儿童药物临床试验安全信息评估与报告

技术指导原则

（试行）

国家药品监督管理局药品审评中心

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I. Background

my country's Drug Administration Law stipulates that the state shall establish a pharmacovigilance system to monitor and manage drugs.

Monitor and identify adverse drug reactions and other harmful reactions related to medication.

Assessment and control. In 2021, the State issued and implemented the "Pharmacovigilance Quality" standard for the first time.

The Good Practice for Clinical Practice (GVP) includes pharmacovigilance during clinical trials.

The purpose of pharmacovigilance is to minimize drug safety risks and protect and

Promote public health.

In recent years, with my country's encouragement and promotion of research and innovation in pediatric medicines, children's...

Clinical trials of pediatric drugs are gradually increasing. Children's physical, physiological, and psychological development is...

It is a dynamic process of drug absorption, distribution, and metabolism after entering the body.

And excretion, as well as response to drugs, may differ significantly between adults and children.

This determines that pediatric subjects may face different challenges than adults in clinical trials.

Other safety risks necessitate special pharmacovigilance assessment for pediatric clinical trials.

To better protect child participants, this guideline aims to provide consideration.

General principles and special considerations for safety information assessment and reporting in pediatric clinical trials

Considerations, etc., provide for the monitoring, identification, assessment and control of safety risks in pediatric clinical trials.

For reference only. In this guideline, unless otherwise specified, "children" refers to individuals aged 18 and under.

Adolescents under the age of 18 and children under the age of 18 (including)

Premature newborns, full-term newborns, infants, and children [1]). Due to the children's part

Major diseases such as congenital diseases, tumors, and rare diseases require continuous treatment.

Alternatively, long-term follow-up may be conducted, or current national policies and actual clinical practice may be considered.

The upper age limit for subjects in pediatric clinical trials should be appropriately relaxed.

This guideline applies to traditional Chinese medicine, chemical drugs, and biological products (preventive use).

(Except for pharmaceutical products). When designing and conducting clinical trials using this guidance, it is necessary to consult with...

Reference was made to the Good Clinical Practice for Drug Clinical Trials [2] (GCP) and the International Code of Human Use.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals (ICH) and other relevant guidelines already issued in China.

in principle.

This guidance only represents the current views and understanding of drug regulatory authorities and is not intended to be construed as such.

It has mandatory legal binding force. As scientific research progresses, this guideline...

The relevant content in this document will be continuously improved and updated.

II. Overall Considerations

(I) Basic Principles

High-quality pharmacovigilance is a fundamental component of any clinical trial program.

In pediatric clinical trials, pharmacovigilance must adhere to the pharmacovigilance guidelines in clinical trials.

A basic requirement is that sponsors should comprehensively collect safety data during pediatric clinical trials.

Information and conduct risk monitoring, identification, assessment and control.

Conducting clinical trials of drugs in children requires thorough ethical considerations and should comply with relevant regulations.

The principles of scientific necessity, maximum benefit, and minimum risk should be followed. If adult clinical...

Trial data can be extrapolated to children or exempted from pediatric clinical trials to conduct adult clinical trials.

The trial aims to minimize exposure in pediatric populations during clinical trials. Based on existing...

Clinical and/or non-clinical safety data, expected participation of pediatric populations in clinical trials

It should provide the greatest benefit and eliminate any potential harm, pain, or discomfort.

Reduced to the minimum.

(ii) Informed consent

When children participate in drug clinical trials as subjects, GCP (Good Clinical Practice) should be strictly followed.

The basic requirements of the relevant clauses.

Generally, children aged 8 years and older are eligible to participate in the trial.

The individual has the capacity to make a decision on whether to consent to participation in a clinical trial, after obtaining the consent of their guardian.

In addition to obtaining the consent of the individual, their consent should also be obtained and they should sign an informed consent form.

Subject to compliance with current laws and regulations, it is recommended that informed consent forms, etc., be included.

The research document requires the consent and signature of any one or all guardians.

Informed consent forms are prescribed and explained, and approved by the ethics committee (EC).

In the process of obtaining informed consent from the child's guardian, in addition to clearly informing them of the trial...

In addition to assessing the expected benefits and risks, special attention should be paid to the guardian's awareness and emotions.

To avoid them making decisions about whether to participate in clinical trials under inappropriate mental conditions.

The decision[3].

(III) Responsibilities of Each Participating Party

As the responsible party, the sponsor should bear full responsibility for pediatric drug clinical trials.

The development and implementation of biosecurity activities. Clinical trial institutions, researchers, ECs, and recipients.

All participating parties, including test subjects and their guardians, shall assume their respective responsibilities and work together to carry out drug surveillance.

