annex

General consideration guidelines for drug clinical trials

I. Overview

The general consideration guidelines for drug clinical trials (hereinafter referred to as the guiding principles) are the current general considerations of the State Food and Drug Administration regarding the study of drugs in clinical trials. The purpose of this guideline is to provide technical guidance for applicants and researchers to develop overall drug development strategies and individual clinical trials, as well as to provide a reference for drug technology evaluation. In addition, when the clinical trials of new drugs for new drugs have been added, the guidelines can be referred to. This guideline applies primarily to chemical drugs and therapeutic biological products.

Second, the basic principles of clinical trials

(1) Subject protection

1 . Implementation of relevant laws and regulations

The clinical trial of drugs must follow the Helsinki Declaration of the World Medical Congress and implement relevant laws and regulations such as the “Quality Management Standards for Drug Clinical Trials” promulgated by the State Food and Drug Administration.

2 . The basis of security

The results of a non-clinical or previous clinical study must be sufficient to demonstrate an acceptable safety basis for the proposed human study prior to any clinical trial.

Pharmacological toxicology data and clinical data should be evaluated dynamically by pharmacological toxicology experts and clinical experts throughout the drug development process to assess the safety risks that clinical trials may pose to subjects. The necessary adjustments should also be made for clinical trial protocols that are or will be conducted.

The parties involved in the clinical trial of the drug shall assume the responsibility of protecting the subject according to their respective duties.

(two) basic methods of clinical trials

1 . General rule of clinical trial

The essence of drug development is to ask questions about effectiveness and safety, and then answer it through research. Clinical trials are studies conducted in the human body to answer specific questions related to the study of drugs to prevent, treat or diagnose diseases. Clinical trials are often described using two types of methods.

According to the research and development stage, the clinical trials are divided into Phase I clinical trials, Phase II clinical trials, Phase III clinical trials, and Phase IV clinical trials.

According to the purpose of the study, clinical trials are divided into clinical pharmacology research, exploratory clinical trials, confirmatory clinical trials, and post-marketing studies.

Both classification systems have certain limitations, but the two classification systems complement each other to form a dynamic and practical clinical trial network (Figure 1).

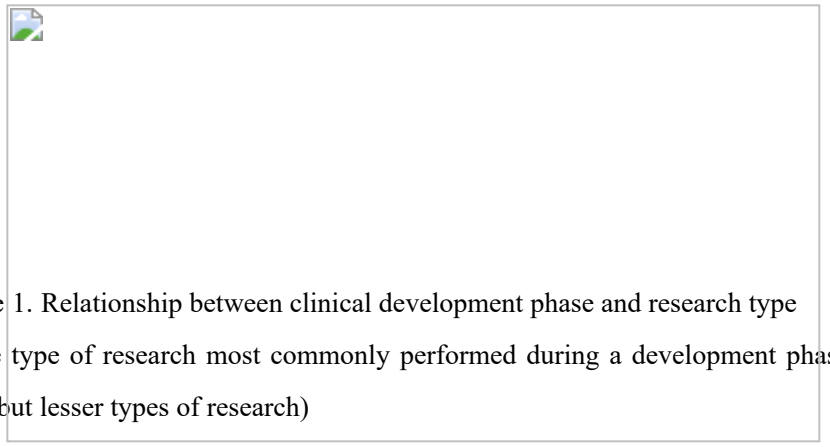

Figure 1. Relationship between clinical development phase and research type

(The filled circle represents the type of research most commonly performed during a development phase, and the open circle represents some of the possible but lesser types of research)

Proof of Concept (Proof of Concept, POC) refers to the pharmacological effects of a drug candidate verification may be converted into clinical benefit, generally at an early stage of clinical study, the effectiveness of the exploring signal for safety tolerated dose, reducing the risk of clinical development.

This guideline describes clinical trials based on the classification of research purposes.

The purpose of clinical pharmacology studies is to assess tolerance, to clarify and describe pharmacokinetic and pharmacodynamic characteristics, to explore drug metabolism and drug interactions, and to assess drug activity.

The purpose of the exploratory clinical trial is to explore the dosing regimen for follow-up studies of target indications, and to provide a basis for research design, study endpoints, methodology, etc. for validity and safety confirmation.

