疫苗临床试验技术指导原则

Center for Drug Evaluation, National Medical Products Administration

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目 录

I. Introduction To

standardize the clinical trials and evaluation of vaccines, in accordance with the "People's Republic of China..."

Drug Administration Law, Vaccine Administration Law of the People's Republic of China, Drug Registration Management

This guiding principle is formulated in accordance with the "Measures" and other relevant regulations.

The term "vaccine" as used in this guidance refers to vaccines used to prevent or control the occurrence of diseases, including influenza.

Yes, preventive biological products used for human immunization. Classified by their composition and...

Production processes can be categorized into inactivated vaccines, live attenuated vaccines, subunit vaccines, and gene vaccines.

Recombinant protein vaccines, nucleic acid vaccines, conjugate vaccines, vector vaccines, etc.

This guidance aims to provide general technical recommendations for vaccine clinical trials.

The clinical trial design and evaluation for specific varieties should also be based on their own characteristics and...

The prevention of disease outbreaks should be determined in accordance with relevant guidelines.

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

As scientific research progresses, the relevant content in this guideline will be continuously improved.

Updates are also required. When applying this guidance, please also refer to the quality of drug clinical trials.

Good Manufacturing Practices (GCP) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

And other relevant guidelines that have been issued domestically.

II. Overall Considerations

(I) Basis for Topic Selection

The rationale for establishing a research project on an experimental vaccine should include the following considerations (including but not limited to):

At):

1. Biological agents that can prevent diseases (hereinafter referred to as target diseases) associated with vaccines.

Characteristics, pathogenic mechanisms, etc.;

2. Disease burden (e.g., morbidity, mortality, etc.) and prevalence of the target disease.

Pathological characteristics and influencing factors, diagnosis and prevention methods, including possible domestic [infections].

External differences, etc., encourage prioritizing research and development among the populations with the heaviest disease burden;

3. Demographic characteristics of the target population for vaccine administration (e.g., age, gender, etc.);

4. The expected mechanism of immune protection provided by vaccines;

5. Status of similar products launched and research progress both domestically and internationally;

6. In certain special cases, such as multivalent vaccines, the potential clinical manifestations of the included virus types should be clearly defined.

Bedside benefits; multivalent vaccines need to be combined with the similarities or similarities in the immunization schedules of each single vaccine.

The necessity and feasibility of the research and development were taken into account.

(II) Clinical Research and Development Plan

Vaccine clinical development follows the general principles of drug clinical development. Preclinical research...

The research results should support the experimental vaccine's entry into clinical trials; and the safety of the experimental vaccine should be verified.

Following preliminary data on sexuality and immunogenicity, exploratory clinical trials and confirmatory assays will continue.

Clinical trials will be conducted to further evaluate the efficacy and safety of the vaccine. However, due to the vaccine...

The unique mechanism of action, with most subjects being non-disease-free individuals exposed to risk factors.

Groups of people may be involved in major public health events, and vaccine clinical development also faces challenges.

Due to the unique characteristics of vaccines, corresponding clinical trial plans should be formulated in accordance with these characteristics.

Bed research and development plan.

The clinical research and development plan focuses on the overall goal-oriented clinical research...

Given this approach, how should we design clinical trials at different stages and for different research objectives?

Evaluate and determine the benefit/risk ratio of experimental vaccines. Each experimental vaccine enters clinical trials.

A clinical development plan should be established before each trial, including the planning of each clinical trial.

Its positioning, role, and implementation sequence, etc.

Although vaccine clinical development is typically divided into Phase I to Phase IV, the general idea of this phased approach is...

The term "phase" is merely for ease of description and not a rigid rule; moreover, the phases of vaccine development may vary.

Overlapping or merging. Therefore, taking vaccine market registration as the node, it is divided into pre-market research and development.

The development stage, the post-market application stage; the pre-market research and development stage, depending on the research objectives.

Clinical trials are divided into exploratory clinical trials and confirmatory clinical trials.

1. Pre-market research and development stage

Exploratory clinical trials provide early, preliminary confirmation of the safety of experimental vaccines.

Simultaneously explore immunogenicity; subsequently, continue to explore immunization dosage, immunization schedule,

Further investigation is needed regarding the safety and preliminary efficacy of the immunization route in a larger population.

Sexuality. Through comprehensive evaluation of immunogenicity and safety, the criteria for entering confirmatory clinical trials will be determined.

The immunization dose and procedure used in the experiment.

Confirmatory clinical trials aim to confirm the efficacy of the experimental vaccine in the target population.