Abstinence activities. In clinical trial protocols, investigator brochures, and informed consent forms, etc.

In the process of developing documents related to clinical trials, scientific advancements and the latest theoretical knowledge should be taken into account.

Based on knowledge, consideration should also be given to all stakeholders, including researchers, participants, and others.

The opinions and suggestions of their guardians (if necessary), academic experts, etc. Through drug warning...

The effective implementation of abstinence activities requires thorough evaluation to ensure minimal risks.

To minimize the risks of children participating in drug clinical trials.

Ensuring the safety of subjects is the most important principle in pediatric drug clinical trials.

Regarding sexual issues, the sponsor should begin implementing safety risk management no later than clinical trials.

The start time of the trial. At the same time, the sponsor decides under what conditions to conduct or

Safety factors should be the primary consideration when deciding whether to continue clinical trials for pediatric drugs.

And it is unaffected by other factors. Therefore, in the design and planning stage of clinical trials,

Applicants should aim to gather the necessary expertise and relevant information, in order to ensure security.

Develop optimal clinical trial protocols based on sex. Sponsors are encouraged to [do something] early in the research and development process.

Develop a preliminary clinical risk management plan, which should include at least the important existing risks.

Preliminary information includes identifying risks, significant potential risks, and important missing information.

And plans and measures for managing risks during clinical trials. As the trials progress...

The applicant should evaluate and update the progress as needed.

Encourage adequate and sound clinical trial procedures for guardians of child participants.

Provide relevant guidance to ensure that during participation in clinical trials, especially at clinical trial institutions...

In settings other than the institution or during long-term follow-up, they possess the basic ability to cope with adverse events.

In particular, serious adverse events (SAEs).

III. Safety Risks Requiring Special Attention in Pediatric Clinical Trials

The safety risks in clinical trials of drugs in children are unique compared to other populations.

Sexuality. For a specific target indication, the onset of the disease in children may be of a different nature and process.

The degree of benefit differs from that in adults, which can affect the benefit or risk profile of the subjects, and thus...

Altering the benefit-risk balance of medications for children. For chronic diseases requiring long-term treatment.

The likelihood of adverse reactions in pediatric subjects is affected by their age and

The influence of growth and development stages. Furthermore, the dosing regimen should be considered during the development of the dosing regimen.

Changes in weight, body shape, and body composition in children of different ages

Feature [4].

Based on current understanding, extrapolation from adult clinical trial data is not always possible.

Obtaining safety data for children usually requires relying on data from children themselves.

Clinical trials conducted [5]. When developing pediatric indications, references can be made to the clinical trials conducted in adults.

The security data obtained from the group, however, in the actual research and development process, on the one hand, regarding...

For experimental drugs that will be tested in children throughout the entire research and development process, such as primary drugs...

For experimental drugs specifically designed for children, adult safety data can be referenced.

The safety profile may be limited; on the other hand, the safety for adults may differ from that for children.

These differences will pose certain challenges to ensuring the safety of child participants.

(a) Important missing information

In some therapeutic areas, pediatric clinical trials are often difficult to conduct or progress slowly.

The research is slow, faces practical difficulties such as enrollment challenges and high dropout rates, leading to decreased research efficiency.

The research information may be reduced or insufficient. Among these, the lack of important information will...

This poses additional safety risks to pediatric clinical trials; sponsors may consider this in conjunction with specific product safety considerations.

Risk assessments were conducted based on species and subject population characteristics. Safety risks related to missing information were also assessed.

The main risks are:

1. The number of clinical trials in pediatric populations is generally small, and the existing safety data is limited.

Based on whether to support conducting new clinical trials;

2. Do the pharmacokinetic data or dose-response studies support this?

Rational use of investigational drugs in children of relevant age subgroups, avoiding investigational drug doses

Too high or too low a dose. Too low a dose may result in insufficient reach of the effective dose or the development of tolerance.

Drug properties; excessive dosage may lead to type A reaction [6] (dose-related adverse reactions).

The incidence rate increased;

3. Are routinely collected safety data sufficient to indicate adverse events in pediatric subjects?

Potential safety signals;

4. The suitability of different dosage forms and tastes for children of different age groups may vary.

Differences may exist, and applicants should assess their reasonableness to avoid applying for unsuitable programs.

Issues such as dosage form and taste may lead to incorrect dosage or local drug concentration.

Excessive levels can cause localized adverse reactions.

(ii) Adverse reactions specific to children

Existing safety data for adults or other populations can be used for children.

Risk monitoring and identification provide a reference. However, existing data can only provide partial information.

