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基因治疗产品长期随访临床研究技术指导原则（试行）

国家药品监督管理局药品审评中心

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目 录

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I. Overview

(I. Introduction

Gene therapy refers to modifying or manipulating the expression of genes to change living cells

The main function of the treatment method is to use the biological characteristics of cells to achieve the purpose of treatment.

The mechanism includes replacing disease-causing genes with normal genes and inactivating genes that do not work properly.

Or by introducing new or modified genes. With the advancement of gene therapy technology

With the continuous development and deepening of clinical research, gene therapy has been used for many refractory diseases.

disease provides new treatment strategies. Currently, there are many genes worldwide

Therapeutic products are approved for marketing, such as AAV2-hRPE65v2 for the treatment of RPE65

Retinal dystrophies caused by genetic mutations, CAR-T cells are used to treat a variety of

Hematological malignancies and retroviral vectors containing human ADA cDNA sequences

Transduced CD34+ cells are used to treat severe joint disease caused by adenosine deaminase deficiency.

Combined immunodeficiency. There are also a variety of gene therapy products for treating different indications in China.

Entering the clinical research stage.

Generally speaking, gene therapy works by causing permanent or long-term changes in the body

To achieve therapeutic effects, these changes persist in the body for a long time and may increase unpredictable

Risks such as delayed adverse reactions, etc. To assess and reduce late-onset adverse effects

reactions and other risks, and to understand the changes in treatment effects over time, it is necessary to

Long-term follow-up of subjects undergoing gene therapy clinical trials. long-term follow-up

Observation methods and study design depend on the risk profile, suitability of the gene therapy product

factors such as the population and route of administration. This guideline mainly focuses on the above factors.

Discussion, general principles that need to be followed for drug clinical trials and other guidelines

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Repeated content of the guiding principles will not be repeated in this guiding principle.

(2) Purpose and scope of application

This guiding principle applies to the drug administration laws of the People's Republic of China,

"Drug Registration Management Measures" and other drug management-related regulations for research, development and registration

Declared products with gene therapy properties, such as plasmid DNA, RNA, genes

Modified viruses, bacteria or cells and products based on gene editing technology, etc.

It aims to provide technical guidance for long-term follow-up clinical studies of such products to ensure

Timely collect signals of delayed adverse reactions, identify and reduce such risks, and

information on the long-term safety and effectiveness of these products.

This guideline is for conducting long-term follow-up clinical studies of gene therapy products.

Suggestions and recommendations on related technical issues are not legally binding.

With the development of gene therapy technology, deepening knowledge and accumulation of experience, this guideline

The relevant content in the rules will be continuously improved and updated. Applicants should always

Adhere to the principle of concrete analysis of specific issues, and suggest that timely consultation with the Center for Drug Evaluation

Communicate the specific design and details of the follow-up study plan.

2. Long-term follow-up clinical study design of gene therapy products

(1) Observation purpose of long-term follow-up

The main purpose of long-term follow-up of gene therapy products is to collect the late

adverse reactions, and understand the persistence of gene therapy products in the body, so as to

Identify and reduce long-term risks for patients receiving gene therapy products. In addition, take the exam

Considering the long-term effects of gene therapy products, observe changes in efficacy over time

The situation is also one of the purposes of long-term follow-up, which helps to evaluate the benefits and risks of the product.

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Condition.

(2) Factors to consider in long-term follow-up observation

1. Potential risk factors related to delayed adverse reactions

When evaluating risk factors for gene therapy products, applicants should consider genetic

Characteristics of the therapeutic product, taking into account both non-clinical and clinical data for the product and

Known data on similar products. Non-clinical studies of gene therapy products are designed to

Clinical studies provide supporting information and key safety characteristics parameters, such as

Biodistribution and persistence, integration/modification of host genome, latency reactivation, and

and potential immunogenicity, etc. For new gene therapy products, reference data include:

is limited, applicants should obtain as much information as possible in non-clinical studies for the assessment of late-onset

Data on the risk of adverse reactions.