The effectiveness and safety of the experimental vaccine will provide sufficient evidence for its market approval.

And provide information for writing the instruction manual. In conducting confirmatory clinical trials of protective efficacy...

Before testing, it is encouraged to explore the protective effects of experimental vaccines with a sample size that has a certain degree of statistical power.

To assess protective efficacy, the definition of clinical endpoints and diagnostic procedures in confirmatory clinical trials should be clearly defined.

To improve the success rate of confirmatory clinical trials.

Confirmatory clinical trials using immunogenicity as a surrogate endpoint for efficacy evaluation

For trials, refer to vaccine clinical comparability studies and immunogenicity bridging clinical trials.

Related technical guidelines.

2. Post-market application stage

Marketing authorization holders should establish and improve the entire life cycle management of vaccines.

Further confirmation of the safety, efficacy, and quality controllability of the vaccine is needed, and data collection is required.

Real-world data is used to assess the effectiveness and security of protection in practical applications.

Some studies of experimental vaccines may continue beyond market launch or require post-marketing intervention.

The process should be carried out in phases. If applicable, the clinical research and development plan should also cover the relevant content.

Or it may be updated dynamically based on the progress of clinical research and development.

III. General Considerations for Clinical Trials

Clinical trial protocols should include the trial objectives, design, implementation, and analysis.

The plan should be scientific, comprehensive, feasible, and risk-controllable, and should comply with ethical principles.

Relevant requirements. The design elements of vaccine clinical trials should follow those of drug clinical trials.

General considerations. Given the unique nature of vaccines, the following considerations also apply:

(a) Study population

Early exploratory clinical trials typically involve healthy adult subjects aged 18 to 59.

Begin. If the target population for vaccination is children, the elderly, pregnant women, etc., it should generally be...

After obtaining preliminary safety data in healthy adults aged 18-59, further studies will be conducted on the target population.

Research is conducted within the group; vaccines for infants and young children are usually administered first to healthy individuals aged 18-59.

The treatment is conducted in the following order: adults, then adolescents, children, and finally infants.

Further exploratory and confirmatory clinical trials should be selected that represent the vaccine's objectives.

The participants in the vaccination population, especially in confirmatory clinical trials, should be selected based on the actual number of participants.

The needs and age characteristics are used to set up age subgroups and the proportion of different subgroups.

Inclusion and exclusion criteria should take into account the characteristics of the vaccine and the physiological characteristics of the target population.

When formulating such a study plan, factors typically considered include the age and health status of the study population.

Immune function status, past medical history, and vaccination history, etc., generally exclude important organs.

Severe organ disease, severe immunodeficiency or immunosuppression, or progressive nervous system disease

Factors such as chronic diseases may affect the immune response or safety evaluation of experimental vaccines.

Or there may be contraindications to vaccination (such as allergies to the main components and excipients of the vaccine).

For some vaccines that may exhibit antibody-dependent enhancement (ADE) or vaccine amplification

For experimental vaccines with a risk of virulent disease (VED), the study population should be carefully considered.

Inclusion and exclusion criteria, such as previous infection status and baseline levels of specific antibodies.

(ii) Experimental vaccines, immunization doses and procedures

Applicants should combine research objectives, pharmaceutical and non-clinical research data, etc., to explore

Antigen formulation (e.g., antigen dosage, necessity of adjuvant, antigen/adjuvant ratio)

(e.g., dosage), route of administration, number of immunization doses, and time intervals between different doses, etc.

To provide a basis for decision-making regarding immunization dosage and procedures in confirmatory clinical trials. Based on the epidemic...

In addition to considering vaccine characteristics, the potential impact of population characteristics on the immune response should also be taken into account, such as...

Age, sex, maternal antibodies, previous vaccination or medication history, natural exposure

This can lead to pre-existing immunity, etc. If necessary, it may be necessary to target different age subgroups, and...

Explore the optimal immunizing agents for different population groups, including those with a history of vaccination and their immune status.

Quantity and procedure.

The target dose and immunization schedule for inclusion in confirmatory clinical trials should be adequately determined.

Data support is available. It is recommended to use commercially produced vaccines whenever possible for diagnosis.

Evidence-based clinical trials are conducted to ensure that the clinical trial data is representative of the vaccine intended for market release.

If pharmaceutical changes following confirmatory clinical trials are unavoidable, they should be handled in accordance with ICH guidelines.

Q5E, Technical Guidelines for Biopharmaceutical Research and Changes During Clinical Trials, etc.