Potential safety information regarding the use of certain medications in children.

The adverse reactions observed in this group require special consideration from the applicant. This applies to this specific group of children.

Specific adverse reactions, mainly related to organ systems (such as skin, respiratory tract, kidneys, etc.).

It is related to the maturation, metabolism, growth, and development of the liver and blood-brain barrier. Special attention is required.

The security risks of particular concern include:

1. Pharmacokinetics and pharmacodynamics of drugs in children may differ from those in adults.

They may be more prone to adverse reactions and have different drug interactions.

feature;

2. Due to the influence of certain excipients, children may experience symptoms that are not present in adults (or...).

Adverse reactions (to varying degrees);

3. Different types or degrees of adverse reactions may be associated with different age groups in children.

For group-related cases, appropriate clinical risk management plans should be developed, and maternal factors should also be considered.

Risk factors for intrauterine exposure, especially for young children;

4. Due to being in the growth and development stage, children's growth and development are prone to [unclear - possibly related to growth and development].

Susceptible to drug-induced effects, or delays not observed in adults.

Adverse reactions. Long-term follow-up data is needed to determine the effects of the investigational drug on bone health.

Poor development and maturation of organs such as the skeleton, behavior, cognition, sex organs, and immune system.

Influence;

5. During critical periods of development, children may be exposed to drugs.

It has permanent effects on the body. Regarding the chain reactions induced by the above-mentioned drugs, [the following should be considered]:

Special consideration should be given to fetal or neonatal age subgroups;

6. Some adverse reactions may only occur in children, but their impact on life is minimal.

Growth and development may not be affected at present;

7. Children with chronic diseases, especially those requiring lifelong treatment.

In cases of treatment, long-term use of medication increases the risk of adverse reactions in subjects.

(III) Other Risks

Pharmacovigilance is crucial throughout the entire drug lifecycle, and limited sample size in pediatric clinical trials is a significant factor.

The size and target population limit the release of investigational drug safety signals during clinical trials.

The identification of rare serious adverse reactions (SARs). Therefore, in clinical practice...

Before commencing a trial, the sponsor should gather as much information as possible about the existing safety data for the investigational drug.

Sexual information, especially adverse reactions already identified in other populations, and in clinical practice

The test protocol should list specific measures to be taken for serious or specific adverse reactions.

Measures and the timing of taking them.

In addition, applicants are advised to investigate any missing data, especially security data.

Regarding drug exposure time, number of subjects, age range and age subgroups, and target...

Risk assessments should be conducted across key dimensions such as indications, and these risks should be incorporated into early clinical risk management.

The plan should clarify the potential risks of the investigational drug to pediatric subjects and formulate corresponding treatment plans.

Appropriate safety data collection strategies and risk control measures should be implemented during clinical trials.

For pediatric subjects, special consideration should be given to whether long-term follow-up is necessary.

The effects of investigational drugs on children can be fully evaluated by combining results from non-clinical studies.

Periodic effects, including impacts on growth, development, and organ/system functional maturation; this

In addition, attention should be paid to whether experimental drugs and participation in clinical trials affect psychological development.

It has an impact.

IV. Safety Assessment and Reporting During Pediatric Clinical Trials

In accordance with the requirements for pharmacovigilance during clinical trials, sponsors may refer to existing guidelines.

The published technical guidelines take into account the unique physiological characteristics of children.

Safety information assessment during pediatric clinical trials (including post-marketing studies)

And management work.

(a) Risk Management Plan

Sponsors are encouraged to develop clinical risk management plans as early as possible in the initial stages of drug development.

Planning. Taking into account the specific characteristics of the child population, measures are being taken to reduce adverse reactions in the adult population.

The risk control measures were assessed and adjusted to make them suitable for pediatric subjects.

During the research and development process, it is continuously evaluated and updated to inform the formulation of the listing application.

This provides a reference for clinical risk management plans at that time.

We recommend considering supporting non-clinical studies for pediatric drug development as early as possible. Based on non-

Clinical data and toxicology data from juvenile animal studies can predict the safety of pediatric subjects.

Full risk; for clinical data, research data obtained in adult populations should support [the findings].

Identify and describe important potential risks and overall safety in pediatric subjects.

Characteristics and measures to mitigate risks. Safety information available for different drugs.

The differences can be significant. For example, a drug may only be approved for use in pediatric trials or...

When simultaneously approving clinical trials for both adult and pediatric subjects, it may be due to prior...

There is no clinical or real-world data in adults. Conversely, if the investigational drug receives approval...

Prior to conducting clinical trials for pediatric indications, a large number of studies had already been conducted in the adult population.

