罕见病基因治疗产品临床试验技术指导原则

（试行）

国家药品监督管理局药品审评中心

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1. Overview

Rare diseases generally refer to rare diseases or rare diseases, which are different from common diseases.

Diseases and frequently occurring diseases are a large group of different diseases scattered across various disease systems.

There is no unified definition of rare diseases in the world.

The meaning is usually expressed in terms of incidence, prevalence or number of patients.

The Disease Definition Research Report 2021 defines rare diseases in my country as “neonatal onset”

The prevalence rate is less than 1/10 000, the disease prevalence rate is less than 1/10 000, and the number of patients is less than 140 000.

A disease that meets any one of the above criteria is considered a rare disease.

Rare diseases are managed in the form of a rare disease catalog.

In September, China’s National Health Commission and other ministries jointly released the “First List of Rare Diseases”

and the Second Batch List of Rare Diseases, which include 121 and 86 types of rare diseases respectively.

As of January 2024, there are 1,000 registered diseases in the China National Rare Disease Registry.

176 types/categories. The U.S. Orphan Drug Act defines a rare disease as a disease that has accumulated in the United States.

Health Canada defines rare diseases as those that affect fewer than 200,000 people.

Life, severe debilitation, or severe chronic illness, and only affects very few patients

(usually less than 5 per 10,000 people).

About 80% of rare diseases are caused by single gene defects. Gene therapy is a treatment

One of the important means of treating rare diseases.

Gene therapy products are products that modify or manipulate gene expression or change

The main function of the product is to utilize the biological characteristics of living cells to achieve therapeutic purposes.

Mechanisms include replacing disease-causing genes with normal genes, disabling genes that do not function properly,

Gene therapy products include

DNA, RNA, genetically modified viruses, bacteria or cells, and gene-based

Gene therapy products used to treat rare diseases

Consider treating the cause of the disease in order to achieve permanent or semi-permanent cure of the disease.

At present, the gene therapy products under development in China are mainly focused on neurological diseases,

Metabolic diseases, blood diseases, eye diseases and other fields.

This guideline will combine the characteristics of rare diseases and gene therapy products.

Provide suggestions for the clinical development of gene therapy products for rare diseases and provide

Provide reference for clinical trials of medical products.

This guideline is intended to provide guidance for

The implementation of gene therapy in accordance with the Drug Registration Management Measures and other laws and regulations related to drug management

Provide sponsors of gene therapy product development and registration applications with information on gene therapy products

Technical recommendations for clinical trials of rare diseases, the content of which is not mandatory.

In addition, applicants should also refer to the common regulations and requirements for clinical trials.

According to the Good Clinical Practice (GCP) and International

The relevant guidelines issued by the International Committee for Harmonization of Technical Documents (ICH) and other related guidelines issued in the past at home and abroad.

The principles that need to be followed in general drug clinical trials and other guiding principles

The repeated content will not be repeated in this guideline.

The opinions expressed in this guideline represent only the current understanding of gene therapy products.

The general understanding of clinical trials for rare diseases cannot cover the problems encountered in new drug development.

As medical science and clinical trials progress, this guideline

The relevant contents will be continuously improved and updated.

Based on the principle of specific analysis of the topic, the data obtained from non-clinical studies and previous relevant

The research results of varieties, scientific design of clinical trials, timely improvement of experimental design and

Risk management plan. Start clinical trials of gene therapy products for rare diseases

Before the application, it is recommended that the applicant communicate with the Center for Drug Evaluation on the clinical development plan and clinical trial method.

This guideline aims to propose clinical guidelines for gene therapy products for the treatment of rare diseases.

Technical guidance generally applicable to clinical trials. For issues not covered,

The applicant actively communicates with the regulatory authorities.

2. General Considerations

It is essential to conduct clinical research on the proposed indications.

To understand the main disease population, pathogenesis, incidence/prevalence,

Diagnostic methods and their accuracy, clinical manifestations/characteristics, and treatment status, diseases

Prognosis, unmet clinical needs, etc., to obtain relatively sufficient clinical data on the disease.

The clinical status of rare diseases can be analyzed through natural history studies, patient registration platforms,

The data were obtained through clinical staff surveys, literature reports, etc.

Identify relevant and specific biomarkers as early in development as possible

and make full use of rare diseases (or related diseases) whose target indications have been made public

Some biomarkers or clinical endpoints are related to the pathogenesis of rare diseases.

closely related to physiology, such as missing metabolites in key biosynthetic pathways,

In this case, changes in biomarkers can be used to guide dose selection.

