subjects understand the content of the research and give their consent voluntarily, also make sure to let the subjects know that they are free to withdraw from the research at any time they want.

3.Trial data collector: record the progression of subjects' disease and complete individual case report.

4.Caretaker: keep close contact with the subjects in order to provide trial-related treatment services and information at any time.

5.Trial project coordinator: participate in the human trial and coordinate all communications pertain to the trial between the caretakers for the subjects and the internal departments of the institution.

6.Coordinating researcher: assist the implementation of the trial project.

In the human trial, nursing staff should possess sufficient human trial knowledge, skills to carry out the trial independently, communication ability to coordinate in the team as well as research data analysis and management abilities; they should also enhance their judgment for medical ethics and laws in order to protect the safety of trial subjects.

VIII.Subject rights and interests leaflet

Entitled interests for participating in the trial

The improvement of medicine builds on the foundation of scientific researches which to some extent rely on human as trial

participants. Therefore human trial is inevitable. As a subject for human trial, you are free to decide whether you would like to participate in the trial after receiving complete information. Participating in the trial will not compromise your rights and interests and you are still entitled to the best healthcare proven effective. The followings are information that you should know about:

As a subject, you are entitled to....

Before asking whether you would like to participate in the trial, a research staff will provide you information regarding the trial. He/she must explain the trial and make sure that you have fully understood it and decided if you would like to participate.

- Freedom to decide whether you would like to participate in the research.

  You can decide whether you would like to participate in the trial or terminate your participation at anytime without affecting your relationship with the doctor (principle investigator). If you have participated in other medical research and decided that you would not participate in this trial, it should not affect the medical care you are entitled to. Your doctor will continue to provide healthcare for you.

- You can ask questions about the trial at any time. The principle investigator will try his/her best to answer your questions.

  Your safety and welfare will be the most important consideration throughout the trial. The principle investigator will demonstrate the best technique and medical care in the research and minimize all risks and discomforts to the lowest degree as possible.

- Privacy and confidentiality

  The principle investigator will investigate your data carefully and respect your privacy and confidentiality.

- You reserve the legal rights entitled to you as it is.

  Participating in the trial will not interfere with any legal rights entitled to you.

- You will be treated with dignity and respect through the trial.

The Institutional Review Board will be responsible for ensuring your rights and welfares. If you have any questions concerning your rights, please contact the Institutional Review Board at the hospital at 02-xxxx-xxxx.

IX.Introduction of informed consent form

An informed consent form is an important document to confirm that the doctor has fulfilled his/her obligation to inform and to ensure the interests and rights of the subjects, and therefore should be approved by the Institutional Review Board. Signing the informed consent form will not compromise the subject's interests. The subject must read the informed consent form carefully and make sure that he/she understands every aspect of the human trial.

1.Background introduction

An informed consent form begins with a simple background introduction on the importance and objective of the trial. If the trial is a new drug clinical trial, the introduction will also include the global market condition.

2.Trial method

This section explains the procedure of the study. It explains how many groups the subjects will be divided into, the chance of receiving the effective treatment, duration of human trial, approximate number of subjects, how to cooperate with the trial (such as birth control and no driving), and what kind of inconvenience the trial will cause (such as how often are the return visits, how many c.c. of blood will be drawn, what kind of tests will be performed etc.). In principle, no information that might reduce the subject's willingness to participate in the trial can be omitted. If invasive tests are to be performed, it must be stated clearly. If the subject cannot obtain sufficient information from the informed consent form, make sure to ask the research personnel.

Should there be any specialized terms incomprehensible, the subject must ask the personnel to clarify the terms. Take a commonly conducted "randomized and double-blinded" trial for example:

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.

3.Potential side effects, risks and treatment procedures

The emphasis of this section is to explain the degree of risks involved in participating in the trial. Therefore it should include detail description of the incidence rate of side effects based on previous data, preferably in figures, without concealing any information. Side effects of low incidence rates can be stated as "side effects with less than 1% incident rate in prior cases". Subjects should be aware of whether the trial involves major risks of death or infertility as well as the incidence rate. Of course they should also be aware of the contact method and procedure in the event of dangerous or emergency condition, possible treatment methods the doctor may adopt as well as the foreseeable circumstances and reasons that might lead to the termination of their participation in the trial.

4.Other potential treatments and introduction

The emphasis of this paragraph is to explain whether the subject's participation is obligatory and other available treatments if the subject chose not to participate in the research.