The purpose of the confirmatory clinical trial is to confirm validity and safety, to provide a basis for benefit / risk relationship evaluation in support of registration , and to determine the relationship between dose and effect.

The purpose of post-marketing research is to improve understanding of the benefits / risk relationships of drugs in the general population, in specific populations, and / or in the environment , to find rare adverse reactions, and to provide a clinical basis for improved dosing regimens.

2 . Goal-oriented clinical development

In the clinical development strategy of drugs, a goal-oriented clinical trial development model should be adopted. The entire clinical development plan must

set clear final goals and clear research paths; each specific clinical trial should have a clear experimental purpose.

3 . Phased clinical trial decision

The process of clinical trials is a process of continuous decision making. At the end of each clinical trial, a phased benefit and risk assessment should be performed in a timely manner to determine termination or continued clinical development. If the data suggest a clear risk (lack of effectiveness or safety issues), the clinical trial should be terminated as soon as possible. If the data suggests that research drugs have research and development prospects, clinical trials should be gradually advanced on the basis of the support of existing research data. The clinical development plan should be appropriately adjusted with the results of the study. For example, the results of clinical validation studies may suggest that more human pharmacology studies are needed. In some cases, depending on the clinical trial screening results, the original proposed indication needs to be abandoned or changed.

4 . Standardize the clinical trial process

Clinical trials should be scientifically designed, implemented, and analyzed to ensure that the test procedures are standardized, scientifically reliable, and fully and truly presented in clinical trial reports.

5 . Overall consideration of safety

In general, the sample size estimation in clinical trials is based on validity considerations, and the sample size for safety evaluation is not necessarily sufficient. The safety assessment should have sufficient sample size and a sufficiently long exposure time. When evaluating the safety of long-term medication in non-critical patients, the following principles should generally be followed:

In the clinical development stage of the drug, the safety characteristics of the drug should be described qualitatively and quantitatively. The time limit for safety observation in clinical trials is recommended to be consistent with the time limit for

clinical long-term drug use. In order to fully expose the safety hazard of the drug, the following points should be considered when setting the sample size: (1) the exposure time limit of the drug ; (2) the time and extent of the adverse drug event within the exposure time limit; (3) the adverse event The trend of prolonged treatment time.

In general, for non-critical patients who are on long-term medication, the total sample size required to expose common adverse events is approximately 1,500 (including short-term exposure). For the first time adverse events often occur in the first few months, clinical treatment period of 6 months, for example, it takes about 300 to 600 cases of sample size to expose common adverse event rates (for example: the overall incidence of 0.5% to 5 %) and trends (increased or decreased). As the treatment time prolonged, the frequency and intensity of some adverse events increased, and some serious adverse events occurred after 6 months of drug treatment . It was found that such adverse events required 100 patients to be exposed for at least 12 months.

In some special cases, it is necessary to expand (reduce) the sample size or extend the observation period according to the actual situation.

Third, the methodological considerations in the clinical research and development plan

Applicants should develop an overall clinical development plan before conducting clinical trials. The clinical research and development program mainly considers two aspects. On the one hand, it considers whether there are sufficient data in non-clinical studies to guide the consideration of the safety and effectiveness of clinical subjects in clinical trial design, and for clinical trials. Study whether the drug has a stable quality basis. On the other hand, under the goal-oriented overall clinical design, how to design clinical trials at different stages and different research purposes.

(1) Basis for conducting clinical trials

1 . Non-clinical research

The design of non-clinical studies should focus on factors associated with subsequent clinical trials: (1) total drug exposure and duration planned for each subject; (2) drug characteristics (eg , long half-life); (3) goals Indications; (4) use in special populations (eg , women of childbearing age); (5) route of administration.

Integrate existing non-clinical findings such as toxicology, pharmacology, and pharmacokinetics to determine the extent to which non-clinical research data supports clinical trials (see the relevant guidelines).

(1) Safety research

Comprehensive evaluation of non-clinical pharmacokinetics, pharmacology, and toxicology data should be performed prior to the first human clinical trial. Non-clinical research data must provide sufficient information to determine the initial dose and safe exposure time of the human body, as well as provide information on the pharmacological and toxicological effects of the study drug.

