药物临床试验期间安全性信息汇总分析和报告指导原则（试行）

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I. Overview

With the release and implementation of the Pharmacovigilance Quality Management Practices, sponsors
A sound pharmacovigilance system should be established to monitor safety risks during drug clinical trials.
assume the main responsibility for risk management. Sponsors should comprehensively collect data during drug clinical trials
safety information and carry out risk monitoring, identification, assessment and control, and promptly issue
existing safety issues, proactively take necessary risk control measures, and evaluate
Evaluate the effectiveness of risk control measures to ensure that risks are minimized and effectively protect people
Tester safety.

The sponsor's safety evaluation during drug clinical trials should include at least
Evaluation of individual safety incidents and summary analysis of safety information. Case safety
A sexual event refers to an incident that occurs to an individual subject during a clinical trial that may interact with a drug.
Use-related adverse events and other safety-related risk events. safety information
Summary analysis of information is provided by regularly reviewing all completed and ongoing
Safety data from clinical trials and other safety-related risk events
Conduct comprehensive analysis to continuously monitor and evaluate safety information. Antidote
Safety information during drug clinical trials is continuously evaluated, which is important for early detection.
Serious safety risks and thus protecting subject safety are of great significance.

To better promote and guide sponsors on drug clinical trials related to registration
Timely evaluation and reporting of safety risk information during the trial, and clear evaluation methods
and reporting requirements to regulatory agencies, we comply with domestic laws and regulations, and
This guideline is formulated based on relevant international technical guidelines. This guiding principle focuses on

Guidance to sponsors on serious adverse events during registration-related drug clinical trials

Serious Adverse Event (SAE) and other potentially serious security incidents

Continuous evaluation and timely reporting of safety risk information during drug clinical trials

Basic considerations for safety evaluation and safety reporting cannot yet cover all situations.

If you have any personalized questions that cannot be clarified, you can communicate with the Center for Drug Evaluation.

This guideline only represents the current views and understanding of the drug regulatory authorities.

With the progress of scientific research, the relevant content in this guiding principle will be continuously improved and

renew.

2. Evaluation and reporting of individual safety incidents

Individual safety events are the basis for safety evaluation during drug clinical trials.

It is an important data source for summary analysis of safety information. During clinical trials,

The sponsor conducts timely review and analysis of individual safety incidents, especially SAE

Analyze and evaluate important safety risks that may be associated with the drug and promptly

Taking effective risk control measures is of great significance.

The sponsor should fully communicate with the researcher to obtain the safety of the case as much as possible

Complete information about the subjects of the incident. When evaluating individual safety events, sponsors should carefully

Carefully review the subject's basic information, including family history, relevant medical history, combined treatments

treatment (prescription drugs, over-the-counter drugs, traditional Chinese medicine, special diet, surgery, physical therapy,

dietary supplements and other alternative medicines), drug allergies, etc. to fully understand

Factors that may affect the evaluation of individual safety events. In addition, the sponsor should also fully

Consider the subject's group characteristics, drug indications, natural history of the disease, and drug

Known Risks and Other Relevant Factors.

Sponsors should carefully evaluate individual applications in accordance with the relevant guiding principles issued by our country.

safety events, if necessary, in accordance with the "Safety Data During Drug Clinical Trials"

Expedited Reporting Standards and Procedures require expedited reporting to regulatory authorities.

3. Summary analysis of safety information

Summary analysis of safety information during drug clinical trials is a case-by-case basis.

An important supplement to comprehensive event evaluation, helping to promptly detect and identify important risks

Signal. Situations for summary analysis of safety information during drug clinical trials include:

Not limited to: (1) Summary of expectations related to investigational drugs alone or in combination with treatment

The incidence of SAE, analyze whether the incidence in the trial population is higher than that in the same population

The incidence rate of the scene can provide a basis for determining the causal relationship between SAE and the experimental drug; (2)

Compare the differences in the incidence of certain SAEs between different trial groups through group summary analysis

Differences provide a basis for determining the causal relationship between SAE and experimental drugs; (3) Through

Through summary analysis, some expected serious adverse reactions, suspected non-

Suspected Unexpected Serious Adverse

Reaction, SUSAR) or pay special attention to adverse events (Adverse Event of

The increased incidence of Special Interest (AESI) has important clinical significance.