Then conduct comprehensive comparability studies, including necessary immunogenicity bridging clinical trials.

The verification process is designed to provide sufficient data support.

The specifications of experimental vaccines are closely related to the immunization dose; it is recommended to combine dose exploration.

Choose appropriate specifications and pay attention to the vaccine specifications during clinical trials and the specifications intended for market launch.

The connection.

For innovative vaccines, we encourage early research into their durability and effectiveness.

This research will provide data support for improving the immunization program.

Whether a joint vaccination study is necessary depends on the specific circumstances. (Infant and toddler stage)

Vaccinations are administered in relatively intensive phases, and it is encouraged to conduct vaccinations with those most likely to be vaccinated at the same time.

Combined vaccination study.

(III) Selection of Comparisons

Controls typically include placebo controls, adjuvant controls, positive controls, and studies.

This includes studies on vaccines that are unrelated to the prevention of other diseases, such as positive controls. Positive controls should be for the prevention of other diseases.

Vaccines that treat the same disease and have sufficient safety and efficacy data should, in principle, be selected.

Products already marketed and widely used in clinical practice domestically. When selecting a positive control,

Generally, consideration should be given to the differences between the experimental vaccine and the target population, immunization schedule, and route of administration.

Consistency in aspects such as route of administration and method of inoculation should be ensured, while also taking into account pharmaceutical aspects.

Positive controls should be used according to the approved instructions. The effectiveness of positive controls can be determined by...

It can be affected by factors such as the prevalence of pathogens and vaccination coverage, and should be fully considered.

These factors may influence the evaluation of the effectiveness of experimental vaccines.

Under the premise of meeting ethical requirements, the selection of controls should be based on clinical trials.

The specific stages and research objectives vary. For example, some studies primarily focus on evaluating safety.

Early exploratory clinical trials for research purposes; innovative vaccines typically adopt...

Using a placebo control, vaccines that are already marketed domestically or internationally can also be used.

Sex control; for vaccines containing new adjuvants or adjuvant systems, clinical trials may be used as a basis if necessary.

Pre-bedroom studies should include an adjuvant control group to allow for a reasonable assessment of safety risks.

Support the conduct of subsequent clinical trials. The primary research objective is to evaluate protective efficacy.

Clinical trials typically use a placebo-controlled design to evaluate absolute protective efficacy, but other methods may also be employed.

The relative protective efficacy was evaluated using a positive control. The primary focus of the study was on evaluating immunogenicity.

When considering the objective, exploratory clinical trials can be selected in conjunction with the accessibility of positive controls.

Selection; confirmatory clinical trials using immunogenicity as a surrogate endpoint for efficacy evaluation

The choice of controls depends on the research objective and the specific circumstances of the variety.

Expanding the target population for vaccination and changing immunization schedules require conducting immunogenicity bridging clinical trials.

During clinical trials, if the experimental vaccine is a marketed product, a batch release certificate should be used.

Next; if the experimental vaccine is not yet on the market, the relevant considerations are the same as for confirmatory clinical trials, and

Focus on the quality comparability with vaccines from earlier clinical trials. This includes vaccines involving pharmaceutical changes.

In pathogen-bridging clinical trials, the original vaccine should be considered as a control.

IV. Immunogenicity

(a) Evaluation Indicators

Vaccines work by inducing the body to produce antibodies against pathogens or their toxins after vaccination.

It functions through a specific immune response; therefore, theoretically, it can be measured experimentally.

The level of adaptive immunity induced by a vaccine can be used to infer its protective efficacy. This is based on vaccine characteristics.

Depending on factors such as sex and route of administration, vaccines can induce humoral immunity, cellular immunity, or mucosal immunity.

Membrane immunity. This is achieved by measuring serum, whole blood, mucosal secretions, or other bodily fluids.

Relevant indicators in samples can assess humoral, cellular, and mucosal immune responses.

Intensity and duration.

Current clinical trials primarily use humoral immunity-related indicators as a measure of immunity.

Indicators for evaluating the origin of the virus, such as neutralizing antibodies and binding antibodies. These are generally measured by measuring the vaccine's...

Changes in specific antibody levels before and after vaccination were used to assess immunogenicity and evaluate [the vaccine's effectiveness].

The metrics include the geometric mean titer (GMT) / geometric mean concentration (GMC) of the antibody.

and its growth fold (GMFR), antibody seroconversion rate, antibody protection rate, antibody seroconversion rate, and antibody seroconversion rate.