It can indicate the activity of gene therapy products.

III. Key points of clinical trial design

In the clinical development of gene therapy products for the treatment of rare diseases,

It is recommended to consider the following key factors:

1. Subjects

The selection of subjects for clinical trials of rare diseases should be based on existing non-clinical

Applicants should consider the clinical and clinical data to select appropriate study populations.

Whether the subject population is suitable for proving the effectiveness and safety of the product.

When selecting subjects with different disease severity, it is necessary to comprehensively consider the patient's

Benefit-risk ratio and whether the adverse reactions of the product can be adequately collected in the target population.

Subjects with severe or advanced rare diseases may have clinical manifestations of their rare diseases.

Confusion with adverse reactions caused by gene therapy products.

Subjects may benefit more from treatment, but those with more advanced disease may

Clinical needs are stronger. Applicants can choose according to the characteristics of gene therapy products.

Suitable population, and it is recommended to first select the product with better benefit-risk in the early stage of product development

Conduct clinical trials on a larger population.

Gene therapy products may produce permanent unintended effects on healthy people

There are potential long-term risks. In addition, gene therapy products may require

Deliver products to specific locations in the human body through invasive procedures, such as under the retina

Intracavitary injection, intracranial administration, intrathecal injection, etc., may cause adverse reactions during the operation.

Especially when delivering products to relatively sensitive sites such as the central nervous system

At this point, invasive procedures will bring greater risks to the overall treatment.

Therefore, clinical trials of gene therapy products for rare diseases usually do not include healthy subjects.

Generally speaking, adult subjects are selected first in clinical trials, but

Most rare diseases are diagnosed at a younger age, so children are included in the rare disease gene panel.

Ethical and regulatory factors need to be considered when conducting clinical trials of therapeutic products.

If the first human trial is planned to be conducted in children, the basis for the topic should be clearly stated.

Fully assess safety risks.

Rare diseases with avoidable serious complications or death may be considered for early diagnosis and treatment at a younger age.

Conduct clinical trials.

For rare diseases caused by gene defects, the applicant should conduct relevant

Related gene testing helps to recruit the correct test population.

Disease can be caused by deletion or functional mutation at different sites.

Therapeutic products may show different safety profiles in patients with different genotypes.

Therefore, early understanding of this situation can help design clinical trials.

If there is a lack of effective genetic diagnostic methods, gene therapy products will not be targeted at different

If there are differences in efficacy among patients with genotypes, it may be necessary to develop companion drugs in the early stages of research and development.

Depending on the diagnostic method.

Pre-existing antibodies to any component of the gene therapy product may be

Potential risks to patient safety and product effectiveness.

Antibodies against gene therapy products produced after treatment may affect

It is necessary to consider the development of pre-existing antibodies and gene therapy products.

Companion diagnostic methods for antibodies to guide medication for target populations.

2. Study Design

In clinical trials of gene therapy products for rare diseases,

The number of cases is small, and the number of patients who meet the inclusion criteria is limited.

Therefore, it is recommended that

During the development phase, sufficient data on each subject should be collected, including adverse events, treatment efficacy outcomes, biomarkers, etc. These data may have implications for the design of subsequent studies. For example, the choice of study population and endpoint is of great significance.

Consider the following:

(1) Randomized controlled trials are generally considered to be the most effective way to determine effectiveness and safety.

Standard design. Encourage clinical trial development of gene therapy products for the treatment of rare diseases Randomized controlled designs are used in the early stages (including first human trials).

If feasible, placebo control is recommended to better analyze safety

If there are multiple dose groups, consider

Some subjects were randomly assigned to receive a placebo.

In order to better analyze the clinical trial data of gene therapy products in rare diseases

Distinctions among patients with different stages or severity levels may be considered by the applicant based on disease

Randomization was stratified by stage and severity.

(2) Some rare diseases involving specific organs or targeting specific organs

For genetic therapy of hereditary skin diseases, the subject's own

Control design. This design avoids the possibility of subject

If the gene therapy product has a local therapeutic effect,

It may be more appropriate to use a self-control.

(3) If it is difficult to conduct a randomized controlled trial, alternative approaches such as single-arm trials may be considered.

The single-arm trial should also set up reasonable controls, such as using

Historical data serve as external controls. In this case, understanding the disease

Natural history is crucial. Data on the natural history of disease can provide a basis for the appropriate setting of historical controls.

Provides a basis, but the premise is that the historical control population and the test population are demographically,

Concomitant treatment, disease status, and other relevant factors should be as consistent as possible.