5.Anticipated trial results and benefits

The emphasis of this paragraph is to explain the benefit for participating in this trial, thus must provide detail information regarding the anticipated effects based on existing data. The content must be thorough and comprehensive, preferably with actual figures. For example: describe the percentage of patients that will be cured; the percentage of condition that can be controlled and etc. The statements must base on concrete evidence and should not exaggerate.

6.Restrictions and limitations during the trial

The section explains the restrictions and limitations that the subjects should cooperate with during the trial such as what type of food or medications are not allowed, adopt birth control methods, no driving and etc.

7.Confidentiality

Even though the trail will strive to protect the subject's privacy, the following statement will be included to explain the responsibility for breach of confidentiality:

We will keep your trial results and diagnosis confidential by replacing your name with a research code. Apart from complying with the regulatory investigation by the authorities, we will protect your privacy carefully. The subject will remain anonymous even when the trial results are published.

8.Indemnification

The informed consent template announced by the Department of Health contains the following statements:

- Losses caused by the adverse reactions arising from the human trial project stipulated in this research will be compensated by the OOO Company (or co-compensated with the OOO Hospital). Anticipated adverse reactions listed in the informed consent form will not, however, be compensated.
- The hospital will provide professional medical care and consultation in the event of adverse reactions or losses arising from the human trial project stipulated in this research. You will not be responsible for the medical charges accrued from the treatment.
- In addition to the above indemnification and medical care, the study will not provide any additional compensation in any other form. If you are not willing to take the risk, please do not participate.
- You will not waive any legal rights by signing this informed consent form.
- (This research is insured against liability. This research is not insured against liability.)

9.Rights and obligations

During the trial, the subject's rights and obligations are usually explained by the following statements:

- The trial institution will defend the rights and interests entitled to the subject during the trial.
- The subject reserves the right to withdraw his/her consent or terminate his/her participation during the trial at any time without causing any unpleasantness or affecting the medical care that he/she might receive in the future.
- When discovering any new information that might affect the subject's willingness to continue his/her participation in the trial, the subject or his/her legal representative must be informed immediately.
- No additional costs are required to participate in this trial.
- There are two copies to this informed consent form. The doctor has returned the duplicate copy to you and has explained in detail the nature and the objective of this research. Dr. OOO has answered all of your questions related to the drug and research.

Finally the contact information for the Institutional Review Board (IRB) will be provided. The IRB is an auditory committee set up to protect the rights and interests of the subjects. Subjects can verify the relevant information with the IRB directly. The following statement might be included in the informed consent form:

Your decision to participate in this project is of voluntary nature. You reserve the right to refuse to participate. If you have any questions regarding your rights and interests for participating in the trial, you can contact Mr. /Ms. OOO at the Institutional Review Board through the following methods:

TEL: ****-**** FAX: ****-**** E-mail:

10.Statement

The informed consent form might conclude with a statement to let the subject know to what trial he/she has given consent. It is preferable that a witness be present at the time of signing to verify that the content of the informed consent form as well as any other written documentation has been provided and explained to the subject or his/her legal representative. The subject or his/her legal representative has understood the content and given the consent voluntarily. The following statement might be included in the informed consent form:

Subject statement:

The above information has been explained to me. I have had the opportunity to ask questions concerning the project. I have also understood and consented to participate in this trial project. If I have questions in the future, I can contact Dr. OOO at the OOO Hospital.

Subject name:

Subject/Legal representative signature:

Date: _____year ___month ___date

Legal representative name (when signed by the legal representative):

Relationship with the subject:

Personnel in charge of informed consent form (person who explains and introduces the content of the subject informed consent form)

Name: _____Signature: _____Date:_____

Witness name: _____ Signature: _____Date:_____

The last part of the informed consent form might include the investigator's statement. If you have any comments or questions about the trial, you can consult the investigator.

Investigator statement:

I hereby assure that I or a member of my research team (representative authorized to undertake the procedure) has explained the trial to the above subject, including the trial objective, method, potential risks and benefits for participating in the trial as well as other alternative treatments currently available to the subject. All questions proposed by the subject have been answered in good faith.

X.Human trial cases

Case 1 Informed consent

Mrs. Lin has breast cancer and needs mastectomy and chemotherapy. After the surgery, the doctor told her there is an on-going human trial on a new chemotherapy drug. Mrs. Lin trusts her doctor completely so she said to the doctor" Whatever you say, doctor! I don't know anything anyway!"