Risks specific to gene therapy products that may cause delayed adverse reactions

Risk factors include:

(1) Genomic integration activity

Gene therapy products may employ technologies that modify the host genome and have

May persist in host cells or tissues. Many gene therapy vectors are based on

Because the integration will not be directed to a specific site in the genome, it may occur at the integration site.

Insertion mutations, or activation of proto-oncogenes near the integration site, thereby destroying critical

It may affect gene function or increase the risk of malignant tumors. For example, many foreign studies have

Research reports on genetically modified cells transduced with gamma-retroviral vectors

Leukemia occurred in treated subjects. Therefore, for products with such risks

products, long-term follow-up clinical studies are necessary to evaluate the occurrence of delayed adverse reactions

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risks of.

Non-clinical research and long-term follow-up of gene therapy products at home and abroad

clinical experience and significant improvements in methods for analyzing genomic integration sites, both

To help better understand the risks associated with integrated gene therapy vectors. usually think,

Many vectors that can mediate the transfer of foreign genes into the nucleus (such as retroviral vectors

entities, transposable elements and gene editing products, etc.) have the potential for genome integration and require

The risk of delayed adverse reactions needs to be observed through long-term follow-up; based on current understanding

Knowledge and research data on plasmids, poxviruses, adenoviruses and adeno-associated viruses (AAV)

Gene therapy products with equal vectors have lower integration risks, and clinical trials conducted internationally

It also showed a lower risk of delayed adverse reactions in trials. When vector or gene therapy

when the original risk profile of the therapeutic product is increased, for example if it is modified to carry a genome

Plasmids that edit components or change administration methods to improve integration capabilities need to be provided.

High requirements for long-term follow-up observation; conversely, it is also possible to conduct late-term follow-up observations that are currently considered

Modification of gene therapy vectors to reduce these risks.

(2) Long-term expression

Compared with other products, the distinguishing feature of some gene therapy products is that they can

Persists and encodes expression in patient target cells or genetically modified cells

factors (functional proteins or gene expression regulatory elements), and through permanent or long-term

Change the function of target cells or tissues to achieve therapeutic effects. At the same time, due to genetic

Long-term exposure or abnormal expression of therapeutically encoded agents in the body may produce

long-term safety risks related to its function, such as uncontrolled cell growth and malignancy

Tumor formation, autoimmune reactions, or other unpredictable late adverse reactions.

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(3) Latent reactivation

Some viral gene therapy products may be reactivated from latency

the possibility of causing the reactivation of an existing viral infection in the body, and there is an infection

associated risk of delayed adverse reactions.

(4) Persistent infection

Replication-competent viral or bacterial vector gene therapy products may be used in

The development of persistent infections in immunocompromised patients further increases the risk of delayed

There is a risk of serious infection.

(5) Gene editing activity

New gene therapy products such as gene editing have unique genome modification functions

can induce site-specific changes or modifications in the human genome and also

Off-target effects may occur in the genome, leading to unexpected gene expression changes,

This in turn increases the risk of unknown and unpredictable late adverse reactions.

(6) Unexpected biological distribution

Some gene therapy products require expression in specific cells or tissues to

To achieve therapeutic purposes, if the gene therapy product acts in unintended cells, tissues or

Expressed or modified in organs, may cause changes in non-target cell function, growth or/differentiation

changes and even cause tumors.

(7) Gene rearrangement or recombination

When the vector used in a gene therapy product and the gene it carries replicate,

Unintended gene expression or changes that are not intended for therapeutic purposes may occur, or may be associated with

Reverse mutation or unexpected replication or formation after complementation of wild-type or helper virus

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New viruses.

(8) Immunogenicity

Due to the continued exposure of gene therapy products in the body or the need for multiple administrations

In the case of drugs, etc., the body may produce factors that target the gene therapy vector or code.

immune response of the child. Due to the expression of gene therapy products in target cells or tissues

Due to differences in time, distribution range or expression intensity, the consequences of the body's immune response may

It can go from a transient immune response with no clinical significance to targeting target cells or

Immune attacks on tissues can even produce serious life-threatening adverse events.