(2) Pharmacology and pharmacokinetic studies

Non-clinical research data is the basis for conducting clinical trials and will also have an impact on the direction of clinical trials. Before conducting clinical trials, applicants should generally obtain the following non-clinical research information: 1 Pharmacological basis for the main action of the drug (drug action mechanism, including molecular markers such as biomarkers, etc.); 2 dose effect or concentration effect relationship, And the duration of action; 3 possible clinically effective routes of administration; 4 general pharmacology, including pharmacological and physiological effects of drugs on major organ systems; 5 study of drug absorption, distribution, metabolism and excretion; 6 if necessary, Related pharmacogenomics, proteomics and other research.

2 . Study drug quality

Prescription characteristics for clinical trials should be adequately described, including any available bioavailability data. The prescription should match the different stages of drug development. Ideally, the formulations provided should be suitable for a range of studies within a range of dosages. It may be important to interpret the results of clinical studies throughout the R&D program by using different formulations of a drug during drug development, using bioequivalence or other methods to correlate the different formulations.

(two) clinical trial development process

1 . Clinical pharmacology research

New drug marketing applications should have clinical pharmacology studies supporting the assessment of the safety and efficacy of the drug. The research content mainly includes the effects of drugs on the human body (pharmacodynamics and adverse reactions), human body treatment (pharmacokinetics), drug metabolism and material balance, dose - exposure - effect relationship, drug interaction, drug genome Learning, quantitative pharmacology, clinical pharmacology of special populations, group pharmacokinetics, etc. The clinical pharmacology research tasks and content are different in different clinical trials.

Clinical pharmacology studies are generally conducted in early clinical trials and can be performed at other stages depending on the needs of drug development. Clinical pharmacology studies are usually non-therapeutic and are generally performed in healthy volunteers to reduce the impact of the disease itself on the outcome. However, some drugs, such as cytotoxic drugs, are harmful to healthy people and can only be studied in patients.

Clinical pharmacology studies usually use random, blind, controlled trial designs, and in some cases other designs.

(1) Tolerance test

The human tolerance test is to determine the maximum tolerated dose in the human body and to discover the nature of the initial adverse effects of the human

body. Modes of administration include single and multiple doses.

Before conducting a human tolerance test, you should have two pieces of information, one is the conclusion of the non-clinical research evaluation, and the other is the clinical research or literature information of the research drug or similar drug. This information is important for estimating the safe starting dose for human trials and for selecting indicators for monitoring clinical adverse events.

1 determine the starting dose of human safety

The determination of the starting dose of the tolerability clinical trial is based on relevant guidelines and related methods (including quantitative pharmacology methods, etc.).

The Maximum Recommended Starting Dose (MRSD) for the first clinical trial in humans should be the dose that is expected to not cause adverse reactions in the human body. In initial clinical dose should be administered to avoid adverse reactions in the body, while the dose should be selected to allow a reasonable speed and gradient resistance termination target quickly reach clinical trials (such as: evaluation based on tolerability, pharmacodynamics Judging indicators of the characteristics of learning or pharmacokinetics).

2 consideration of the termination of the tolerance test

The tolerance test termination criteria should be set prior to the human tolerance test, ie, which adverse events occur or what exposure concentrations are reached, the dose escalation test should be terminated.

A few considerations when setting the termination criteria: When conducting tests in healthy volunteers, try not to bring health hazards to the subjects. The criteria for termination of the trial should be determined based on the characteristics of the target population of the drug to be developed. In addition, for some potentially high-risk drugs, special attention should be paid to the possible species differences between safety data from animal experiments and human safety. Especially for

biologics and drugs developed based on new mechanisms, new targets, new signaling pathways, etc.

3 single and multiple dose tolerance studies

When the drug is first used in the human body, the MRSD should generally be calculated and determined first , followed by a single dose tolerance test of the dose. For drugs with potentially serious safety risks, consideration should be given to the possible differences in animal test results and human body due to limited safety data that can be referenced. The first human tolerance test should be conducted in a small number of individuals, such as organisms. For macromolecular drugs, the first tolerability test should start with a single subject and, after obtaining safety data, decide on subsequent tests to reduce risk and protect the subject. The test implementation organization shall have appropriate facilities and personnel.

