药物临床试验适应性设计指导原则

（试行）

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I. Overview

The design of confirmatory clinical trials is generally based on the results of preliminary exploratory studies.
Many times rely on very limited data, which can result in design elements
There is a large deviation, which directly affects the success or failure of the experiment. With drug development
With the promotion of clinical research, technical methods of clinical research have been continuously developed, and adaptive design
It is also subject to more and more research and applications. Adaptable design allows for trial periods to be
Modify the experimental design based on the data accumulated over time to correct deviations from the initial design.
Thereby increasing the success rate of the test and improving the efficiency of the test.

Group sequential design is the earliest adaptive design used in clinical trials.
Later, adaptive design was more widely used to re-estimate the sample size, and now it is gradually
It has been popularized and developed into various types of experimental designs, such as two-stage design, flat
More complex designs such as bench test design. As theoretical methods continue to mature,
With the improvement of simulation and computing capabilities, as well as the accumulation of practical experience, adaptive design
Counters are increasingly used in clinical trials.

This guideline defines adaptive design as:
plan and use the data accumulated during the trial to respond to the trial in the interim analysis
Modified clinical trial design. On the one hand, adaptive modification is "according to preset
"plan" rather than a temporary modification plan; on the other hand,
Adaptive modification is a self-learning process, that is, through constant changes in accumulated data
Continuously learn and modify experimental protocols accordingly to adapt to the changing research environment.

Therefore, adaptive design aims to better improve ongoing clinical trials without
It is done due to flaws in the design itself that are highly likely to lead to clinical trial failure.
Temporary remedy.

In practice, sometimes a decision is made based on sufficient and reasonable external data.
modifications to a clinical trial in a clinical trial if such modifications are based solely on external data,
It is not within the scope of adaptive design according to the definition of this guideline. This refers to
The guidelines focus on discussing the basic concepts and principles of adaptive design, commonly used adaptive
Adaptive design types, considerations when using adaptive design, and regulatory requirements
etc., with the purpose of guiding and standardizing how sponsors adopt and implement adaptive design.
When designing an adaptive clinical trial plan, the sponsor should also refer to other relevant
ICH guidelines and national guidelines. This guideline mainly applies to pharmaceutical
Confirmatory clinical trials of products are also of reference significance for exploratory research. Book
The guiding principles only represent the current views and understanding. As research and understanding deepen,
It will be revised and improved.

2. Factors to be considered in adaptive design

Before deciding whether to adopt adaptive design, weigh the appropriateness thoroughly and thoroughly.
The advantages and disadvantages between adaptive design and traditional design, especially the role of adaptive design in design,
complexity in implementation and statistical analysis, and the resulting
unavoidable operational bias and various other challenges that may be introduced during implementation.
The adoption of adaptive design requires comprehensive consideration of many factors, especially the
fitness for purpose, validity, completeness
(integrity) and feasibility (feasibility).

(1) Applicability

The suitability of an adaptive design refers to whether the planned experiment is suitable for use Adaptable design. Generally speaking, confirmatory clinical trials require good and appropriate testing Experimental design, including trial objectives, subject population, enrollment allocation, primary endpoint, Analytical methods and many other aspects, deviations in each link may lead to Test failed. Although adaptive design can achieve self-learning, re-evaluation of current Pre-test plans and can adjust design deviations to find better methods to achieve the same goal, but it was not designed to address the mistake.

Whether to adopt adaptive design, you should first consider what kind of adaptation is needed modification, what kind of data, what kind of hypothesis to test, what kind of decision-making methods, what conditions enable it to be implemented in practice, etc. If one adapts Sexual design cannot bring about the expected increase in test efficiency and improvement in test quality. Or if it is extremely difficult to implement, the design is not suitable. also, Adaptive design requires investing a lot of time in the design phase for in-depth research. Research and plan carefully.