Case analysis:

When treating patients, doctors usually consider the most beneficial treatment for the patients. "Human trials" are different from "treatments". A "treatment" has undergone researches and is well-understood. We are certain about the result of a treatment, what kind of side effects will happen and how high the incidence rate is. Human trials on the other hand have unspecified steps and unknown results. Therefore it is not obligatory, but voluntary, for patients to participate in trials. They should understand the content of a trial before considering whether or not to participate. Doctor will try to use simple language to help patients understand the trial.

Results from human trials can enhance human health. But before you participate, you must make sure that you know what kind of research you are about to participate, understand the benefits and short-comings of your participation, know every aspect of the trial and ask all the questions. Therefore it is better that Mrs. Lin reads the informed consent form carefully and assesses her own condition first before making the decision herself!

Case 2 Subjects can withdraw from the trial at any time without compromising their rights and interests

1. Liu has recently signed an informed consent form for a human trial. He needs to take a 10mg sleeping pill every night for 3 weeks. The trial period lasts over 2 months but now he has changed his mind. Does he have the right to withdraw from the trial? Will he still receive reimbursement?

2. Ru agreed to participate in a human trial after reading the informed consent form and receiving instructions from the medical staff. Two weeks later, Ru was worn out by the side effects of the new medical technology. She informed the doctor that she wanted to withdraw from the trial. The doctor told her that the trial will end shortly in a week and hoped that Ru can hang on and help to complete the research. He also promised that he will do his best to eliminate her discomfort as soon as the trial's over and that if she withdrew now, he might not have time to provide medical care for her anyway.

Case analysis:

According to the regulation, "the trial investigator and personnel should not coerce the subject into participating or unseemly affect the subject's willingness to participate in a clinical trial. During the trial, the trial investigator and personnel should not coerce the subject into remaining in the trial or unseemly affect the subject's willingness to remain in the trial." "Subjects are free to withdraw from the clinical trial at any time without having to justify for their withdrawl." The subject in this case can report directly to the IRB at the hospital and request for assistance. If the subject is not satisfied with the feedback from the IRB, she can also file a complaint with the Department of Health.

Case 3 Benefits of participating in a human trial

Chang was hospitalized for liver cancer. He saw that Yuan, who lives next to him and also suffers from liver cancer, was given a drug and carefully cared by the research nurse everyday. One day he couldn't help but asked the doctor" What has the patient next to him been taking? Why is it

different from my medication?"

Case analysis:

Patients participating in human trials are not only exposed to new treatment before other patients but can also receive stringent and thorough care from the research team during the trial. Nevertheless, they have no idea about what the result from the new treatment will be and might even be injured by unknown side effects. Therefore the patient should understand the content of the trial before considering whether or not to participate.

Case 4 Authorized consent

Tin comes from a poor family and is a temporary state of unconsciousness. The doctor told her family that there is currently a new drug on trial and asked if they would like to enroll her in the human trial. He also told them that not only was the treatment free of charge, they would also receive a subsidy from the hospital. Since Tin was unable to exercise her rights to consent, her mother would sign the inform consent form and receive the reimbursement on her behave.

Case analysis:

According to the regulation, in the event that the subject him/herself is rendered unconscious (coma) or mentally insane, his/her spouse or family member residing with him/her is authorized to sign the informed consent form on behave of the subject to enroll the subject in a human trial.

XI.Human trial Q&A

Q1: What is an "Institutional Review Board"?

An "Institutional Review Board" is an auditory committee set up to ensure that the human trials comply with the scientific and ethical standards. It consists of medical personnel, legal experts, social justice, representatives of local organizations, non-governmental group representatives and non-medical professionals to help research staff understand the condition of subjects and to ensure their rights and interests. Subjects with questions concerning their rights and interests for participating in the research can consult the Institutional Review Board at the hospital directly. In addition, there are also "Joint Institutional Review Boards" that operate independently from the hospitals to ensure subjects' rights and interests.

Q2: Will I make a profit by participating in a human trial?

In principle you will make a profit. Subjects might be taking certain amount of risks by participating in a trial but their disease might be cured. In principle they are not paid to participate; however, they might be compensated for the inconvenience caused by the trial.

For human trials not designed to treat diseases, the subjects are burdened with risks without being able to make a profit. Compensations are provided according to the level of inconvenience. The amount of compensation is calculated according to the level of inconvenience instead of risk. The payment method, amount and procedure are reviewed and confirmed by the Institutional Review Board.