Sex ratio, etc. If existing immunogenicity indicators correlated with protective efficacy have been established...

(ICP) and having already achieved the protective threshold of antibodies, the focus is more on vaccination.

The percentage of subjects whose immune response level reached or exceeded the threshold after the event. If not yet...

Establishing a protective threshold requires combining antibody seroconversion rate, positivity rate, and GMT/GMC.

Comprehensive evaluation. Clinical trials typically use the intergroup GMT/GMC ratio or intergroup positive results.

The difference between the conversion rate and the positive rate was used to evaluate the overall immunogenicity.

Cellular immune response indicators are mostly the count of antigen-specific immune cells and

The most common method for assessing the expression levels of specific cytokines is detection and quantification.

The vaccine sensitizes the subject's T cells and characterizes the major cytokines released.

The induced cellular immunity mechanism is quite complex, and the detection reagents and methods, evaluation indicators, etc.

There is still a lack of broad consensus on standardization and other aspects. Mucosal immunology also currently faces challenges in specimen selection.

The collection time and method, preservation conditions, specimen processing, detection methods, and many other aspects

Limitations. If the expected mechanism of action of the vaccine relies primarily on cellular or mucosal immunity,

It is recommended to explore appropriate evaluation indicators and detection methods in order to evaluate the immune response.

A: It is used to support the selection of target immunization doses and procedures, etc.

(II) Sample collection and testing

It is recommended to collect samples from the study population before vaccination in order to obtain antibody seroconversion rate,

Research data on evaluation indicators such as growth rate were used to explore the effect of pre-existing immunization on vaccination.

Potential impact on immune response. Post-vaccination sampling time should be based on similar products and trials.

Testing vaccine preclinical studies or clinical trials for peak immune response data after vaccination

Accumulation of data, selecting time points that best reflect the immunogenicity characteristics of the vaccine for sample collection.

This can be adjusted in clinical trials as data accumulates.

For vaccines with unknown immunogenicity characteristics or limited evaluable data

Furthermore, research should focus on the dynamic changes in the immune response throughout the entire research process.

During the research phase, samples are collected periodically at pre-defined intervals.

Duration of immunity is an important criterion for evaluating vaccine effectiveness, and its follow-up should be based on...

Based on disease characteristics, target population, vaccine properties, vaccination strategies, and efficacy, long-term follow-up is necessary.

The visit was confirmed.

A detection method capable of effectively evaluating immunogenicity should be established, and the method should be further refined.

Verification is required. To ensure the accuracy and reliability of test results in clinical trials, [further verification is needed].

Evidence-based clinical trials should employ centralized testing. Encouraging testing throughout the entire clinical development process is crucial.

Use the same testing methods in the same laboratory. If the testing method is changed, there is no...

If the change cannot be avoided, a comprehensive assessment and explanation of its impact on the clinical trial results and conclusions should be provided.

Potential impact.

(III) Experimental Design and Evaluation

Confirmatory clinical trials using immunogenicity as a surrogate endpoint for efficacy evaluation

Trials, including comparative designs based on positive controls, include superiority, non-inferiority, and equivalence designs.

Its specific design and evaluation can be carried out with reference to relevant technical guidelines.

Determining the "critical value" is one of the key elements of the above experimental design. (Non-dominated)

The efficacy cutoff value should not exceed the maximum acceptable range of difference in clinical practice and should be relatively conservative.

Key considerations include the severity of the target disease and the sensitivity of the detection method.

In terms of accuracy, precision, and reliability.

V. Protective Effect

Protective efficacy is the direct evidence and gold standard for evaluating vaccine effectiveness. (Disease)

Epidemiological characteristics, existing interventions, immunization strategies for study populations,

Geographical distribution and other factors determine the selection of the test site and the effectiveness of the protection test.

Feasibility. Unless there is sufficient reason or research data to support it, experimental vaccines should...

The effectiveness of the first-line protective efficacy test has been confirmed.

(a) Experimental Design

The design elements of vaccine efficacy trials followed ICH E8 (R1). Protection

For efficacy trials, multicenter, randomized, blinded, and controlled designs are preferred. Other trial designs...

For any calculation, sufficient reasons or research data must be provided to support it.

Sample size estimates are typically based on validity considerations and depend on the clinical trial design.

Scientific evidence from statistical, clinical, and epidemiological perspectives, including...

The most crucial factors are the morbidity rate in the target population, the expected efficacy level of the vaccine, and...