(9) Shedding and spread

For some gene therapy products with infection or replication ability, from subjects

After being excreted or shed from the patient's body into the natural environment, it may be transmitted to the subject.

close contacts, including relatives of patients and medical staff, etc., resulting in virus transmission or

Risk of infection.

(10) Other considerations

In addition to product-related factors, long-term risk assessment of gene therapy products should also

Consider target cells/tissues/organs, patient population (age, immune status, risk of death)

risks, etc.) and the characteristics of related diseases and the impact of combining other treatments. If base

Because therapeutic products can be distributed and exert their effects in gonads, germ cells and other tissues and organs,

effect on the fertility, pregnancy, and fetus of the subject or his/her spouse.

produce unpredictable late effects.

2.Clinical research population

If a gene therapy product carries a risk of delayed adverse reactions

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Risk, when long-term follow-up observation is required, all patients receiving gene therapy products

All subjects should be enrolled in long-term follow-up clinical studies after signing the informed consent form. Under construction

When planning long-term follow-up clinical studies, the target subject population and characteristics should be considered.

symptoms, overall health, and expected survival of patients who receive treatment

Impact on the collection of delayed adverse effects. Generally speaking, when clinical researchers

certain characteristics of the population (such as short life expectancy, multiple comorbidities, and exposure to radioactive

or other drugs such as chemotherapy) that may interfere with the observation and analysis of delayed adverse reactions

will affect the effectiveness of long-term follow-up observation in assessing and mitigating risks to subjects.

It is used when the disease is mild or more limited, and the comorbidities and accompanying treatments are limited or less

In stable subjects, assessment data collected through long-term follow-up observations may

Easier to analyze.

3. Observation time for long-term follow-up

The duration of long-term follow-up should be sufficient to observe the effects of the product on subjects

Risks resulting from characteristics, exposure conditions (biodistribution and route of administration), etc., should

Not shorter than the expected occurrence time of delayed adverse reactions.

In general, recommendations for different types of gene therapy products are as follows:

ÿ Vectors with genome integration activity (such as gamma-retrovirus and lentivirus

Viral vectors) and transposable elements are recommended to be observed for no shorter than 15 years.

ÿ Bacteria or diseases that can cause persistent infection or have a risk of latent reactivation

Viral vectors (such as herpes simplex virus) are recommended to be observed for 15 years or until data indicate that they are no longer

There is no risk (infection or reactivation).

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ÿGene editing products are recommended to be observed for 15 years or until data indicate that there is no longer any What risks.

ÿ Adeno-associated virus vectors are recommended to be observed for 5 years or until data indicate that they are no longer present any risk.

The above recommendations for long-term follow-up time are mainly based on gene therapy product categories. Type, the follow-up time of a specific product depends on the characteristics of the product and the time it exists in the body, Transgene expression time, expected time and incidence of delayed adverse reactions, affected Subject indications and expected survival, route of administration, and other long-term follow-up Observation purpose. As follow-up data accumulate, investigators and study sponsors may Will be continuously evaluated based on product presence, transgene expression and clinical performance circumstances, extending or shortening the duration of long-term follow-up. If the study sponsor determines Its gene therapy products have low safety risks and do not require long-term clinical follow-up. research, or if you want to change the follow-up time, you should reasonably explain the basis or reason for the change. and communicate with the drug regulatory authorities.

4. Effectiveness

Although the efficacy of gene therapy products generally lasts longer, over time Over time, gene therapy based on plasmids, non-viral vectors or viral vectors, etc. The transgene expression level of the product in the body may gradually decrease, and the product may contain vectors or viruses. The number of target cells that are poisoned may also gradually decrease. The above factors may cause genes to The effectiveness of treatment products gradually decreases. Long-term follow-up observation helps to understand gene therapy how the effectiveness of therapeutic products changes over time and, if possible, again When and how to receive treatment.