Most adaptive design methods are designed to meet the specific needs of clinical trials And generated, may not possess certain optimal properties in statistical theory, but it may be the most appropriate way to solve a particular problem in a clinical trial, so before considering Adaptive design should be based primarily on the special problems that need to be solved. In addition, suitable Adaptive design clinical trials are more complex and complex than traditional trials in operation and implementation.

Difficulty, therefore, the simplicity of experimental design methods sometimes becomes a factor in whether to adopt appropriate

An important consideration in responsive design.

(2) Reasonability

The rationality of the adaptive design refers to whether the overall Type I error rate of the experiment can be obtained

control, and the ability to ensure the credibility, interpretability and persuasiveness of trial results.

To judge whether the adaptive design is reasonable, the most important criterion is the system used.

Whether the calculation method can control the overall Type I error rate. Adaptive modification generally requires consideration of the system

The problem of multiplicity of the test is to be considered, and the Type I error rate of the test needs to be controlled in advance.

set level. In addition, for some adaptive designs, if bilateral

test, because *the p* -values before and after adaptive modification cannot reflect the comparison between groups.

direction, potentially making the meaning of the final overall *p*- value difficult to interpret, to avoid

In this case, one-sided testing can be selected in the experimental plan; but for other adaptations

Sexual design, such as asymmetric two-sided hypothesis, two-sided test would be a more appropriate choice

select.

Keeping experiments justified also means having the right statistical inference methods

method, such as for calculating adjusted *p*- values, estimated effect sizes, and confidence intervals,

and measuring the consistency of treatment effects at different stages.

Adaptive design may involve multiple target groups, multiple hypotheses, multiple

end point or multiple tests, so it has a high degree of rationality in the statistical analysis method.

Require. If there is no corresponding reasonable statistical method for adaptive modification, it is not appropriate

Use this design. Due to the complexity of adaptive design, in some cases there is no

There are applicable theoretical formulas or analytical formulas for statistical inference, which need to be based on simulation methods.

method to verify the rationality of statistical methods, which to a certain extent adds additional Certainty.

If adaptive design requires merging data before and after adjustment, then it is necessary to consider Consider the rationality of data merging (including differences between before and after data and merging methods, etc.) and the interpretability of pooled efficacy estimates. If the final system of adaptive modification Although the test results are positive, the clinical benefit is too small and insufficient to support the verification of drug efficacy.

(3) Integrity

The integrity of adaptive design refers to whether it can control the introduced bias. Maintaining the integrity of the trial means following predetermined Plan to make adjustments to the protocol and maintain blinding of interim analysis results to maximize Minimize operational bias.

Avoiding the introduction of operational bias is the most basic requirement for all clinical trials. adapt Because the sexual design involves modifications in many aspects of clinical trials, it may affect subsequent The execution of the test adds an additional layer of difficulty to maintaining the integrity of the test. therefore In confirmatory trials, interim analyzes of adaptive designs should generally be performed by independent Data Monitoring Committee (DMC) and its application It is completed by an independent statistical support team other than the organizer and guarantees the results of the interim analysis. Not be known to the sponsor, investigators and subjects so as not to affect subsequent trials Implementation and introduction of operational bias. Since adaptive modification involves multiple links, a An effective firewall to prevent the leakage of interim analysis results and possible manipulation Operating bias is the most important task in execution. To this end, adaptive design solutions

Should contain a complete operational process, especially information on how to set it up

access rights. At the same time, in order to avoid the influence of uncontrollable factors on the test results,

Also consider how to avoid being indirectly pushed out of the period based on changes made to the trial.

The results of the analysis. Sponsors should be prepared to conduct all required standard operating procedures for the trial

process, and include relevant processes involving adaptive modifications, and record them at the same time.

The actual operation process. All of the above should be carefully considered during the design phase of the trial.

considerations and need to be strictly implemented during the test to avoid affecting the integrity of the test.

sex.

(4) Feasibility

The feasibility of adaptive design refers to whether the adaptive modification of the experiment can be implemented in practice.