In general, multiple dose tolerance tests are usually performed after the results of a single tolerance test, and are usually performed after obtaining a single dose of human pharmacokinetic test results. The results of a single tolerability test and a single pharmacokinetic test should be able to guide the design of multiple dose tolerance tests, such as dose selection and determination of the mode of administration, the relationship between administration and meals, and the nature of adverse reactions. And degree, etc.

In many cases, a single pharmacokinetic study can be performed at the same time as a single administration tolerance test, and the pharmacokinetic study of multiple administrations is performed simultaneously with the tolerance test of multiple administrations. The tolerability test is a clinically early safety trial. To obtain a more reliable study, randomized, double-blind, placebo-controlled trial designs are recommended if possible.

(2) Pharmacokinetics study

Studies of the absorption, distribution, metabolism, and excretion characteristics of drugs in the human body usually follow the entire research and development

program. The preliminary determination of these pharmacokinetic characteristics is an important goal of clinical pharmacology research. Pharmacokinetic studies can refer to relevant guidelines.

Pharmacokinetics can be evaluated by multiple independent studies or as part of pharmacodynamic, safety, and tolerability studies. Pharmacokinetic studies are particularly important in assessing systemic exposure, distribution, clearance, predicting possible accumulation of prodrugs or their metabolites, and potential drug-drug interactions.

A pharmacokinetic study of a single administration aimed at understanding the rate and extent of absorption of the drug in the human body, the relationship between the dose and the concentration of the drug, and the half-life of the drug. A pharmacokinetic study of multiple administrations after obtaining a single pharmacokinetic study of the drug to understand the extent of drug absorption after repeated dosing, the time at which the drug reaches steady state concentration, and the extent of drug accumulation in the body Wait. In general, the results of pharmacokinetic studies of drug half-life obtained from a single agent, can be administered in multiple kinetics of pharmacokinetic dosing interval is set to provide important information, such as for the short half-life of the drug, several The number of doses of the drug for 24 hours in the administration study may be required to be multiple times, and it is also necessary to perform comprehensive analysis and judgment in combination with other data such as the mechanism of action of the drug.

To understand the relationship between drug dose and concentration, at least one of the low, medium and high doses of single and multiple doses of pharmacokinetic studies should be performed between the MRSD and the maximum tolerable dose.

For oral medications, the effects of food on bioavailability should generally be studied, which is more important for drugs that may alter release behavior. In

general, in a single-dose pharmacokinetic study, a suitable dose should be chosen for the study of the effects of food on the drug.

Special population pharmacokinetic information should also be considered within the scope of the study, such as : organ dysfunction (kidney or liver disease) patients, the elderly, children, pregnant and lactating women and ethnic subgroups.

Different types of pharmacokinetic studies, including population pharmacokinetics, may be needed in subsequent studies to answer more targeted questions.

(3) Pharmacodynamic evaluation

As described above, pharmacodynamic studies and blood concentration effects studies can be performed in healthy volunteers or patients based on developed drug characteristics. If appropriate methods are available, early assessment of drug activity and potential effectiveness can be made based on pharmacodynamic data in patients, and can be administered for subsequent doses and dosing regimens in target populations. The determination provides the basis.

2 . Exploratory clinical trial

The first clinical trial in patients to explore the effectiveness of the trial can be considered the beginning of an exploratory clinical trial.

Exploratory clinical trials typically perform rigorous screening of subjects to ensure homogeneity in the subject population and to closely monitor subjects.

Early exploratory clinical trials can be used in a variety of research designs, including parallel controls and self-controls. Subsequent clinical trials are usually randomized and controlled studies.

An important goal of exploratory clinical trials is to determine dosing dosages and dosing schedules for confirmatory clinical trials. Early exploratory clinical trials often use a dose-increasing design to initially assess the relationship between drug dose and effect. For the indications in question, post-exploratory clinical trials often use a well-recognized parallel dose-response design. The dose of the drug used in

the exploratory clinical trial is usually lower than the maximum tolerated dose suggested by the Institute of Clinical Pharmacology. If it is higher than this dose, the corresponding clinical pharmacology study should be supplemented to provide the necessary data support.