Q3: Does it cost to participate in a human trial?

In general, the participation in the treatment of human trial is free of charge. Since human trials have not become conventional medicine, they are different from other treatments. Therefore, in principle, it is free to enroll.

However, after participating in a human trial, the frequency of return visits might increase, hence the increase in costs. More blood might be drawn for the tests requested in the trial. Therefore, before participating in a human trial, you should ask if the trial will provide reimbursement for transportation or subsidies to reimburse you for the extra costs.

Q4: Can I participate in a human trial without signing an informed consent form?

No, the informed consent form is the most important tool to confirm that the research personnel have fulfilled their obligation to inform and to ensure subjects' rights and interests. An informed consent form is not a binding contract but an evidence to prove that research personnel have obtained the inform consent from the subject prior to the commencement of research.

The subject's name will not show up anywhere in the trial except for the informed consent form, which might be the only place with the patient's name. Therefore the research personnel are responsible for properly maintaining these forms. In the case of leakage from research personnel, the person will be legally responsible for such breach of confidentiality.

When a research staff is questioned for inadequately obtaining subject information, the informed consent formed signed by the subject will serve as the best evidence to prove that the conduction of research comply with the ethical standards. The informed consent form does not only ensure the subjects' rights to "know" but also protect the integrity of research personnel. Therefore signing the informed consent form is a critical step in participating in a human trial.

Q5: Can I withdraw after participating in a human trial?

Of course. The informed consent form will usually state clearly that "the subject is free to withdraw his/her consent and terminate his/her participation at any time during the trial without causing any unpleasantness or affecting the medical care he/she might receive in the future." Therefore you are free to withdraw from the trial at any time without having to provide any reason or affecting any treatment you are entitled to receive. Should you have any unpleasant experience or concern, you can report to the Institutional Review Board or file a complaint with the Department of Health.

Q6: I don't know if I would like to participate in this human trial. What should I do?

If you still cannot decide whether to participate in this human trial after listening to the instructions given by the research personnel and asked all questions, please double check first if the trial has been approved by the Department of Health, Executive Yuan and the Institutional Review Board. Once you've confirmed that, please try to answer the questions in chapter 5 of this handbook (How do I know for sure that I have understood this trial well enough to make a decision?) to see if you have understand this experiment well enough.

If you can answer all the questions, it means you have understood this trial well enough. However, if you still cannot decide whether to participate in this human trial, that means you still have doubts about it and should consider not participating.

Q7: Is there any risk involved in participating in a human trial?

Of course there are risks involved. Human trials are researches. The purpose of conducting a research is to explore the unknown. Since it's about exploring the unknown, there are unknown risks involved. "Researches" are different from "treatments". A "treatment" has undergone complete researches and has a known potential treatment effect, side effects and incidence rates. A "research", on the other hand, involves unknown procedures and results.

Therefore it is not obligatory, but voluntarily, for you to participate in a research. The informed consent form will state clearly to what extent the risks to this trial has been understood. With the development of the trial, research personnel will also inform you of the updated information. If you are concerned, you are free to withdraw from the trial without affecting any medical treatments you are currently receiving from the trial doctor. In the event of any unpleasantness or concern, you can also report to the Institutional Review Board or file a complaint with the Department of Health.

Q8: I have a bad liver. Can I still participate in a human trial?

You might be able to. Every subject must go through a screening process before participating in a human trial to evaluate his/her health condition. Only those qualified will be able to participate. Nevertheless, each trial has different screening criteria; you might still be qualified for certain trials, even with a bad liver.

Q9: Is it safer to participate in an insured human trial?

No. Insured human trials are not necessarily safer. For those insured trials, you receive compensation from the insurance company instead of the hospital in the event of unpredicted serious adverse reactions. Therefore whether a human trial has been insured or not does not concern the subject. It doesn't matter whether the compensation comes from the hospital or the insurance company, the subject will always be entitled to their rights.

Q10: Do I need to have a witness when signing the informed consent form?

No, an informed consent form is the evidence to prove that research personnel have obtained the subject's informed consent form before conducting the research. When the subject's illiterate, senile or has mental disorders that might result in the questioning of his/her decision-making capacities, in addition to the evidence of the written informed consent form, a witness should also be present to verify that the informed consent was obtained properly. Therefore the witness must ensure that the subject has fully understood the content of the all information and that his/her consent is of voluntary nature before signing and dating the informed consent form.