(1) Source of information

Sources of aggregated analysis security information include but are not limited to: All and registered

Relevant safety data from completed and ongoing clinical trials of the drug,

and other important safety information, such as: non-clinical study data, non-interventional
Research safety findings, domestic and foreign regulatory agency reports, post-market safety
discoveries, scientific literature, etc.

(2) Summary analysis plan

Sponsors should establish a safety information summary analysis plan to facilitate timely analysis
Safety data and other safety data from all completed and ongoing clinical trials
safety-related risk events. When developing a meta-analysis plan, focus should be placed on drug
SAE, SUSAR, AESI, etc. that occurred during drug clinical trials, and other
Information about potentially serious security risks.

The safety information summary analysis plan should at least include:

1. Analysis content and indicators, such as the occurrence of SAE, SUSAR, and AESI
Rate;

2. Responsibilities of safety data review and analysis parties;

3. The frequency and basis of summary analysis;

4. Safety data update plan, such as major safety issues in non-clinical studies
New discovery;

5. The statistical method, graphic or tabular form to be used for summary analysis;

6. The unblinding conditions, methods and processes to be used in the blind trial.

Sponsors should proceed based on the obtained drug safety information and clinical development
Develop and timely update the safety information summary and analysis plan during clinical trials.

(3) Summary analysis method

For blinded trials, in order to maintain the blindness of the clinical trial implementation team, the application

Authors may commission other organizations or individuals to act as independent aggregate analysts of security information.

Analyst, responsible for reviewing and evaluating safety data accumulated during drug clinical trials

and other security-related risk events and conduct summary analysis. For non-blind

test, the sponsor can proceed based on the test without affecting the integrity of the test.

You can set up your own summary analysis method.

1. Basic requirements

The summary analysis party should understand the basic information of the experimental drug, indications, and experimental subjects.

group characteristics to make a scientific evaluation of the safety of the experimental drugs. when appears

When new security risk information is received, the aggregation analyst should add relevant experts as needed.

professional personnel.

It should be noted that the summary analysis method for blind trials should have certain requirements.

independence. To maintain trial integrity, pooled analysts should not participate in clinical trials

The implementation of the clinical trial should be carried out, and the blindness of the personnel involved in the implementation of the clinical trial should always be maintained. remove

Unblinding safety data for designated participants or reviewing and analyzing unblinded data

Except for the personnel of the aggregation and analysis party, no other internal or external personnel of the aggregation and analysis party shall have access to the unblinding

safety data. When it is deemed necessary to conduct a “benefit-risk” assessment of a drug

When estimating, aggregate analysts can view partial effectiveness data.

2. The composition of the summary analysis party

If the sponsor has established an Independent Data Monitoring Committee (Independent Data Monitoring Committee)

Data Monitoring Committee (IDMC), which can regularly monitor the security

Complete data review and summary analysis. Summary analysis of safety data focuses only on
It is used to identify and describe the safety risks of experimental drugs and does not involve effectiveness evaluation;
When a benefit-risk assessment is deemed necessary, the IDMC may simultaneously
Look at some of the effectiveness data. If a pooled analysis reveals that ongoing clinical trials
If there are serious safety risks in the test, IDMC may propose to the sponsor to suspend/terminate
recommendations for clinical trials, and take necessary risk control measures in a timely manner to fully protect
Protect subjects.

If IDMC is not used as the aggregator, the sponsor may also delegate
Other organizations or individuals conduct aggregate analysis of security data. For blind trials,
A separate review approach may be considered, such as having the sponsor determine the conditions and methods for unblinding.
Act, entrust other organizations or individuals to conduct unblinding and unblinding the safety data
Conduct review and meta-analysis.

(4) Analysis frequency

The frequency of pooled analyzes will depend on the circumstances and should take into account the safety profile of the investigational drug.
The degree of understanding of characteristics, indications, trial population and subject enrollment rate, etc.
For example, aggregate analysis every 6 months or more frequently, or by safety risk
The risk situation determines the frequency of summary analysis. Under normal circumstances, the sponsor can base its accumulated
safety data, the number of subjects who have completed recruitment (e.g. every 25% of the planned
Recruitment numbers), changes in the expected incidence of SAEs, etc. are regularly summarized and analyzed.
If new serious security risk information emerges, the summary can be modified as needed
Frequency of analysis.