The "critical value" in hypothesis testing. If epidemiological data for the target disease is lacking,

Encourage epidemiological investigations in the areas where trials are planned to be conducted prior to the commencement of efficacy trials.

Epidemiological surveys are conducted to obtain epidemiological data such as incidence rates, which are used for sample size calculations.

Provide supporting evidence. Furthermore, the demographic and social data upon which the sample size estimate is based should also be considered.

Characteristics, such as disease burden, and whether they are homogeneous with the study population, should be considered.

Depending on the degree of urgency of the application and clinical needs, the "critical value" for hypothesis testing may vary.

Different. Applicants should determine the estimation target based on the research objectives and include it in the experimental protocol.

The sample size should at least ensure sufficient evaluation of the primary estimation objective.

The testing effectiveness is good, while also taking into account the requirements and feasibility of safety evaluation.

Protective efficacy tests often employ a multicenter experimental design. It is worth noting that...

Yes, my country has a vast territory, and the epidemiological characteristics of different regions may vary (e.g.,

(Incidence rate, pathogen type distribution, etc.) requires close attention to the disease flow in each center.

The representativeness of the target usage area. If the target disease in each center is lacking...

Based on the epidemiological data, it is recommended that the applicant conduct a clinical trial feasibility assessment. For example...

If the pathogen exhibits a significant seasonal prevalence, it encourages the development of protective measures that span across the epidemic season.

Force research. If multi-regional clinical trials are involved, ICH E17 should also be followed, and emphasis should be placed on...

Pay close attention to whether there are differences between pathogens circulating domestically and internationally, especially the pathogens themselves.

When the popularity of something exhibits dynamic changes such as phases or cycles.

(II) Evaluation Indicators

The evaluation indicators for protective efficacy trials are determined by the characteristics of the experimental vaccine and the research objectives.

Determined. Generally, the clinical endpoint is defined as the disease to be prevented, based on its incidence and duration.

Time and other factors are used as evaluation indicators.

If a pathogen can cause different types of diseases, the target should be clearly defined.

Disease type. If different pathogen types are involved, the type covered by the vaccine is generally selected.

The primary endpoint is the disease caused by infection; if non-clinical or existing clinical data are available...

It is clear that vaccines may not be effective against different pathogens or against the same pathogens not covered by the vaccine.

Same type provides cross-protection, and the primary endpoint may also be caused by different pathogens or similar pathogens.

Diseases caused by any type of pathogen. The appropriate determination should be based on the characteristics of the vaccine.

The start time of case collection in the primary endpoint is usually the time when the target immunization program is completed.

The start time is defined as the point at which vaccination is expected to produce protective effects.

Secondary endpoints typically include infection with each type of pathogen contained in the vaccine.

Diseases caused by all types of infection, diseases caused by non-vaccine-associated infections

Diseases of varying severity, clinical symptoms or signs, and the duration of detoxification.

Intervals, etc. For some vaccines, cases occurring in the experimental vaccine group will be compared with those in the control group.

Comparing the severity of new cases may be very important in order to determine vaccination.

Does it reduce or increase the severity of the disease?

(III) Monitoring and determination of clinical endpoints

The sensitivity and specificity of the monitoring system, and the accuracy and reliability of the diagnostic methods.

Sex, sampling procedure (frequency and method), sensitivity of detection methods and reagents and

Specificity is crucial for evaluating the effectiveness of experimental vaccines.

Clinical trial protocols should reasonably define suspected cases and establish trigger visits.

Standards, etc. It is recommended to consider the local disease prevalence intensity, case surveillance resources, and prevention...

The research period, etc., should be used to reasonably define suspected cases, including clinical symptoms or signs.

The severity range and its extent must be determined to ensure the sensitivity of the case surveillance system.

For suspected cases, a combination of clinical symptoms/signs and laboratory test results is usually used.

The results are used to determine confirmed cases. Clinical trial protocols should clearly define confirmed cases.

Diagnostic criteria and procedures, especially those involving composite endpoints, co-infection, and multiple episodes.

In cases of illness, etc. If the clinical endpoint is based on histological examination results, it should be included in the protocol.

The criteria for phases and progress are predefined in the text.

Case information is generally collected through a combination of active and passive surveillance.

The follow-up frequency of dynamic monitoring should ensure that it is sufficient to obtain important laboratory test data, etc.

According to reports, in addition, strict procedures for collecting pathogenic samples should be established, and it is recommended to adopt...

Pathogen detection is performed using recognized and validated testing methods.

Throughout the trial and at each center, case monitoring, sampling, and pathogen identification should be ensured.