In addition, trial related personnel cannot serve as a witness to avoid their objectivity being questioned.

Q11: Can patients with terminal illnesses participate in a human trial?

They might be able to. Every subject must go through a screening process before participating in a human trial to evaluate his/her health condition. Only those qualified will be able to participate. If a terminal illness is one of the screening criteria, patients with such illness might be able to participate in such human trial. If such illness is not one of the criteria, those patients should not become study subjects.

In addition, terminally ill patients are frail and vulnerable, and therefore can be persuade more easily. They might agree to participate before understanding the content of the trial fully. Therefore, to enroll terminally ill patients in a trial, other than making sure that the patients have fully understood the benefits and shortcomings of the trial, it is better to let the patient's family know and agree.

Q12: Can I give my oral consent without signing the informed consent form when participating in a human trial?

No, the informed consent form is the most important tool to confirm that the research personnel have fulfilled their obligation to inform and to ensure subjects' rights and interests. An informed consent form is not a binding contract but an evidence to prove that research personnel have obtained the inform consent from the subject prior to the commencement of research.

In the event that the subject's illiterate or incapable of signing the informed consent form, a witness should be present. A witness should sign and date the informed consent form after confirming that the subject has understood the content of all information fully and ensuring that the consent from the subject is voluntary.

In addition, trial related personnel cannot serve as a witness to avoid their objectivity being questioned.

Q13: Can I have somebody else sign the informed consent form for me when participating in a human trial?

You might be able to. The regulation stipulated that the informed consent form must be signed and dated by the subject him/herself. Under the condition that the subject is declared interdicted, the legal representative is authorized to sign on behave of the subject. In the event that the subject is rendered unconscious or mentally disordered to sign on his/her own, his/her spouse or family member residing with the subject is authorized to sign on behave of the subject.

(Attachment)

【Attachment 1】

The provisions pertain to human trials in the Medical Law

(May 20, 2009, amended)

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 new medical technologies, medicaments, 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 70 Medical care institutions shall appoint appropriate location and personnel for the storage of medical records, which shall be retained for at least seven years. However, medical records of minors shall be retained for at least seven years after their coming of age, and medical records for human trials shall be retained indefinitely.

Medical care institutions which cease to practice due to certain reasons shall transfer the medical records to the successor for retentions in accordance with the law. Those without successors shall retain the medical records for at least six months before destruction.

When the medical institution is not able to save the medical record for legitimate reasons, those should be saved by the local competent authority

Medical care institutions shall ensure that the destruction method of medical records which exceed retention period shall not disclose the contents of the medical records.

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 consent from the trial 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 consent referred to in the preceding Paragraph, and shall inform the trial subject of the following before obtaining his/her or legal agents' consent:

1.Purpose and method of trial;
2.Possible risks and side-effects;
3.Expected trial results;
4.Explanation of other possible treatment methods;
5.Withdrawal of consent at anytime by trial 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 Except for the regulations otherwise provided, the human trial related matters set forth in the previous two

articles, including application procedures, guidelines of reviewing procedure and principles of avoiding conflicts of interests, information disclosure, supervision and management, audit, and other items for 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 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 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 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.

【Attachment 2】

Human Research Ethics Policy Guideline

Date: July 17, 2007 Announcement Wei-Shu-Yi-Tzu No. 0960223088

1. Human research 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.

【Attachment 3】

Good Clinical Practice

Date: January 6, 2005 Announcement Wei-Shu-Yi-Tzu No. 0930338510

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 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 limited legal capacity, and 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 identities 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 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:

1.The objectives of the trial cannot be met by means of a trial in subjects who can sign the informed consent form personally.

2.The foreseeable risks to the subjects are low.

3.The negative impact on the subject's well being is low.

4.The trial is not prohibited by law.

5.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 on 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, lists 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:

1.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;

2.to comply with procedures for data recording and reporting;

3.to permit monitoring, auditing and inspection; and

4.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 these systems.

3.Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and 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 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 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 ensures 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 an 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 within 7 days, 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 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 caution as a good administrator to properly 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 fatal 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 fatal or life threatening events and should provide detailed written information.

The verbal and written reports referred to in the first 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 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 are 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.

【Attachment4】

Clinical trial subject instruction and informed consent form

(To protect the patient's rights and interests, please mark the warning words which describe the possible trial caused risks to the patient.)