Other objectives of exploratory clinical trials include evaluation of study endpoints, treatment regimens (including combined dosing), and target populations (eg, mild to severe disease comparisons) that may be set in the next clinical study. Group data and multiple study endpoint analyses were performed and the results of the analysis were used for further exploratory clinical trials or confirmatory clinical trials.

3 . Confirmatory clinical trial

The determination of treatment benefit is the primary purpose of the trial.

Conclusive clinical trials are intended to further corroborate the prima facie evidence of the efficacy and safety of the study drug in an exploratory clinical trial with the aim of providing sufficient evidence to obtain a marketing permit. The study involved further exploration of the relationship between dose effects, or studies of a wider population, different stages of the disease, or concomitant medications. For drugs that are expected to be taken over a long period of time, trials of delayed drug exposure are usually performed in confirmatory clinical trials, although such studies may begin in exploratory clinical trials. These guidelines are not addressed in the consideration of clinical safety data for long-term use and medication for the elderly . Confirmatory clinical trials need to provide important clinical information for improving drug specifications. In the confirmatory clinical trials, population pharmacokinetic studies, pharmacogenomics studies, etc. can be performed at the same time.

4 . Post-marketing research

According to the research purpose, post-marketing research can be divided into two categories: (1) Regulatory requirements: to describe all post-marketing

research requirements based on regulations, including mandatory post-marketing safety studies and registration requirements. Research content; (2) Self-implementation: In addition to the requirements of the regulatory authorities, the applicant or a third party undertakes or conducts research on their own. Post-marketing studies typically include the following: additional drug-drug interactions, long-term or large-sample safety, pharmacoeconomics, and end-point events that further support the use of drugs for licensed indications (eg , mortality / morbidity) Research, etc.).

According to the purpose and content of the research, appropriate research models or tools should be selected to carry out the corresponding work. Research methods include clinical pharmacology studies, clinical trials, observational drug epidemiology studies, and meta-analysis. The results obtained by different research methods are different and the problems solved are different.

5 . Supplementary application

After obtaining the initial drug marketing approval, follow the relevant laws and regulations to conduct research on new indications and indications, new dosage regimens, new routes of administration, or other patient populations. If it is a new dose, a new prescription or a combination drug study, clinical pharmacology studies should be added. The use of data from original R&D plans or post-marketing research and applications has the potential to omit certain studies.

(3) Special considerations

1 . Drug metabolite research

For major active metabolite shall be identified, a corresponding study pharmacokinetics.

2 . Drug interaction study

If there is a potential interaction between drugs, it is recommended that the drug interaction study be conducted at an early clinical study stage. If the drugs are often used in combination, it is necessary to conduct drug interaction studies in non-

clinical studies or in human trials (if possible), which are known to alter the absorption or metabolism of other drugs, or their own pharmacokinetic behavior may be affected by other drugs. The drug is especially important.

3 . Special population

Compared with the general population, the benefit-risk ratio of the special population may be different, or it is expected to adjust the dose or time of administration. This special population should be subjected to special clinical trials. Pharmacokinetic studies in patients with renal and hepatic insufficiency are critical to assessing changes in drug metabolism or excretion that may occur (see relevant guidelines).

(1) Research in women during pregnancy

If the study drug is not intended for use in pregnancy, women in pregnancy should be excluded from the study. If the patient is pregnant during the clinical trial, the trial should generally be terminated, promptly reported to the ethics committee for follow-up, and follow-up evaluation of pregnancy, fetus and child. Similarly, clinical trials of drugs planned for pregnancy involve pregnant women, and follow-up evaluations of pregnancy, fetuses, and children are also important.

(2) Research in lactating women

If possible, the secretion of the drug or its metabolites in human milk should be tested. If lactating women are recruited into clinical trials, the drug should also monitor the impact of their babies, if necessary, and the children carry out follow-up.

(3) Research in children

The research that needs to be done depends on the current knowledge of the drug and the possibility of extrapolation from adults and children of other age groups. Certain drugs may be used in children at an early stage of development.