(5) Unblinding method

For ongoing clinical trials, sponsors should develop detailed blinding protocols in advance.

Dynamic security data review standards and summary analysis process, summary analysts should master

and strictly enforce it. Summary analysis of blinded collection of safety data during clinical trials

Only when it is suspected that there may be serious risks after the overall analysis and it is deemed necessary to unblind

Ability to unblind safety data. Sponsors should develop detailed unblinded bids in advance

standards and operating procedures, and clearly designate personnel who can participate in unblinding. Those who uncover the blindness should hold the palm of their hands

Understand and strictly implement unblinding standards and operating procedures, and retain relevant records to ensure unblinding

The blinding process is traceable.

The summary analysis mainly involves the following unblinding situations:

1. Trigger threshold unblinding

Trigger threshold unblinding is suitable for pre-set trial populations that cannot be excluded.

Except in the case of background incidence of SAEs causally related to the trial drug, when blinded

The overall analysis results showed that the incidence rate in the total trial population significantly exceeded the background incidence rate in the population.

Unblinding is triggered when a child is born. For example, predetermined incidence of myocardial infarction in the elderly population

rate is the threshold that triggers unblinding, if it is found during the summary analysis of blinded safety data

The incidence of myocardial infarction in the total trial population exceeds the prespecified unblinding trigger rate

threshold, the safety data related to myocardial infarction can be unblinded into groups and compared.

Differences in the incidence of myocardial infarction between the experimental group and the control group, and differences in timely judgment

Whether the difference has clinical significance.

Sponsors should try their best to comprehensively synthesize existing data to pre-determine the candidates to be enrolled.

Certain SAEs in the total trial population that cannot be excluded as causally related to the trial drug

Background incidence. For example, refer to the safety data of similar drugs, existing epidemics

Scientific or specific disease surveillance data, literature reports, etc.

2. Group analysis and unblinding

When the trial population cannot be determined in advance, certain factors related to the trial drug cannot be excluded.

For preclinical studies or existing clinical trials, the background incidence of SAEs may be

For experimental drugs with higher safety risks, the sponsor may consider using certain

Period group summary analysis.

The hierarchical unblinding method can be used for summary analysis.

SAEs related to trial drug causation are regularly analyzed in aggregate by trial group. Pass

Compare the difference in the incidence or number of such SAEs between each trial group through summary analysis.

differences, determine whether further unblinding post-evaluation is needed to identify safety risks as early as possible

risk. For example, for a trial using an active drug control design, if a certain test group in different test groups

If the cumulative difference in the number of SAE occurrences reaches three or four or more, it will prompt a trial

There may be certain differences in the incidence rate of this SAE between groups as the testing progresses, and a summary analysis is required.

Consider conducting periodic group summary analysis of this SAE.

Unblinding safety data during clinical trials may compromise trial integrity

Significant impact, sponsors need to plan carefully, strengthen process records and control measures

To protect the integrity of clinical trial data.

(6) Precautions

1. Comprehensive evaluation based on medicine

Due to the difference in SAE incidence rates between the experimental group and the control group, bias may exist.

Therefore, the results of the pooled analysis should be comprehensively evaluated based on medical knowledge. medicine

In the early stages of drug clinical development, there is less safety data accumulated and trials are usually not available.

The difference in incidence between the group and the control group was not statistically significant to rule out SAE and trial

Drug causation. Therefore, sponsors need to be aware of the safety of drug clinical trials

comprehensive assessment of safety data and safety information from other sources, such as SAE

time of production, available pharmacological data, similar serious adverse reactions to similar drugs

occurrence and findings from nonclinical studies. In addition, the sponsor should also combine the contract with

Comprehensive evaluation of other SAEs classified by a medical system, such as the sponsor's

When evaluating adverse events of pulmonary embolism, other data accumulated in clinical trials should also be considered.

Comprehensive analysis of other thromboembolic events (such as deep vein thrombosis).