Consistency of physical examination, case diagnosis methods, and standards. It is recommended to establish quality control measures.

The system fully leverages the role of the Clinical Trial Data Monitoring Committee (DMC) and endpoint assessment.

The role of the Expert Committee (EAC).

(iv) Evaluation of protective effectiveness

The overall protective efficacy in clinical trials is generally evaluated by comparing the effects of different trial periods.

Calculation of incidence rates (person-hour incidence rate or cumulative incidence rate) between the experimental and control groups

Point estimates and corresponding confidence intervals (generally two-sided 95%). Consider needle...

Different subject subgroups (e.g., age, sex, region, baseline antibody status, etc.)

Analyze them separately.

Efficacy analyses are typically performed after the target immunization schedule for the investigational vaccine has been completed.

The vaccination was conducted in a randomized population that had received at least one dose of the investigational vaccine.

Secondary analyses were conducted within the population. Some vaccines require defining effectiveness based on baseline levels.

The analysis should be conducted on a population with specific sexual characteristics, but the reasons should be fully explained and the relevant definitions should be clearly stated.

Based on the expected incidence of the disease, the importance of the duration of protection, and long-term...

The feasibility of follow-up studies and whether the vaccine can address unmet urgent clinical needs.

The key analytical point for protective efficacy could be the specific immune response after the target immunization program.

When a predetermined number of endpoint events are reached within a set time period or at a predetermined number of endpoint events. For example, the background of a disease.

When the morbidity rate is clear, it can be achieved after the last subject has received the experimental vaccine.

Primary analyses are performed at specific times or upon exiting the study; unpredictable or uncertain diseases.

When calculating the accumulation speed of examples, the main calculation can be based on the number of endpoint events required for accumulation.

To analyze (event-driven experimental design).

If an interim analysis is required, it is recommended to clearly state the purpose of the interim analysis in the plan, and note...

Issues such as maintaining blindness, Type I error inflation, and experimental integrity, with specific requirements.

It is recommended to refer to relevant statistical guidelines.

Different types of vaccines have different standards for evaluating acceptable protective efficacy.

In such cases, the effectiveness of existing prevention and treatment methods for the target disease, the disease burden, and public health should be considered.

Public health hazards and their sociological impacts, as well as the protective efficacy and insensitivity of experimental vaccines.

A benefit/risk assessment should be conducted for adverse reactions (including potential safety risks).

Where applicable and feasible, subjects in protective efficacy trials should undergo [further testing/initiative].

Long-term follow-up is necessary to evaluate the duration of protective effect and assess the effectiveness of vaccination.

Breakthrough cases involving a decrease or increase in disease severity, and changes in etiology.

If the primary analysis indicates that the experimental vaccine is highly effective, the control group can be maintained.

If ethical requirements cannot be met, then follow-up of vaccine recipients is permissible.

Monitor the number of cases each year, and combine this with pathogen prevalence and disease transmission.

Factors such as changes in seeding intensity should be comprehensively assessed to determine whether the protection effect persists over time.

And weaken.

Encourage the continued collection of immunological information and analysis of antibody levels in breakthrough cases.

The correlation between occurrences is used to accumulate data for obtaining protective thresholds.

VI. Safety

The safety risks of vaccines mainly stem from the safety characteristics associated with the vaccine itself.

Safety related to vaccine quality, safety related to vaccination procedures, etc.

(a) General considerations

1. Subject Enrollment

Exploratory clinical trials, especially first-in-human trials, should focus on safety.

Sexuality. To protect subjects, safety is generally determined based on factors such as age and dosage.

The relevant factors are divided into groups, and "sentinel" subjects can be set up if necessary, and control is maintained.

Enrollment rate. The enrollment interval can be adjusted based on the characteristics of the experimental vaccine, its level of innovation, and its non-invasiveness.

Clinical research data should be formulated reasonably, and it is recommended that there be at least a 7-14 day interval between groups.

Viral vector vaccines, nucleic acid vaccines, and live attenuated vaccines, etc., are, in principle...

The treatment period should be at least 14 days. Innovative vaccines should be based on existing safety data.

The entry interval should be reasonably considered based on the accumulated data.

2. Suspension/Termination Criteria

Suspension/termination criteria are crucial for controlling safety risks in clinical trials.

Key. This is usually based on the characteristics of different vaccines, combined with their potential safety risks,

Reasonable criteria for suspension/termination of vaccination should be set for the target population. Suspension criteria should generally include...