For drugs intended for use in children, evaluation should be conducted in the appropriate age group for children. If a clinical trial involves a child, start with a high age group and then extend to a lower age group.

4 . Pharmacogenomics research

Pharmacogenomics research can begin in the non-clinical research phase. In early clinical trials, data on dose, efficacy, or safety associated with the genome, although limited by the size of the sample, lacked certainty, but provided for drug doses and selection of subjects in later clinical trials (confirmed clinical trials) The basis. In terms of R&D strategies, researchers can use accurate and effective dosing doses in early clinical trials, select a reasonable subset of patients, combine sensitive and accurate pharmacodynamic biomarkers, or rational alternative clinical endpoints. Get the direct regulation of the drug on the target as soon as possible, and understand the effectiveness of the disease, so as to achieve the purpose of mechanism verification or proof of concept. It may provide a clinical basis for decision-making and orientation of research and development.

Fourth, the consideration of a single clinical trial

The following principles should be followed when planning the purpose, design, implementation, analysis, and writing of a clinical trial. Each part should be clearly written into the clinical trial protocol before the study begins.

(First, the purpose

The purpose of the clinical trial should be clearly stated. The purpose of clinical trials may be to evaluate pharmacokinetic parameters, either to assess the pharmacological, physiological, and biochemical effects of the drug, or to explore or confirm the validity or safety of the study drug.

(2) Design

A reasonable clinical trial design is a prerequisite for obtaining valuable conclusions. Clinical trial design includes parallel control, group sequential, crossover, factorial, adaptive design, etc. It is generally recommended to use a parallel control design. In order to achieve the purpose of clinical trials, the applicant should clearly describe the test population, select a reasonable control, explain the primary and secondary endpoints, and provide a basis for estimating the

sample size. Methods for assessing safety based on clinical symptoms, signs, and laboratory tests should also be described. The follow-up procedure for subjects who prematurely terminated the trial should be described in the design. The statistical analysis plan refers to the relevant guiding principles.

1 . Selection of the test population

The choice of subjects should take into account the stage and indications of the study as well as the existing non-clinical and clinical trial background. In the early trials, the subject's group variation can be selected with relatively homogeneous criteria using rigorous screening criteria, but as the trial progresses, the subject population should be expanded to reflect the treatment outcome of the target population.

Depending on the development process and the level of concern for safety, certain trials need to be performed in a closely monitored environment (such as hospitalization).

Subject to rare cases, subjects should not participate in two or more clinical trials at the same time. If there is no adequate time interval, subjects should not repeat clinical trials to ensure safety and avoid delay effects.

Women of childbearing age should generally use effective contraception when participating in clinical trials.

For male volunteers, the risk of drug exposure to their sexual partners or offspring should be considered in the trial. When a hazard exists (for example, if the test involves a drug with mutagenic efficacy or reproductive system toxicity), the test should provide appropriate contraception.

2 . Selection of control group

A reasonable control should be chosen for clinical trials. The controls were of the following types: placebo control, positive control, self-control, test drug dose control, no treatment control, historical control, and the like. The choice of control

should be based on the purpose of the test, and in the case of ethical risks, it should also meet the scientific requirements. A placebo control is generally recommended. If other controls are selected, it is recommended to communicate in advance. Historical (external) comparisons can also be used in very rare cases after argumentation, but special attention should be paid to the risk that the error may increase.

Positive control drugs should be carefully selected. A suitable positive control should be: (1) recognized and widely used; (2) with good evidence-based medical evidence; (3) validity expected to be reproducible. Relevant clinical advances should also be fully considered in the trial design.

3 . Sample size estimation

The scale of the trial is influenced by the disease being studied, the purpose of the study, and the endpoint of the study. The estimation of the sample size should be based on the expected size of the treatment, the estimation of the degree of variation, the statistical analysis method, the false positive error rate, the false negative error rate, and the like. In some cases, determining the safety of a drug requires a larger data set.

4 . Research indicator

Research indicators should be clearly defined, including the attributes of the indicators (qualitative, quantitative, semi-quantitative) and their specific methods of observation.