Based on research data or post-market experience, there is relatively more available safety data.

Safety and risk considerations derived from existing research information can help applicants.

The organizers and researchers decide whether it is necessary to take special risk control measures.

To identify and characterize the risks to pediatric subjects, sponsors are advised to consider the following:

The following aspects will be analyzed in detail:

1. Changes in drug-target organ or tissue interactions with age;

2. The impact of individual development on the absorption, distribution, metabolism, and excretion of active ingredients.

Impacts, including the effects of individual structural changes on their management (such as the blood-brain barrier).

3. Different metabolites and different levels of exposure lead to different potential effects than in adults.

Adverse reactions;

4. Long-term effects on the development of vital organs and tissues;

5. The known pathogenesis of adverse reactions and its impact on immune system maturation.

And its impact on the transition from maternal passive immunity to the maturation of the infant's immune system.

The above analysis can help sponsors assess the drug's effectiveness in pediatric populations.

Does the risk of adverse reactions differ from that in the adult population, and are its pharmacological characteristics different?

This suggests a developmental risk. Similarly, if it is speculated that a child population or its specific characteristics pose a risk...

Specific age subgroups (e.g., post-adolescent children, those over a certain age or...)

When the safety risks to children (of similar weight) are no different from those to adults, [the following should be provided]:

Supporting evidence. After analysis and assessment, if significant child safety risks are identified and...

For safety issues in the clinical risk management plan, post-marketing safety assessments should be considered.

Safety studies have verified this.

(ii) Individual security reports

The completeness of Individual Security Reports (ICSRs) is crucial for signal identification and risk assessment.

Control is of great importance. Given the unique characteristics of pediatric subjects, primary attention should be paid to...

Age information of the subjects. The report should record the age information of child subjects in detail.

Information should be accurately and correctly filled into the corresponding element fields, and should also be included in the event description.

For example, the number of days since a newborn's birth, the age in days or months of an infant, etc.

Children's and adolescents' ages in months or years, etc. In addition, ICSRs should specify the recipient's age as much as possible.

Age of the test subject at the time of adverse event/adverse reaction. For premature infants and newborns.

For infants, gestational age information should also be provided in the report. If the sponsor bases its decision on data preservation...

If specific age information cannot be obtained or provided due to guardianship or other reasons, then at least...

Please specify the corresponding age subgroup. If the applicant fails to provide or accurately and completely fills out the form...

When age information or related fields are entered, regulatory agencies may request follow-up visits as appropriate.

Applicants are required to complete the relevant fields of information. Individual developmental stages of children.

The degree of variation is significant, especially when adverse reactions are associated with them. Therefore, among ICSRs...

It should also include information on important developmental milestones of the subjects (such as prematurity, puberty) as much as possible.

(This includes developmental stages, critical stages of cognitive and motor development, etc.). Meanwhile, parents during pregnancy...

Drug exposure during pregnancy or during pregnancy, or transmission of drugs to newborns and infants through breast milk.

Adverse reactions may also occur due to drug exposure, and sponsors should pay attention to this.

Furthermore, in accordance with the requirements of ICH E2B(R3) and regional implementation guidelines, ICSRs

Information such as drug indications, dosage form and strength, and administration dosage should be provided as comprehensively as possible.

Information such as dosing frequency, dosing cycle, and the child's physical condition when adverse reactions occur.

Weight and height (length) information. This information directly affects the assessment quality of ICSRs.

quantity.

For the safety assessment of ICSRs during clinical trials, comparison with adults should be considered.

The expected differences between them, focusing on medical events particularly relevant to children, namely

Compared to adults, pediatric subjects experienced more severe and frequent occurrences of [unspecified symptoms].

Adverse reactions. The nature and severity of adverse reactions in pediatric subjects were related to the organs involved.

This is related to the level of maturity; applicants are encouraged to use appropriate methods to identify adverse reactions.

It should be correlated with age subgroups. If the number of participants and information are sufficient, it should be correlated with age subgroups.

Subgroup-based stratified analysis of ICSRs helps to obtain more security information.

It is recommended that applicants employ staff with pediatric-related specialties or experience.

Conduct the review and processing of ICSRs for children.

(III) Safety Update Report During Research and Development

After a pediatric drug is approved for clinical trials, the sponsor should comply with ICH E2F.

The requirements of the Research and Development Safety Update Report (DSUR) and regional implementation guidelines

Request the writing and submission of DSUR reports on drug-related data collected during the reporting period.

A comprehensive annual review and evaluation of safety information is conducted to assess the benefits of the investigational drug.

- Risk balance is continuously monitored.

DSURs should clearly state whether they were found in children or different age subgroups.