It possesses highly sensitive characteristics, such as: ÿ15% of subjects experiencing grade 3 or higher non-responsiveness.

Adverse events (including laboratory test results), and ÿ1 case of unexplained adverse events in subjects.

Exactly exclude vaccination-related deaths or life-threatening SAEs, etc. If involved...

Sentinel subjects should have their suspension/termination criteria set separately. This is innovative.

The criteria for suspending/terminating vaccine trials can take into account the benefit/risk ratio and be based on non-clinical trials.

The risk warnings for clinical trials and the safety characteristics of similar vaccines should be reasonably adjusted.

3. Safety Observation

A reasonable safety follow-up plan needs to be developed during the trial. Generally, all...

All participants who received one less dose of the experimental vaccine were observed for safety.

Caution should be exercised when conducting comprehensive safety observations only in a subgroup of subjects. Safety observation

Generally, a combination of proactive and reactive approaches is adopted.

(1) Safety observation within 30 days

Safety monitoring should be conducted after each dose of vaccine. Typically, it is necessary to monitor for safety after vaccination.

For vaccines with unknown safety or limited data, a 30-minute on-site observation period is recommended.

The observation period at the observation site can be appropriately extended, or even hospitalization may be required. For any anticipated...

In the event of serious adverse reactions or adverse events, appropriate procedures should be established at the clinical trial site.

Emergency response measures.

Collection of adverse events: generally 0-7 days or 14 days after vaccination.

Use diary cards to collect solicited negative events. The diary cards should list all solicited events in detail.

Adverse sexual events. The content of the survey for adverse sexual events and the observation period should be based on the vaccine's own information.

Personal characteristics, target population characteristics, safety risks suggested by non-clinical studies,

Reasonable design of safety risk information in clinical trials or post-marketing surveillance of similar vaccines

Place.

Collection of non-collected adverse events: 0–7 days or 0–14 days post-vaccination

Use diary cards, or contact cards every 8-30 days or 15-30 days, to collect non-collectible negative information.

Event. For live attenuated vaccines, and vaccines with unknown safety or limited data, [further action should be taken].

The adverse event collection period should be appropriately extended based on the characteristics of the vaccine. For multiple doses of vaccine...

For experimental vaccines, non-recruitive adverse events during the intervals between doses should be considered if necessary.

Observation of the event.

The collection of both solicited and unsoliciting adverse events should ensure that...

Follow-up frequency.

(2) Long-term safety observation

Long-term safety observation and follow-up should cover the entire study period, generally at least

Six months after the target immunization schedule. Usually 30 days after the target immunization schedule.

The company will conduct long-term safety monitoring and continue to collect data on serious adverse events (SAEs).

Other specific relevant information, such as adverse events of special concern (AESI), etc.

The accumulation of safety data for innovative vaccines is limited, and the safety period should be appropriately extended.

The observation period is recommended to last at least 12 months after the target immunization schedule.

If a special security risk is discovered, it can be considered based on the characteristics of the security risk.

Follow-up frequency. It is generally recommended to have follow-up visits at least once a month.

(3) Laboratory indicators and other tests

Innovative vaccines or similar vaccines with safety risk warnings.

In exploratory clinical trial protocols, sample collection at appropriate time points should be set.

Laboratory tests (such as complete blood count, urinalysis, blood biochemistry, etc.) are performed.

Specific testing indicators can be based on safety findings from non-clinical studies or existing marketed products.

The safety data for vaccines should be set appropriately. For vaccines with specific safety risks...

The vaccine shown may need to have additional indicators such as myocardial enzymes, coagulation function, and blood glucose levels tested.

The test, or other examinations such as electrocardiogram, imaging, etc.

For clinically significant abnormal laboratory indicators detected or collected or

The test results should be followed up until the indicators stabilize or return to normal, or until other clear results are found.

The factors can reasonably explain this outlier.

(4) Observation of pregnancy events

For clinical trials whose study population includes women of childbearing age, enrollment is generally required.

Pregnancy screening should be performed before each dose and before the administration of each dose. Pregnant women during clinical trials should generally be...

Terminate vaccination with the experimental vaccine and continue follow-up until a pregnancy outcome is achieved.

Newborns should undergo regular safety follow-ups. The timing of these follow-ups should be determined based on the specific circumstances.

For innovative vaccines, follow-up is recommended for at least 12 months after birth.

Based on vaccine characteristics and non-clinical research data, male subjects may be considered if necessary.

The couple was observed to have pregnancy events.