Implemented internationally. Since adaptive design is more complex than traditional design, and implementation

and analysis are more difficult and may need to be considered before planning to adopt adaptive design

Consider the following factors: The adaptive adjustment strategy can ensure the rationality and integrity of the trial

sex; relative to the test period, there is sufficient time to analyze the accumulated data from the test

Make adaptive modifications and carry out follow-up experiments based on the analysis results; mid-term data collection

Sets and data cleansing can be completed quickly so that interim analysis can be completed on schedule

and adjustments; have the ability to quickly modify randomization procedures/drug supply systems; have

the ability to manage adequate drug supplies and be able to afford increased drug supplies;

Prepare an adaptively designed data collection system in advance; ensure coordination with all relevant parties

Communicate smoothly and effectively; be able to equip professional software to complete complex designs and related analysis

Analytical calculations, etc. At the same time, during the trial design phase, the sponsor can also communicate with the study

Communicate with stakeholders and evaluate whether the adaptive design under consideration can proceed smoothly in practice.

feasibility. If the relevant adaptation modifications are difficult to implement, other options should be considered

count.

In summary, if you plan to adopt adaptive design, you need to carefully evaluate its

Are there any advantages? If decisions cannot be made, simulation methods can be used to assess adaptation

efficiency of sexual design. If the adaptive design does not reflect many advantages after evaluation,

situation, it is recommended to carefully consider adaptive

design. 3. Commonly used adaptive designs

(1) Group sequential design

Group sequential design means that the plan is pre-planned to be carried out during the experiment.

One or more interim analyses, with follow-up decisions based on the results of each interim analysis

Trial decision-making usually has four possibilities: ÿ Terminate the trial based on superiority;

ÿ Terminate the test based on ineffectiveness; ÿ Terminate the test based on safety; ÿ Continue the trial

test. The timing of interim analysis is generally based on the proportion of accumulated data, such as subjects entering

Group proportion or proportion of the number of target events that occurred, or calendar time. If midterm

If there is at least one superiority analysis and there is a possibility of early termination of the trial, then the

Adjust the type I error rate of the analysis to control the overall type I error rate within the preset

level. Common methods to adjust the Type I error rate include Pocock's method, O'Brien

& Fleming method and Lan & DeMets method, etc. Since the interim analysis only uses

Part of the data was used, and the results still have large uncertainties. To evaluate early superiority

It is generally recommended to use a more conservative approach in order to increase the efficacy when terminating the trial.

reliability of the conclusion. The setting of invalidity boundaries is divided into binding and non-binding. binding

Boundary The trial must be terminated once the results of the interim analysis cross the futility boundary.

Unbound boundaries generally terminate when interim analysis results cross the invalidity boundary.

trial, but in some cases based on a comprehensive evaluation by an independent data monitoring committee

It can still be recommended that the trial continue. For unbound boundaries, no need to adjust the maximum

Type I error rate for the final analysis.

The choice of timing for interim analysis also needs to be carefully considered. If grouped sequentially

In the overall plan, there is the possibility of early termination of the trial based on superiority, and the selection of time points

Consideration should be given to whether the amount of data at the interim analysis is sufficient and whether the follow-up period

Sufficient to provide reliable efficacy estimates and safety assessment results, and also

Estimates of important secondary endpoints as well as some important subgroup outcomes are included. If expected

The mid-term analysis is to verify the safety and effectiveness of the drug, and the time point should focus on

on how to best protect subjects.

(2) Re-estimation of sample size

Sample size re-estimation refers to the use of a pre-set interim analysis plan to

Recalculate the sample size using accumulated trial data to ensure final statistical testing

Able to achieve pre-set goals or modified goals while also being able to control I

Class error rate.

Estimates of initial sample size often depend on effect size, variation in primary endpoint

degree, trial follow-up time, subject dropout rate and many other factors, which often

Based on previous research data. In most cases, the sample size during the trial design phase

The parameter information required for estimation is often insufficient, which may lead to sample size estimation.