New safety concerns apply not only to pediatric subjects who have been approved for use, but also to...

Drugs used in assessments of data from other populations related to pediatric subjects

Property safety information. This mainly includes the following two scenarios:

1. Off-label use of medication, including using medications that are not appropriate for the age of the study population.

Dosage forms or investigational drugs used in unapproved pediatric age subgroups;

2. Identified adverse reaction signals associated with children.

DSUR should address drug exposure levels in children and different age groups during the reporting period.

Subgroup subject/patient exposure status and methods for calculating or estimating exposure data

Please provide an explanation.

Regulatory agencies may require sponsors to make adjustments based on the risks associated with the investigational drug.

The reporting cycle of DSUR, or the sponsor's suggestion to adjust the reporting cycle, and

An agreement was reached with regulatory authorities.

(iv) Post-market safety studies

Safety data for pediatric drugs is usually limited when they are approved for marketing, therefore,

Post-marketing safety studies are an important supplement to pre-marketing clinical trials of pediatric drugs.

The regulatory body may also require applicants to conduct post-listing procedures based on the review results.

Safety studies. Sponsors conduct post-marketing safety studies in children or...

Including pediatric subjects in post-marketing safety studies is of great significance, especially

In the following cases:

1. The effects of investigational drugs on children's development may occur several years after drug exposure.

Only then did it become apparent;

2. The development of pediatric drugs or indications for children relies primarily on adults or children.

Extrapolation of subgroup validity data;

3. Safety data for long-term medication is needed, especially for patients with...

Innovative mechanisms of action and/or expected effects in infants and young children (i.e., newborns, infants, and children aged 6 years and older)

Medications used long-term in children;

4. Children are more likely to use medications off-label, which may lead to complications.

Biosafety issues.

Sponsors are encouraged to plan for market launch as early as possible, while simultaneously defining their clinical development plans.

Post-market security studies are crucial for integrating data obtained before and after market launch.

The collected data provides valuable support. Once a drug obtains marketing authorization, [the process can begin].

Post-market research allows for faster resolution of safety issues that arise before market launch.

Sponsors may refer to the relevant requirements of the "Good Manufacturing Practice for Pharmacovigilance" and combine them with...

Post-marketing safety studies should be designed in a way that takes into account the characteristics of children.

(v) Security Information Communication

With the continuous improvement of laws and regulations, children, as subjects, are increasingly being used in clinical treatment.

The impact of treatment decisions is growing. For example, GCP stipulates that when children are capable of doing so...

When issuing a decision to allow participation in a clinical trial, the individual's consent should be obtained. Therefore,

It is necessary to consider children's information comprehension and processing abilities, as well as their interests and hobbies.

Adjust the way clinical information is presented to pediatric subjects. Safety information communication.

Communication-based risk control measures should consider different target audiences, such as children.

Doctors, guardians, and child participants, through effective communication, ensure...

Subjects with disabilities should select appropriate clinical studies and actively participate in pharmacovigilance activities.

Based on the characteristics of pediatric participants, it is recommended that sponsors base their research on existing information.

The following should be explained as appropriate in the researcher's handbook, informed consent form, and other clinical trial-related documents.

question:

1. Recommendations for the proper use of investigational drugs;

2. The effects of the investigational drug on school attendance and physical activity;

3. The interaction between the test drug and other pharmacologically active substances such as alcohol.

Interaction;

4. Risk of administering the investigational drug to others.

Children's preferences for information media differ from adults'; they prefer illustrations, comics, and visual media.

Information carriers and tools that are age-appropriate may be more beneficial to children.

Understanding of relevant information. Additionally, when developing risk control measures, it is recommended that...

Sponsors are considering how to integrate this into the daily lives of child participants, and

How can we make it more acceptable and accurately reflect the severity of the risk in an appropriate manner?

degree.

Safety information communication or educational materials should help researchers and children.

The examinee and their guardian should discuss and explain the specific risks. If applicable, this should also include...

Recommendations addressing common sensitivities and concerns, such as the effects of experimental drugs on reproduction,

Growth and development, cognition, potential long-term safety effects, and the occurrence of pregnancy complications.

Measures for handling items, etc.

(vi) Communication and Exchange

Regarding safety risks and related issues that arise during drug clinical trials,

The scientific validity and feasibility of post-market safety research methods, and clinical risk management.

Plans, etc., encourage sponsors, clinical trial institutions, and other participants to refer to the "Drug Research and Development Guidelines".

The "Administrative Measures for Communication and Exchange between the Development and Technical Review Departments" and other relevant regulations and regulatory agencies

Promote communication and exchange[7].

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