Situations where randomized controlled trials are not feasible but adequate data on the natural history of the disease are available

In such cases, applicants may consider clinical data for rare diseases based on existing treatments (e.g.

If adequate disease

For natural history data, an introduction period may also be considered.

(4) When the number of subjects is small, the clinical stages and physiological conditions of the subjects are different.

When there is a large difference in the status of the subjects, consider using a trial that can make full use of the limited subject data.

Design and statistical methods. For example: A clinical trial uses a

The degree of change of clinical indicators in the natural development process is used as the evaluation standard.

It helps to interpret the results of clinical trials with small sample sizes and to control the sample size.

to the extent feasible.

(5) Clinical protocols should take measures to minimize bias, such as setting up blinded

The clinical outcomes were evaluated by an independent committee.

3. Dosage regimen

When designing a clinical trial for a rare disease, all available sources of information (e.g.

Such as: non-clinical research data, published research results, experience with similar products,

experience in relevant patient populations) to guide dose selection, dosing intervals, and other aspects of gene therapy products.

Provide the basis for each interval.

Make full use of non-clinical research data (disease animal models and in vitro studies),

In some cases, evaluation of nonclinical study data may be an estimate of the initial efficacy in humans.

The only way to determine the dosage is to use in vitro enzyme kinetic studies and other relevant models.

Obtain additional information to guide dosage selection.

For patients with serious or life-threatening rare diseases

In early clinical trials, ideally, the starting dose should be a potentially effective dose.

The optimal therapeutic dose will then be determined through exploration.

If the gene expression or efficacy of a single dose of a gene therapy product changes over time

Repeated administration may result in an enhanced immune response.

In this case, it is necessary to study the immunogenicity and clinical

relationship with clinical performance (e.g., decreased effectiveness, increased safety risk),

Clarify the benefit-risks of repeated dosing.

4. Effectiveness evaluation

Evaluating the effectiveness of gene therapy products through clinical trials should comply with drug research

In some cases, when evaluating the clinical benefit of gene therapy products,

Gene therapy products require additional consideration before and after marketing.

Characteristics, for example: the biological activity of the protein expressed by the gene therapy product may be different from

Biological activity of enzyme replacement therapy in the traditional sense.

If there is no clear specific efficacy endpoint for a rare disease,

Consider the following factors:

(1) The applicant should fully understand the rare

The pathophysiology and natural history of the disease will help determine the primary efficacy endpoint

points and may also help select potential surrogate endpoints with clinical significance.

(2) If an alternative endpoint is used to apply for marketing approval, the applicant should provide sufficient

Data to support the relevance of surrogate endpoints to clinical benefit.

(3) The applicant should determine whether the treatment is meaningful to patients with rare diseases and whether the treatment is beneficial to patients with rare diseases.

A clear clinical benefit resulting from the therapeutic product.

(4) Through continuous clinical evaluation and monitoring of subjects,

Changes in symptoms and signs of subjects before and after treatment.

(5) Encourage patients to participate in R&D. Patients' opinions should be included in all aspects of drug development.

Its significance and value can be reflected in all stages.

Problem formulation, overall R&D plan, before clinical trial starts, during clinical trial implementation

Patients can be included in the whole process of clinical trials and after completion of clinical trials.

Patient experience data can provide other information related to the clinical benefits of gene therapy products.

Important information: Encourage the use of patient-reported outcomes in rare disease drug development

Patient-reported outcome (PRO) is a measure of the impact of a drug on the health of patients with rare diseases.

Improvement of quality of life, experience and its clinical value, and use PRO as the main end point

The development of PRO scales and their methodological validation are encouraged.

PROs may also be considered as one of the primary endpoints or a key secondary endpoint.

Communicate with regulators the feasibility of using PROs as primary endpoints to support regulatory decisions

Action nature.

5. Safety evaluation

Content and timing of safety evaluation of clinical trials of gene therapy products for rare diseases

The timing should be based on an understanding of the patient's disease and the gene therapy product, including dosing

Frequency, nonclinical studies and pharmaceutical information, and proposed or related products

Previous human experience (if applicable).

The acceptable toxicity or severity of adverse reactions of gene therapy products requires

The applicant should make a judgment based on the severity of the rare disease and the expected benefit-risk.

The methods of exploration should be clearly defined in the research protocol.