The calculation is not accurate enough. Sample size re-estimation in adaptive designs for this type of problem

Provides effective solutions.

Sample size re-estimation methods can be divided into blind methods and non-blind methods.

Law.

Blind method, also known as non-comparative analysis method (non-comparative

analysis), an interim analysis that does not use information from the actual trial groupings, or

The authors did not conduct any analysis involving comparisons between groups.

The blind method re-estimates the sample size by calculating

important parameters of sample size (such as pooled variance or pooled event rates), then

Re-estimate the sample size. Because the efficacy ratio between groups was not involved in the interim analysis

Comparatively, there is generally no need to adjust the Type I error rate. This method is relatively easy to implement,

Generally, operational bias will not be introduced, and the relevant statistical methods are relatively complete.

All it takes is pre-planning during the trial design phase. Sample size for blind method

Reestimation can also be done by the sponsor.

Non-blind method, also called comparative analysis method (comparative analysis),

Refers to the use of trial grouping information (including the real names of each group) in the interim analysis

or distinguishable grouping codes), the analysis involves comparisons between groups.

Sample size re-estimation for unblinded methods is based on cumulative data and

group information, calculate important parameters of sample size (such as trial effect size), and then

The sample size was re-estimated because the interim analysis involves comparison of efficacy between groups.

Type I error rates usually need to be adjusted accordingly.

Sample size re-estimates for unblinded analyzes need to be included in the study protocol in advance

Clarification, including timing of re-estimation, criteria used in decision-making, re-estimation

methods used when testing, methods for adjusting inspection level ÿ, methods for performing non-blind analysis

personnel, as well as those who perform the entire operation process, etc. It should be noted that a

It is not advisable to re-estimate the sample size too many times in an experiment. when reassessed

When the sample size is less than the originally designed sample size, a reduction in sample size is generally not accepted.

Adjustment.

Whether to use unblinded sample size re-estimation depends on several factors. example

For example, if there is relatively reliable early data, the sample size can be re-estimated in a non-blinded manner.

Whether it is necessary; the cost of using unblinded sample size re-estimation (such as inspection level adjustment)

Whole) Compared with slightly enlarging the sample size in the initial design, is it beneficial? Mid-term analysis

Can the analysis be completed quickly? Is it possible that there is not enough time due to the rapid enrollment?

Time is used to adjust the experiment; whether the time node and inference method of the interim analysis are reasonable;

Whether the existing data can support the planned interim analysis, etc. Therefore, it should be based on

Characteristics of the trial itself, carefully consider various factors, and then make appropriate decisions.

(3) Design of adaptive seamless dose selection

The design of adaptive seamless dose selection refers to the seamless connection of two trials,

Dose selection is made at the end of the early phase trial and the selected dose is used in the later phase trial.

The final analysis included all subjects enrolled in both the early and late trials.

Subject's data. This guideline uses Phase II/III trials as an example of adaptive seamless

The design of dose selection is explained and can be used as a reference for other seamless design situations.

In traditional designs, independent phase II dose selection typically involves multiple agents

Dosage group, the purpose is to select the appropriate dose and use it in phase III trials. Phase III trial

is a separate trial from the Phase II trial, and its final analysis does not include results from the Phase II trial.

data. Phase II/III trials with this specific goal are also often referred to as Phase II/III operations

Seamless design. Operational seamless design excludes subjects from Phase II trials from Phase III

type I error is not required in the final analysis of phase III

Rate adjustment. Another type of design, called Phase II/III extrapolated seamless design, refers to the

The final analysis included all subjects from phase II trials at selected and unselected doses.

tester. Adaptable Phase II/III extrapolated seamless dose selection is designed to extrapolate seamless

Special case of design. This design has many advantages, such as shortening the length of the

The time interval between the end of the Phase II trial and the start of the Phase III trial, reduction of trials

The total sample size, shorten the duration of the test, reduce the cost of the test, etc. at the same time,

Because subjects enrolled in Phase II have longer follow-up times, it is sometimes possible to observe earlier.