(The protocol investigator or the designated representative thereof should personally explain the contents of this form to the subject in detail, and invite the subject to sign only after careful consideration.)

You are invited to participate in this clinical trial study. This form provides you with relevant information of this study, and the study investigator or study nurse will explain the study contents to you and answer any of your questions.

Trial Protocol: Chinese: Einglish:	
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 or Power of Attorney's Name:

Relationship with Subject:

Gender: Date of Birth:

ID Number:

Mailing Address:

Telephone:

1.Brief introduction to the present global market of drugs, medical techniques and medical instruments

Overview of Drug in Global Market:

2. Trial Objective:

3. Major Inclusion and Exclusion Criteria:

4. Trial Method and Related Examinations:

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

6. Other Alternative Treatments:

7. Anticipated Trial Benefits:

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

9. Confidentiality:

_____The hospital will keep confidentiality of the records regarding your identity and your private information in accordance with the provisions, and will not publish them. If the trial results are published, your identity will still be kept confidential. You will also understand that your signature on the consent form means your agreement for that your original medical records will be directly reviewed by the monitors, auditors, the ethics committee and the competent authority, so as to make sure that the clinical trial process and the incurred data meet the requirements under relevant laws and regulations; the above personnel promise never to destruct the confidentiality of your identity.

10. Damage Indemnification and Insurance:

(1)As the clinical trial protocol stipulated for this study, the damage caused by the occurrence of adverse reaction shall be OOO company's responsibility for the indemnification. However, the anticipated adverse reactions indicated in the Informed Consent Form shall not be indemnified.

(2)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.

(3)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.

(4)You will not lose any legal right by signing this Informed Consent Form.

11. Subject's Rights:

(1)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.

(2)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: _____.

(3)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.

12. Withdrawal and Termination:

You are entitled to freely choose to participate in this study or not; You may cancel the consent 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.

13. Signature

(1)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

(2)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

* A legal representative makes the acts if the subject has no capacity to make juridical acts (a minor under seven years of age or a person who has become subject to the order of the commencement of guardianship); a guardian serves as

the legal representative for the person who has become subject to the order of the commencement of guardianship.

* The subject with a limited capacity to make juridical acts (a minor over seven years of age) should have the approval of the legal representative.

Signature of the person with the approval right:

Date: month day year

*When the subject is not able to effectively communicate or judge due to confusion or mental disability, although he/she is not a person having no or a limited capacity to make juridical acts, the person who has the approval right should make the acts therefor. The aforementioned person having the approval right means the spouse or lineal relative.

(1)Witness:

Name:

ID No.: Telephone:

Mailng Address:

Signature: Date: month day year

* When all of the subject, legal representative or person with the approval right cannot read, a witness should be present in all the discussions about the subject consent. In addition, after it is affirmed that the subject, legal representative or person with the approval right is completely willing to make the consent, signature should be made with dates indicated on the informed consent. The personnel involved in the trial cannot be the witness.

【Attachment5】

Guidelines for Recruitment of human Trial Subject

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

【Attachment6】

Consultation channels

(contact of hospitals and Institutional Review Boards)

NO.	Hospitals and Institutional Review Boards	Tel	Address
1.	Human Subject Research Ethics Committee	02-27898722	No.128, Sec. 2, Academia Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.)
2.	Institutional Review Board, Taipei Veterans General Hospital	02-28757384 #307,#303 #305,#309	Department of Teaching and Research, No.201, Sec. 2, Shipai Rd., Beitou Dist., Taipei City 112, Taiwan (R.O.C.)Institutional Review Board, Taipei Veterans General Hospital
3.	Mackay Memorial Hospital Institutional Review Board	02-25433535 #3486 #3487	No.92, Sec. 2, Zhongshan N. Rd., Zhongshan Dist., Taipei City 104, Taiwan (R.O.C.) Mackay Memorial Hospital Institutional Review Board