The endpoint of the trial was used to evaluate research indicators related to pharmacokinetic parameters, pharmacodynamic assays, drug efficacy, and safety. The primary endpoint should reflect the primary clinical outcome and should be selected based on the primary purpose of the study; the secondary endpoint is used to assess other effects of the drug and may or may not be associated with the

primary endpoint. The test endpoint and its analysis plan should be pre-clarified in the study protocol.

The surrogate endpoint is an indicator associated with the clinical endpoint, but it is not a direct evidence of clinical benefit. The surrogate endpoint can be used as a primary indicator only if the surrogate endpoint is highly likely or known to reasonably predict the clinical endpoint.

The method used to evaluate clinical endpoints, whether subjective or objective, should be recognized for accuracy, precision, and responsiveness (sensitivity over time).

5 . Bias control method

(1) randomization

In controlled trials, randomized grouping was a priority consideration to ensure comparability between groups and to reduce selection bias. The randomization method generally uses a block randomization method and / or a stratified randomization method. When multiple stratification factors need to be considered, dynamic randomization can be used to reasonably assign subjects to maintain inter-group balance across layers.

(2) blind method

According to the degree of blindness, it can be divided into double-blind, single-blind and open. Blindness is another important means of controlling the bias of research results. A double-blind trial means that the subject, the investigator, and the clinically relevant sponsor are not aware of the subject's treatment group; the single-blind trial means that the subject is unaware of the treatment group. Placebo-controlled trials in double-blind trials often use a single simulation technique to maintain the blind state of the trial; positive drugs are used as controls. If the positive drug is sensoryly distinguished from the test drug or is administered differently, it should be maintained using dual simulation techniques. Test blind state. If the simulation is difficult to achieve, other masking measures can be used to

achieve double blindness, and the operating procedures of the masking technique should be clearly defined in the scheme. Regardless of the degree of blindness, data management personnel and statistical analysis personnel should be blind. A double-blind trial design is generally recommended.

(3) Compliance

The method used to assess the subject's use of the test drug should be stated in the protocol and the exact use should be documented.

(3) Implementation

Drug development should be carried out in accordance with the requirements of these guidelines. The investigator must follow the protocol; if the R&D program needs to be modified, an annex to the research protocol must be provided to clarify the rationality of the modification and promptly submit it to the ethics committee for approval. Adverse event reports must be provided in a timely manner during research and development and should be documented. Rapidly report security data to relevant regulatory agencies.

(4) Analysis

There should be a special statistical analysis plan in the clinical trial protocol, which should be consistent with the purpose of the test and the design of the test.

The statistical analysis plan should consider the method of assigning the subjects and the hypothesis testing method of the effect indicators. The statistical analysis should be as close as possible to the principle of intention to treat (ITT), and the subjects who fall off and violate the program should be considered in the analysis. Subjects who were excluded after random enrollment should be as few as possible. If they are excluded, the specific reasons for rejection must be listed. The statistical methods used and the statistical analysis software and its versions should be clarified. The timing of the planned interim analysis should also be explained in the plan.

The analysis of clinical trial data should be consistent with the pre-defined plan in the protocol, and any deviation from the plan should be stated in the report.

In some trials, early termination of the trial is pre-planned, in which case the control of the total class I error rate (false positive rate) should be clarified in the protocol . If the sample size is adjusted during the research, the adjustment should be provided, and it is recommended to adjust in the blind state. The adjusted sample size should be larger than the planned sample size in the original plan, and the adjustment will not damage the test. Integrity.

Safety data should be collected in all clinical trials, presented graphically or in a tabular format, and should be categorized based on the severity of the adverse event and the relevance of the study drug.

The statistical analysis plan, statistical analysis report and research report of the test data are based on the relevant guiding principles.

(5) Report

Clinical trial reports should be written in accordance with relevant guidelines.

V. References

1 . General Considerations for Clinical Trials (ICH E8)

2 . The Extent of Population Exposure to Assess Clinical Safety for Drug Intended for Long-term Treatment of Non-Life-Threatening Conditions (ICH E1)

3 . Statistical Considerations in the Design of Clinical Trials (ICH E9)

4 . Choice of Control Group in Clinical Trials (ICH E10)