The long-term safety of the drug was observed.

Designs using adaptive phase II/III seamless dose selection require multiple considerations.

factor. Since the phase II data may not be fully and in-depth during the interim analysis,

Analysis, if you know little about the experimental drug, you should generally choose to adapt it carefully.

The design of seamless dose selection for phase II/III phase II, because the data from phase II trials need to include

Adding to the final analysis that Phase III trials are already underway, and if using

Two separate trials can have more options. There are also some factors, such as

For example, the primary endpoint of a Phase III trial requires a longer follow-up period, while a Phase II trial may only

A surrogate endpoint can be used to make judgments when the surrogate endpoint is not related to the primary endpoint.

When surrogate endpoints are used to select doses for phase III trials, there are significant consequences

Big uncertainty. As another example, it should also be considered whether there is sufficient production capacity in the short term

Provide drugs required for Phase III within the time limit.

The design of adaptive phase II/III seamless dose selection discussed above can also

Directly applicable to other similar trials, such as combination and single drug selection,

Or the choice between different drugs, etc.

(4) Adaptable enrichment design

An adaptive enrichment design means that the trial will be based on the results of the interim analysis, based on

Pre-set criteria are adapted to the target population to determine post-trial

The target group for the continued stage. Subsequent phases of the trial may continue to include the entire population.

OK, or only enroll subgroups and may need to make some corresponding adaptive adjustments.

Or increase the sample size and continue to enroll the entire population, which will also naturally increase the number of sub-

The number of people joining the group. The final analysis target of the trial may only be the entire population or subgroups,

Or both the entire population and subpopulations are included. The final analysis of the trial will include both

The data of all subjects enrolled in each stage, and there are corresponding adjustment methods to control

Type I error rate.

If the investigational drug is known to be effective only for a specific subpopulation, then clinical trials

The trial should only recruit subjects from this subpopulation. But in practice, the more common situation is

It is possible that the experimental drug has a greater effect on a certain subgroup, but it is not clear how effective it will be on the entire population.

Is the group also effective enough? In this case, if the test drug is

If there is a large enough therapeutic effect in the entire population, enrolling only a subgroup of subjects will lose the efficacy.

The chance of being effective for the entire population; if the trial drug is less effective for the entire population but is less effective for a certain

It is effective for subgroups, and it is very likely that subjects enrolled in the entire population will not obtain the expected positive results.

results, and also loses the opportunity to show efficacy for subpopulations. adaptive enrichment

Designs to select target populations can take into account both, taking advantage of the results of the trial itself

This will allow us to select the target population more scientifically and increase the success of drug research and development.

Rate.

Since the selection of the target population in the adaptive enrichment design involves the entire population and sub-

groups, as well as interim analysis using unblinded comparisons between groups, so they should be clearly

Define the statistical assumptions and corresponding statistical methods for the two populations and control Class I

Error rate.

The selection criteria for the target population can be based on disease characteristics, prognostic biological

markers or predictive biomarkers. Generally speaking, the accepted

disease-related characteristics or prognosis-related biomarkers to select target groups and try

The design and operation of the experiment will be relatively simple. Currently, predictive biomarkers are used to

There is an increasing number of studies on selecting target populations, but many predictive biomarkers

The bed value is unclear. If a trial were to use a new predictive biomarker

To select the target population, corresponding diagnostic methods must be available. Diagnostic methods used

It must have been approved for marketing by the regulatory authorities. If not, it may need to be developed at the same time.

hair.

(5) Two-stage adaptive design

Two-stage adaptive design refers to dividing an experiment into two stages.

The stage before adaptation is stage 1, and the stage after adaptation is stage 2. at 1st

An interim analysis will be conducted at the end of the stage, and based on the preset modification plan, the

Phase 2 trials were adapted.