Gene therapy products usually remain in the human body for a long time after administration, causing

Permanent or long-term changes in the body can achieve therapeutic effects, but they are also accompanied by long-term

Safety risks, such as uncontrolled gene expression affecting normal physiological functions of the human body

and metabolism, gene integration may activate or inactivate adjacent genes, resulting in adverse

Therefore, in order to evaluate safety, it is necessary to conduct

Long-term follow-up observation should be carried out. Factors to be considered in long-term follow-up observation include genomic integration activity

long-term expression, unexpected biodistribution, immunogenicity, gene therapy products

Potential effects of the product on reproduction, shedding and transmission, hematopoiesis, immunity, and neurology of the subjects

Adverse reactions of the nervous system, serious adverse reactions related to tumors, etc.

Long-term follow-up plans should be developed based on product characteristics and disease information.

It is recommended to refer to relevant guidelines for specific content requirements of test technical evaluation.

For gene therapy products that integrate into the genome, nonclinical studies should be provided.

The data on insertion sites, clonal amplification, etc. in the study were also referenced to similar varieties.

It is recommended to monitor the insertion site, clonal expansion, etc. when technically feasible.

For example, when transducing hematopoietic stem cells with an integrating vector, this type of

monitoring.

6. Statistical considerations

In principle, the sample size of the pivotal study design for rare disease drugs should be based on

Statistical relevance principles are determined based on the statistical assumptions for the primary endpoint.

For data analysis, statistical methods corresponding to the design should also be selected.

See Statistical Guidelines for Clinical Research of Disease-Drugs.

7. Immunogenicity studies

For one or more components of a gene therapy product (e.g., vector, target

Innate or adaptive immune responses to proteins may affect the safety and

Effectiveness. Early development of assays to detect pre-existing antibodies and targeted gene therapy

The antibodies of the product are helpful to enroll the correct population and understand the production and safety of antibodies.

The correlation between safety and effectiveness is crucial to product development.

Antibody production was monitored during clinical trials.

8. Pharmacokinetic and pharmacodynamic studies

Determining the persistence of gene therapy products and the duration of their activity is also

An important part of the clinical trial evaluation of gene therapy products.

Evidence of the presence of the vector or virus in fluids, tissues, or cells to assess the persistence of the product

by looking for physiological effects (e.g., target protein expression, biomarkers

These evaluations can be done by sampling from the site of administration.

or the expected site of expression, or biological fluids carrying the virus, such as:

Urine, tears, etc.

It is recommended to pay attention to the clinical sample collection method, sample collection frequency and monitoring cycle

Explore the relationship between pharmacodynamic indicators and efficacy endpoints to better

Better guide the research and development of gene therapy products.

9. Combined medication

Clinical trial subjects may continue to use

The drugs used are used to treat concurrent diseases or the rare disease itself. For example, stopping the drug may

Can cause significant risks. If the combined drug does not affect the safety of gene therapy products

If the drug's efficacy and safety are not determined, the marketed drug can continue to be used.

Doses are recommended to be taken regularly over a specific period of time (e.g. until the primary efficacy determination

period of time) and described in the clinical protocol.

IV. Risk Management

Risk management of gene therapy products for rare diseases should be integrated throughout the product

Life cycle, combined with the mechanism of action, route of administration, non-clinical

Safety information and known safety information of similar products, and formulate detailed risk management

Management measures and strict implementation.

1. General considerations for risk management of gene therapy products for the treatment of rare diseases

Develop disease-specific clinical trials based on findings from studies of the natural history of the disease.

Heterogeneous risk control measures, timely optimize risk control when new discoveries are made in research

measure.

Clinical trials of gene therapy products for rare diseases should be conducted in

The clinical trials should be conducted in research centers with rich experience in diagnosis and treatment, especially when the clinical trials include

High-risk groups, such as patients with rapidly progressive and life-threatening rare diseases, have been included

It is recommended to organize a multidisciplinary team to carry out risk management.

Gene therapy products themselves and the proteins they express may induce local

or systemic immune response (including innate immune response and/or adaptive immune response)

A), this immune response can lead to inflammation, a significant reduction in gene expression in the body and even

disappearance, transduction cell destruction, resulting in adverse reactions, such as autoimmunity

Sexual diseases, hepatotoxicity, etc. The applicant uses the detection method developed in the early stage of drug development

Methods were used to monitor the immune response of the subjects.

For subjects with

Assess the possible correlation between the event and immune response.

Due to the potential impact on the safety of therapeutic products, the subjects may be

To reduce the impact of immune response on the safety and

In clinical trials, if immunosuppressants such as glucocorticoids are used,

Preparations, adverse reactions during use of subjects should be closely monitored.