4.	Institutional Review Board, Cathay General Hospital	02-27082121 #6984	No.280, Sec. 4, Ren-ai Rd., Xinyi Dist., Taipei City 110, Taiwan (R.O.C.)
5.	Institutional Review Board, Taiwan Adventist Hospital	02-27718151 #299	No.424, Sec. 2, Bade Rd., Songshan Dist., Taipei City 105, Taiwan (R.O.C.)
6.	Institutional Review Board, Shin-Kong Hospital	02-28332211 #2019	No.95, Wenchang Rd., Shilin Dist., Taipei City 111, Taiwan (R.O.C.)
7.	Joint Institutional Review Board	02-28737133	Floor 3, ZHI-DE Building No.322, Sec. 2, Shipai Rd., Beitou Dist., Taipei City 112, Taiwan (R.O.C.)
8.	National Taiwan University Hospital Research Ethics Committee	02-23123456	Floor B4, Building AB, No.7, Zhongshan S. Rd., Zhongzheng Dist., Taipei City 100, Taiwan (R.O.C.),
9.	Tri-service General Hospital Institutional Review Board	02-27936995	Room 5113, 5th Floor, Medical Building, No.325, Sec. 2, Chenggong Rd., Neihu Dist., Taipei City 114, Taiwan (R.O.C.)
10.	Institutional Review Board of Wanfang Hospital	02-29307930 #1467	No.111, Sec. 3, Xinglong Rd., Wenshan Dist., Taipei City 116, Taiwan (R.O.C.)
11.	Taipei City Hospital Institutional Review Board	02-25553000 02-28267000 #5459 02-27093600 #3802	No.145, Zhengzhou Rd., Datong Dist., Taipei City 103, Taiwan (R.O.C.)
12.	Taipei Medical University Hospital Institutional Review Board	02-27372181 #3749	7th Floor, First medical Building, No.252, Wuxing St., Xinyi Dist., Taipei City 110, Taiwan (R.O.C.)
13.	Far Eastern Memorial Hospital Institutional Review Board	02-89667000 #2152	No.21, Sec. 2, Nanya S. Rd., Banqiao City, Taipei County 220, Taiwan (R.O.C.)
14.	Chang Gung Hospital Institutional Review Board	03-3196200 #3645, 3703~3705	No.123, Dinghu Rd., Guishan Township, Taoyuan County 333, Taiwan (R.O.C.)
15.	Chung Shan Medical University Hospital Institutional Review Board	04-24739595 #34320	3th Floor, Administrative Building, No.110, Sec. 1, Jianguo N. Rd., South Dist., Taichung City 402, Taiwan (R.O.C.), Institutional Review Board

16.	China Medical University Hospital Institutional Review Board	04-22052121 #1925,1926	9th Floor, First Medical Building, No.2, Yude Rd., North Dist., Taichung City 404, Taiwan (R.O.C.)
17.	The Institutional Review Board of Taichung Veterans General Hospital	04-23592525 #4006,4085	No.160, Sec. 3, Taichung Port Rd., Xitun Dist., Taichung City 407, Taiwan (R.O.C.)
18.	Show Chwan Memorial Hospital Institutional Review Board	04-7256166 #66060,66061	No.542, Sec. 1, Zhongshan Rd., Changhua City, Changhua County 500, Taiwan (R.O.C.), Institutional Review Board Or Floor B2, Show Chwan Memorial Hospital Yan Ping Building, No.38, Nanping St., Changhua City, Changhua County 500, Taiwan (R.O.C.), Institutional Review Board
19.	Changhua Christian Hospital Institutional Review Board	04-7238595 #4077	No.135, Nanxiao St., Changhua City, Changhua County 500, Taiwan (R.O.C.)
20.	Chia-Yi Christian Hospital Institutional Review Board	05-2765041	No.539, Zhongxiao Rd., East Dist., Chiayi City 600, Taiwan (R.O.C.)
21.	Dalin Branch of Buddhist TZU CHI General Hospital Institutional Review Board	(05)2648000 #5920,5921	No.2, Minsheng Rd., Dalin Township, Chiayi County 622, Taiwan (R.O.C.)
22.	Chimei Hospital Institutional Review Board	06-6226999 #77853	No.201, Taikang, Liuying Township, Tainan County 736, Taiwan (R.O.C.)
23.	National Cheng Kung University Hospital Institutional Review Board	06-2353535	No.138, Shengli Rd., North Dist., Tainan City 704, Taiwan (R.O.C.)
24.	The Institutional Review Board of Kaohsiung Veterans General Hospital	07-3422121 #1571	Teaching and Research Building, No.386, Dazhong 1st Rd., Zuoying Dist., Kaohsiung City 813, Taiwan (R.O.C.), Institutional Review Board

25.	Kaohsiung Medical University Chung-Ho Memorial Hospital Human Experiment and Ethics Committee	07-3121101 #6646	8th Floor, Building A, No.100, Ziyou 1st Rd., Sanmin Dist., Kaohsiung City 807, Taiwan (R.O.C.), Institutional Review Board
26.	Antai Medical Memorial Hospital Institutional Review Board	08-8329966	No.210, Sec. 1, Zhongzheng Rd., Donggang Township, Pingtung County 928, Taiwan (R.O.C.)