The group sequential design discussed above (if there is only one interim analysis), sample

Cost re-estimation, adaptability Design of seamless dose selection for phase II/III, adaptability

Enrichment designs are both two-stage adaptive designs. Two-stage adaptive design also includes

Other common designs, such as starting from Phase 1 during the interim analysis at the end of Phase 1

Select an appropriate primary endpoint for Phase 2; select an appropriate primary endpoint from Phase 1

Select an appropriate target subgroup from two or more target subgroups for Stage 2

paragraph; modify the single main hypothesis in stage 1 to multiple main hypotheses, etc.

There are two points to note: First, group sequential design and adaptive group sequential design

There are differences between designs. Both are only included in interim analysis, early termination of trials and samples.

Cost quantities are re-estimated similarly; if an adaptive group sequential design includes other

If other adaptive modifications are made, the standard analysis method in group sequential design will not be suitable.

use. Another point is that when a two-stage adaptive design analyzes survival with survival as the end point,

During the trial, no matter at which stage the endpoint event of the subjects enrolled in stage 1 occurred

segment, they should be included in the results of the first stage when calculating, otherwise the results of the two stages

The independence assumption will no longer hold, resulting in an increased Type I error rate.

Most adaptive designs fall into the two-phase category. Two-stage adaptive design

The principles and methods of design can be similarly extended to multi-stage or multi-adaptive design.

(6) Experimental design of adaptive main plan

The main protocol trial design refers to an overall clinical trial protocol containing multiple sub-

Program, different sub-programs can test the clinical efficacy of a drug on multiple diseases at the same time

clinical effect, and can also test the clinical effect of multiple drugs on a disease at the same time.

Or test the clinical effects of multiple drugs on multiple diseases at the same time. every sub

The protocol can be a single-arm trial or a randomized controlled trial. If there is a child

The cases are randomized controlled trials and the patient groups are the same. These randomized controlled trials are likely to

They can share a control group, or they may have separate control groups. The main program test is also
Used to refer broadly to patient-specific characteristics (e.g., disease, histological type, molecular markers
clinical trials as markers. Master protocol trials have many advantages, such as the ability to
able to provide patients with the greatest chance of enrollment and selection of the most appropriate trial drug
Chance. Common main scheme designs include basket test, umbrella test and platform test
experimental design.

Basket designs are designed to evaluate a drug therapy with the same biological profile
clinical effects on different disease types, each sub-program targets one or more
disease type. Umbrella designs are designed to evaluate multiple drugs targeting the same disease or
Clinical effects of biomarker-type targeted therapies. The platform is designed to evaluate
Clinical efficacy of various drugs against various diseases. Platform tests usually maintain the test
The test will be carried out for a long time and new experimental drugs will be allowed to be added to the test platform at any time. At the same time,
Comparator medications may also change over time.

Although master protocol trials have many advantages, due to their complexity, they are
planning, execution, establishment of a unified management structure, especially statistical analysis, etc.
Facing greater challenges. If a master protocol trial is planned, all aspects of the trial should be
After conducting comprehensive, in-depth and detailed research on various issues that may be involved in each aspect,
Choose carefully again.

Adaptable master plan design means that the master plan design includes one or more
An adaptive design that can flexibly adopt a variety of adaptive adjustments.
For example, adding one or more new sub-plans, ending one or more sub-plans early

case, re-estimate the sample size, adjust the test hypothesis, primary endpoint and main statistics
planning methods, or make different adaptive adjustments to different sub-program designs, etc.

(7) Multiple adaptive design

Multiple adaptation design refers to the use of more than one adaptation in an experiment
Experimental design for adjustment methods. All of the adaptive design methods discussed above can
used simultaneously in the same clinical trial. For example, a clinical trial in Phase 1
At the end, the dosage for the next stage is determined, and then the target population can be selected.
The sample size can then be re-estimated.