When there is evidence suggesting a potential causal relationship between the SAE and the investigational drug

When necessary, the sponsor should take necessary risk control measures in a timely manner to fully protect the subjects

By.

2. Use appropriate standards to classify and summarize

Sponsors should adopt appropriate methods based on the purpose and design of different clinical trials of the drug.

Appropriate methods for assessing safety data from all completed and ongoing clinical trials

A summary analysis was conducted. Usually based on drug indications, subject baseline characteristics,

Different dosing plans, etc. are summarized separately.

3. Maintain the integrity of the test

To maintain the integrity of the trial, the sponsor should develop detailed blinding protocols in advance.

Maintain standard operating procedures for both blinded and non-blinded maintainers

All should be mastered and strictly implemented. Sponsors should take strict measures to maintain blindness and

Set up a "firewall" between non-blind maintainers to conduct unblinded reviews or participate in security

Persons submitting the comprehensive summary analysis report should not be involved in the conduct or results of the trial

analyze. If an organization outside of IDMC is required to review aggregated security data, the

Organizations should only review safety unblinded data in relation to aggregated analysis and not

efficacy data and other trial data not relevant to the aggregated analysis data.

If the pooled analysis finds that the investigational drug has potentially serious safety risks,

Sponsors should communicate with researchers in a timely manner to fully protect subjects. Sponsor to

When researchers submit summary analysis reports, if there are concerns about unblinding, they can only report to the researchers

Submit a description and summary of the summary analysis report. Sponsors may contact investigators by

A letter informing all investigators involved in the trial of the potentially serious safety hazards of the trial drug

sexual risks, as well as planned updated risk control measures, such as modified plans, informed

Consent, Investigator's Manual, etc.

4. Use the correct Medical Dictionary for regulatory activities (Medical Dictionary for

Regulatory Activities, MedDRA) Coding

Sponsors should carefully review the concept of adverse events in the protocol before conducting the trial

The consistency of the description with MedDRA medical terminology was reviewed during the development process.

Check SAE reporting terminology for accuracy and perform correct MedDRA coding.

For example, for the medical event renal failure, preferred terms (PT)

May include renal failure, acute kidney injury, renal impairment, azotemia, urinary tract

Various concepts such as reduced output, post-operative renal failure, and other related terms, sponsor

Accurate coding should be based on the specific circumstances of the adverse event.

Standardized MedDRA queries (Standardized

MedDRA Query (SMQ), High Level Term (HLT) or

Sponsor-defined sets of medical concepts provide aggregate analysis of SAEs of the same type.

4. Reporting of serious safety risk information

(1) Situation and method of rapid reporting

Evaluation of the “benefit-risk” of experimental drugs with significant effects found in meta-analyses

estimated information, may consider changes in usage, or affect the overall drug development process

Information about other potentially serious safety risks during clinical trials that sponsors

You should communicate with the Drug Evaluation Center in a timely manner, write a summary analysis report, and press

Reporting requirements must be reported to the Center for Drug Evaluation.

Sponsors can use " Applicant window — Other potentially serious safety risks

Risk information submission column"Submit a summary analysis report, and at the same time take strict measures to report

Establish a “firewall” between the report submitter and the clinical trial implementation team to avoid accidental

External blindness.

(2) Contents of quick report

The content of the rapid report should at least include key targets such as SAE/SUSAR

Summary analysis results of events and lists all the

SAE/SUSAR case adverse event information. If the summary analysis uses

If SAE has reported expeditiously according to SUSAR, each SUSAR needs to be listed

Globally unique case identifier of the individual case (C.1.8.1).

The summary analysis report content should at least include:

1. Summary and analysis of subject information and description of individual adverse events narrate. Including: subject's gender, age, symptoms, family history, relevant medical history, Relevant examination and test results, combined treatments, and the time of SAE/SUSAR occurrence, The causal relationship between drug exposure and SAE/SUSAR, etc.

2. A description of the summary analysis methods and results. Includes: Aggregated Analysis Security Sources of information, summary analysis methods, analysis methods, results and conclusions, clinical trials changes to trial-related documents (e.g., informed consent form, investigator manual), and plans planned risk control measures, etc.

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