Gene therapy vectors may have target organ toxicity, such as some adeno-associated diseases

Adeno-associated virus (AAV) vectors are hepatotoxic.

It is recommended that the applicant determine the product based on the non-clinical research experience and clinical research experience of similar products.

Toxicity target organs and major toxicity target organs of the determined vector, adverse reaction types and diseases

characteristics of the organ in order to develop risk control measures for specific organs during clinical trials

Applicants can limit the inclusion and exclusion criteria to exclude products that may cause target organ toxicity.

high-risk population for sexual intercourse and closely monitor the organ function during clinical trials.

Take targeted treatment measures to control risks when necessary.

It is recommended to explore the virus excretion characteristics in the early stage of gene therapy product development.

Assess the risk of transmission to the environment and surrounding population and develop prevention and control measures.

Gene therapy products usually remain in the human body for a long time after administration, accompanied by

Long-term safety risks should be updated in a timely manner based on safety information obtained from long-term follow-up.

Risk management measures for new gene therapy products, investigator manuals, instructions, etc.

If any major safety issues are found during long-term follow-up, they should be reported promptly to the

Regulatory reporting.

If the gene therapy product is administered via surgery or invasive procedures,

The drug delivery technology will directly affect the safety risk of the product and have a great impact on the safety of the product in clinical trials.

Personnel responsible for the operation are trained on special drug administration methods and standard procedures are written

The process helps to increase the safety of product administration.

Recording and observation help determine whether the operator is administering the drug according to the protocol.

Recording can also help determine the correlation between differences in drug administration practices and clinical outcomes,

Improve the clinical drug administration method. Even if the drug administration is unsuccessful, the subjects should be treated

Monitor risks arising from drug administration or pretreatment.

For rare diseases that are rapidly progressive and life-threatening or cause malformation and disability, subjects

The disease may be caused by the lack of efficacy or reduced efficacy of the gene therapy products under development.

The condition worsens and serious adverse consequences occur. For such rare diseases, clinical trials should be

More frequent efficacy evaluation and safety monitoring should be carried out during this period.

Relevant standards should be formulated for emergency treatment.

2. Consider the risks of conducting gene therapy for rare diseases in children

Applicants should consider the characteristics of rare diseases in children and their physiological characteristics.

Gene therapy products may affect children.

Normal growth and development of children's organ systems, such as reproductive system, immune system,

Nervous system, skeletal muscle system, etc., should be monitored and evaluated in clinical trials.

Theoretically, children who receive gene therapy products

The long-term safety risk of drugs is higher in children than in adults.

Follow-up to assess product safety and developmental effects is important, especially for

Testing on infants or young children.

3. Considerations from the perspective of clinical trial design

In the early stages of gene therapy product development, when research data is still lacking,

Giving drugs to subjects may expose the subjects to greater risks.

Set a reasonable enrollment interval between trial subjects (at least the starting dose group), and

Setting reasonable dose escalation rules and dose-limiting toxicity definitions can

Limit the number of subjects who may be exposed to unexpected safety risks.

The time interval between groups in the trial phase should be sufficient to observe the acute adverse reactions of the product.

Dose escalation rules and definition of dose-limiting toxicity should take into account the effects of gene therapy products.

characteristics of the product, the severity of the rare disease, and the tolerance of the subjects, and

Consider non-clinical research data and adverse reactions observed in clinical trials of similar products

Formulate.

Due to the lack of knowledge on the severity and incidence of adverse reactions to gene therapy products

Understand and design reasonable test termination/pause criteria.

Determine the severity, number or proportion of adverse events, serious adverse events

The number or proportion of deaths should be suspended immediately once the suspension/suspension criteria are met.

The enrollment and administration of the drug will be continued until the safety issues are resolved.

The plan may reduce the risk to the subjects, including modifying the inclusion and exclusion criteria, reducing the

Dosage of medication, change of pretreatment and administration method, change of clinical follow-up plan, etc.

The revision of the plan should be scientific, complete, feasible and risk-controlled.

Reasonable study termination criteria can limit the number of people exposed to risk and allow researchers to

Researchers should promptly assess the risks found in clinical trials and ensure that the risks are kept within the

An acceptable range.

The number of patients with rare diseases is small, the access to clinical information is limited, and the number of genetic

There are few therapeutic products on the market, and there is little clinical experience to refer to for the treatment of rare diseases.

This guideline does not cover clinical trials of gene therapy products for rare diseases.

All questions should always focus on the clinical value assessment of gene therapy products.

Benefits and risks, key technical issues in the R&D process and regulatory authorities

Communicate when.

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