In principle, if a clinical trial design includes multiple adaptive adjustments
Integration, as long as it meets the requirements of applicability, rationality, completeness and feasibility, many
Heavy adaptive design can be considered. However, due to the complexity of multiple adaptive designs,
Whether it is necessary to introduce too many adaptations in a trial, it is recommended to sponsor
be carefully considered. 4.

Other considerations

(1) Modifications based only on external data

Modifications based solely on external data refer to modifications based solely on
External data that make certain modifications to an ongoing clinical trial are not included in this guide.
In the Guidelines, it is not considered an adaptive modification as defined.

During the course of the trial, there will often be new information related to the trial.
appear, and this information is generally based on information that did not exist at the time of current trial design.
of recently completed experiments or research. Based on external data for an ongoing
Certain modifications to clinical trials must be well-founded and should not undermine the trial

The rationality and completeness of the information must be communicated with the regulatory agency in advance for confirmation.

This can be reflected through amendments to the trial protocol. Sponsors should pay special attention to these revisions

The changes are based solely on external data and not on the results of the ongoing trials themselves.

There may be other unfinished trials of the same drug at the time of the current trial design.

Other trials of the substance are ongoing that are relevant to the current trial and are

are preset during design, this is also considered external data and can be tested through

be reflected in the amendments to the bill.

If the results of a phase II trial need to be used to determine the biological

The threshold value of the marker is determined based on the accumulated data analyzed during the current trial period.

Modifications are classified as adaptive modifications in this guideline. At this time, they need to be adapted to

sexual modification plan.

(2) Other considerations for supervision

As part of the trial protocol, adaptation plans should be included in the clinical trial

Pre-set in the test protocol before starting.

If a sponsor plans to use an adaptive design in a confirmatory trial or

If Bayesian methods or simulation methods are used in statistical inference, the sponsor should

Communicate with regulatory authorities during the plan design stage.

The information submitted by the sponsor in the communication should contain important information to support

Use adaptive design literature and data for regulatory review. accuracy of information

Preparedness should focus on the details of a pre-established adaptation plan, including its appropriate

usefulness, rationality and completeness, etc.

Sponsors should discuss the rationale for adaptive design in communications materials,

Including advantages compared with traditional design, specific problems that need to be solved by adaptive design

The specific problems and solutions, the interpretability of the results after adaptive adjustment, etc.;

It should also include details of predetermined adjustment plans, such as the timing of interim analysis.

time and purpose, statistical rules for determining adaptation, and statistical checks for final analysis.

methods, methods to control Type I error rates, etc.; and key implementation adaptability

Designed operating procedures, specific measures to ensure test integrity, etc.

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Appendix: Glossary

Adaptive design : According to a preset plan, the data accumulated during the trial are used to make corresponding modifications to the trial during the interim analysis.

clinical trial design.

Group sequential design (Group **sequential** design): refers to the plan in advance

Plan to conduct one or more interim analyzes during the course of the trial, with each

The results of the analysis are used to make experimental design decisions for subsequent experiments.

Blinded/Non-comparative analysis method:

It means that the actual trial grouping information is not used in the interim analysis, or no involvement is made.

and analysis of comparisons between groups.

Unblinded/Comparative analysis method (Unblinded/**Comparative**

analysis): refers to the use of trial grouping information (including the

real name or distinguishable grouping code), the analysis involves between-group

Compare.

Master protocol **with adaptive designs:**

It refers to a design that includes one or more adaptive adjustments in the main scheme design.

Multiple adaptive design : refers to an experiment

An experimental design in which more than one adaptation method is used.

Bayesian method : Bayesian method generally refers to the

When making statistical inferences about unknown parameters, it first uses prior information (the prior distribution function

(number) makes an initial judgment on unknown parameters. After collecting new data, it makes an initial judgment based on

Bayes' principle summarizes prior information and new data in another function (posterior distribution function) and make statistical inferences based on this posterior distribution.

Simulation method : refers to the use of computer technology to create Create virtual patient data and predict patient clinical outcomes based on pre-specified models results to simulate the conduct of clinical trials.