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(3) Design and implementation of long-term follow-up

1. Informed consent

Informed consent should follow the relevant provisions of the "Good Clinical Practice Practice for Drugs"

Requirements to explain to subjects the possible foreseeable safety risks of participating in clinical trials,

The content must include the purpose, research procedures, duration, interviews, etc. of the long-term follow-up study.

Depending on the interval and the contact information of the researcher, ethics committee or sponsor, etc. when

Modified risks of gene therapy products identified in non-clinical studies or clinical trials

When changes occur, the informed consent form should be updated in a timely manner and the subject should be informed. informed consent form

The collection and storage of human tissue samples and genetic testing during long-term follow-up should also be done.

Wait for explanation.

2. Design and implementation

In long-term follow-up clinical studies of gene therapy products, a feasible set of

A monitoring plan is used to record and collect all study-related data from subjects,

Adverse events can be recorded, reported and assessed in a timely manner. Typically, long-term follow-up

Clinical studies should detail the monitoring plan for subjects, including visit schedules,

Sampling plans, monitoring examination methods, and target clinical outcomes in long-term follow-up clinical studies

Bed incident etc. It is recommended that the sponsor provide a concise and scientific follow-up record guidance,

For researchers and related medical personnel (including doctors and nurses other than researchers)

Record all observations and all data relevant to the study. If in clinical trials

important information that alters the risks of gene therapy products should be obtained during testing or after marketing.

Revise the follow-up plan in a timely manner and implement it.

Within 5 years after the subject receives gene therapy (or depending on the product-specific

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During the long-term follow-up period for which the risk is determined), clinical follow-up should record the subject's brief

Medical history, use of carcinogenic or mutagenic drugs and other drugs and related

Adverse event information, new, recurring or worsening diseases (e.g. malignant tumors,

Neurological disorders, immunogenic or autoimmune diseases, infections, and even death

death, etc.) and related physical and laboratory examinations, pregnancy and pregnancy of subjects and their spouses

Fertility status, etc. At the same time, relevant samples should be collected at appropriate follow-up time points as much as possible.

This, using validated and sufficiently sensitive methods to detect the effects of gene therapy products on

persistence in the body and analysis of associated effects until data indicate that there is no longer

any risk. If any abnormalities suspected to be related to gene therapy products occur during follow-up,

adverse events, should be timely based on clinical, laboratory, molecular biology, cytogenetic

Evidence obtained from histological, histological or HLA analysis or deep sequencing data, etc.

Cause-and-effect analysis of correlations, and if necessary, increase the frequency of follow-up or increase the content of follow-up.

For gene therapy products with a follow-up period of more than 5 years, complete the first 5 years

After follow-up, it can be collected through telephone or written questionnaires and other methods as much as possible.

For relevant samples, subjects should be followed up at least once a year until the end of the follow-up period.

If the early follow-up shows that the product continues to exist in the body, it is recommended to observe until the data shows

There is no longer any risk.

The sponsor submits a clinical trial application (IND) to the drug regulatory authority

Long-term follow-up research plans should be included. Long-term follow-up studies can be

Clinical trial plans for different stages are integrated together or can be designed separately as one

Regardless of the form of the research plan, the sponsor needs to pay attention to the consistency of implementation

and consistency, if long-term follow-up research plans are carried out during the clinical trial

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Update, should ensure that every subject in each phase of clinical research is updated according to the latest plan

Plan follow-up visits and update informed consent documents in a timely manner. The sponsor should during the research and development period

The periodic security update report (DSUR) summarizes the long-term

follow-up research results and promptly report the clinical trial period in accordance with relevant regulatory requirements

Adverse events occurred during the period.

(4) Special considerations for different gene therapy products

1. Special considerations regarding integrative carriers

If the subject receives an integrated vector gene therapy product, such as a transposon

software, gamma-retrovirus, lentivirus and other retroviral vectors, or use

Cells modified in vitro by integrating vectors or transposon-based vectors

During the visit, special attention needs to be paid to the genome integration risks of gene therapy products, and it is recommended to apply for

Analysis of gene therapy vectors in the genome of target cells or related surrogate cells

Effects of integration (e.g. whether there is clonal growth, whether there is a dominant clone,

Whether clonal growth leads to malignant tumors, etc.).