【Attachment7】

Relevant websites

National websites		
1.	Department of Health, Executive Yuan, R.O.C.(Taiwan)	http://www.doh.gov.tw/
2.	Human Subject Research Ethics Committee	http://proj1.sinica.edu.tw/~irb/index.htm
3.	Institutional Review Board, Taipei Veterans General Hospital	http://homepage.vghtpe.gov.tw/~mre/goodexp/content.htm
4.	Mackay Memorial Hospital Institutional Review Board	http://www.mmh.org.tw/taitam/irb/index.htm
5.	Institutional Review Board, Cathay General Hospital	http://www.cgh.org.tw/tw/content/depart/IRB/index.html
6.	Institutional Review Board, Taiwan Adventist Hospital	http://www.tahsda.org.tw/medicalethic/
7.	Institutional Review Board, Shin-Kong Hospital	http://www.skh.org.tw/ECIRB/index.htm
8.	Joint Institutional Review Board	http://www.jirb.org.tw/Default.aspx

9.	National Taiwan University Hospital Research Ethics Committee	http://www.ntuh.gov.tw/RECO/default.aspx
10.	Tri-service General Hospital Institutional Review Board	http://www.tsghirb.ndmctsgh.edu.tw/mCenter.asp
11.	Institutional Review Board of Wanfang Hospital	http://www.wanfang.gov.tw/edu/06_irb/index.html
12.	Taipei City Hospital Institutional Review Board	http://www.tpech.gov.tw/cgi-bin/SM_theme?page=49026e8c
13.	Taipei Medical University Hospital Institutional Review Board	http://203.71.88.129/edunew/paperindex.php
14.	Far Eastern Memorial Hospital Institutional Review Board	http://irb.e-pharm.info/
15.	Chang Gung Hospital Institutional Review Board	http://www.cgmh.org.tw/intr/intr1/c0040/web/C/C.htm
16.	Chung Shan Medical University Hospital Institutional Review Board	http://www.csh.org.tw/各類委員會/人體試驗委員會/index.htm

17.	China Medical University Hospital Institutional Review Board	http://www.cmuh.org.tw/irb/
18	The Institutional Review Board of Taichung Veterans General Hospital	http://www3.vghtc.gov.tw/der/irb/index.htm
19.	Show Chwan Memorial Hospital Institutional Review Board	http://www.scmh.org.tw/INTERNET/PUBLIC/Pub/PUB_News02.aspx?Theme=13ed9604-7755-4751-a3aa-6d8c9fd0ca12
20.	Changhua Christian Hospital Institutional Review Board	http://www2.cch.org.tw/IRB
21.	Chia-Yi Christian Hospital Institutional Review Board	http://www.cych.org.tw/cych/
22.	Dalin Branch of Buddhist TZU CHI General Hospital Institutional Review Board	http://dlweb01.tzuchi.com.tw/dl/Med/IRB/
23.	Chimei Hospital Institutional Review Board	http://www.chimei.org.tw/main/right/right02/clh_department/79012/index.htm
24.	National Cheng Kung University Hospital Institutional Review Board	http://www.ncku.edu.tw/~nckuhirb/

25.	The Institutional Review Board of Kaohsiung Veterans General Hospital	http://www.vghks.gov.tw/erli/IRB/irb.htm
26.	Kaohsiung Medical University Chung-Ho Memorial Hospital Human Experiment and Ethics Committee	http://www.kmuh.org.tw/www/IRB/index.htm
27.	Antai Medical Memorial Hospital Institutional Review Board	http://www.tsmh.com.tw/depindex.htm

International websites		
1.	World Health Organization	http://www.who.int/en/
2.	Public Responsibility in Medicine and Research	http://www.primr.org/
3.	United States Department of Health and Human Services	http://www.hhs.gov/ohrp/
4.	Forum for Ethical Review Committees in the Asian and Western Pacific Region	http://www.fercap-sidcer.org/home.asp
5.	The World Medical Association	http://www.wma.net/e/