If analysis of risks associated with genomic integration is feasible, the following points should be noted:

ÿ Within the first 5 years of receiving the gene therapy product, the time between testing

It is recommended that the sampling interval should not exceed 6 months. Thereafter, it will be tested at least once a year until the

Test data shows that there are no longer any security risks.

ÿ The sensitivity, specificity and reproducibility of the detection method should be validated and

Design appropriate positive and negative controls;

ÿ When the proportion of vector sequence-positive target cells or surrogate cells in the body exceeds

When the range is expected, an assessment of clonal growth should be performed.

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ÿ If there is dominant clone or monoclonal growth, it should be done in no more than 3 months.

Test and confirm again within a certain period of time, and conduct integration site analysis as soon as possible.

ÿ After the integration site of the vector is determined, it should be compared with the human genome database and

Compare with other cancer genome databases to determine the gene function of the integration site

to assess whether it is related to any disease, including cancer.

ÿ If clonal growth of vector-positive cells occurs in the subject, or

If the test finds that the gene integration site is near an oncogene or cancer-related gene, it should be shortened.

Test intervals should be no more than 3 months and monitor closely for signs of malignancy until testing

No gene therapy vector was detected.

ÿ For gene therapy products based on lentiviral/retroviral vectors, such as

Adverse events that may be related to replicable viruses should be investigated.

Viruses (replicable competent lentivirus/retrovirus, RCL/RCR)

detection.

2. Special considerations regarding gene editing products

Gene editing products In addition to the general considerations applicable to gene therapy products and

In addition to special considerations for integrative vectors, additional attention should be paid to off-target risks during long-term follow-up.

risk, quantitatively assess the correlation between off-target activity and on-target activity, or use

target activity to predict the level of off-target activity. If the gene therapy product passes through the body

drug delivery, safety monitoring during long-term follow-up not only includes target organs or

Off-target activities in target tissues should also include those that may occur in other tissues and organs.

Off-target activity in the organ.

Analysis of genomic integration or off-target activity often requires invasive

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When testing methods are used to obtain samples, technical and ethical feasibility must also be considered when implementing them.

properties, such as gene therapy products targeting tissues such as the retina or liver, may be difficult to

to sample target cells, which may require close clinical follow-up

Indirectly assess risk through other methods; at the same time, choosing alternative cells that are easy to sample can also

Can provide information on relevant information, such as gene therapy targeting bone marrow hematopoietic stem cells

Products can be observed by collecting peripheral blood cells or enriching peripheral blood stem cells.

Check.

3. Implementation suggestions for long-term post-marketing monitoring plan

During clinical studies, the number of subjects who receive gene therapy is usually relatively

limited. At the same time, when a product is approved for marketing, the basis for clinical trials is

Because subjects for therapeutic products often have not completed long-term follow-up clinical studies, clinical

Safety data collected in trials were insufficient to assess all possible late effects

Risk of adverse reactions. Therefore, after obtaining marketing approval, the sponsor may still

It is necessary to continue to carry out long-term follow-up clinical studies to establish traceability of products and users.

traceability system. The sponsor should follow my country's laws and regulations related to post-marketing surveillance of drugs.

The guiding principles require that a pharmacovigilance system be established and improved to proactively collect patient information.

information on adverse events, encourage patients to proactively report adverse events, and improve the quality of data collection

quantity.

It is recommended that sponsors contact drug reviewers before submitting a new drug application (NDA).

The evaluation department communicates whether it is necessary to conduct long-term post-market follow-up of gene therapy products.

Clinical studies to continuously evaluate the safety and effectiveness of products. If necessary,

It is recommended to provide post-marketing research or clinical trial plans when filing NDA, including

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Including research purpose, research population, observation content and duration, etc. In addition, on

Postmarket risk management plans help assess and control the safety of gene therapy products

sexual risks, it is recommended that the sponsor communicate with the drug review department during the NDA review process

Communicate the specific contents of the post-marketing risk management plan.

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