(ii) Special considerations

1. Considerations related to the technical approach

In addition to routine safety evaluations, live attenuated vaccines (viral or bacterial) should also...

Early consideration should be given to research on detoxification, contact transmission, genetic stability, and virulence reversion.

Research is needed. Monitoring of viral shedding requires consideration of pathogen and disease characteristics, vaccine properties, and...

The route of administration, combined with data from preclinical studies and similar marketed vaccines, was determined.

Conduct a scientific and reasonable design, such as clearly defining the research objectives, evaluation indicators, and sample types.

Type, pathogen detection time and methods, etc.

Viral vector vaccines should focus on the impact of the vector virus on the human body, while also considering...

Considerations include pre-existing antibodies in the subject's body and whether they replicate again.

Nucleic acid vaccines should be selected based on their formulation composition, structure, and manufacturing process, such as...

The use of novel delivery systems/excipients, their biodistribution in vivo, and their duration of survival, etc.

Pay attention to the corresponding security risks.

2. Adjuvant-related considerations

For vaccines employing novel adjuvant/adjuvant systems, clinical trials may be conducted as necessary.

Previous research results suggest establishing an adjuvant/adjuvant system control group in exploratory clinical trials.

To evaluate safety. Adjuvant/adjuvant system-related issues that occurred during exploratory clinical trials.

Adverse reactions should be included in the stigmatization of adverse events in confirmatory clinical trials.

Allow.

(III) Sample size for safety observation

The sample size for safety observation prior to market approval needs to be considered in conjunction with the vaccine's innovation level.

Based on the degree of non-clinical research data, safety data from similar vaccines, and current...

The representativeness of the target population and other factors were taken into consideration.

Generally, the sample size for safety observation should be at least sufficient to estimate the trial vaccine.

Occasional adverse events (occurring in 1/100 to 1/1000) were observed in the seedlings.

If the experimental vaccine contains a new antigen component/form, or a new adjuvant/adjuvant system

For example, a larger sample size might be needed. If the data is from non-clinical research or exploratory studies...

Clinical trial data and safety data from similar vaccines suggest that the experimental vaccine may have side effects.

The potential risks of occasional or even rare adverse events that require special attention may need to be considered.

To further expand the sample size, statistical analysis of the safety endpoints may be conducted as needed.

Learn testing.

Considering the varying tolerance levels among people of different ages and physiological characteristics, safety is paramount.

Sexual outcomes may vary. This could be due to differences in the age range of participants in clinical trials.

For populations with different physiological characteristics, the sample size of each population should be appropriately set.

This comparison is used to ensure that the overall security data is representative.

(iv) Safety assessment

Based on the inherent characteristics of vaccines and the characteristics of the target population, vaccine clinical trials...

In addition to following the general principles of drug clinical trial evaluation, safety evaluation also has...

Other considerations.

The severity grading of adverse events can be referenced from adverse events in vaccine clinical trials.

The process will be guided by grading standards and other principles. It should be noted that solicitation or non-solicitation only...

For the specific implementation of collecting security information, solicited adverse events do not represent

Adverse events related to the investigational vaccine but not solicited do not necessarily indicate a connection to the investigational vaccine.

Irrelevant. Relevance assessment should be performed on both reported and unreported adverse events.

The determination of the relevance of adverse events can refer to the adverse event relevance assessment in drug clinical trials.

Price and other guiding principles.

VII. Special Populations

Pregnant and lactating women, the elderly, and those with immunodeficiency (including immune dysfunction)

The physiological characteristics of populations such as those with low blood pressure are unique, and clinical treatment involving these populations is crucial.

In addition to following the general principles of vaccine clinical trials, the trials also need to pay attention to the following:

Allow:

(a) Pregnant women and breastfeeding women

Vaccination during pregnancy may protect the fetus from intrauterine infections.

Maternal antibodies provide continuous protection for infants in the early postnatal period, as well as protection for pregnant women.

Clinical significance in gynecology, etc.

Clinical trials involving pregnant women need to be combined with non-clinical studies and non-pregnant women.

The benefit/risk ratio was comprehensively considered, taking into account data and experience in developing similar products. Based on the trial...

The level of innovation in a vaccine may require obtaining qualifications including reproductive and developmental milestones before clinical trials can be conducted.

Non-clinical research data, including toxicology studies related to pregnancy, on the effects on pregnant women and fetuses.

Potential risks should be assessed, especially when the experimental vaccine has not yet been approved for use in non-pregnant women.

In such cases, relevant clinical data from non-pregnant women of childbearing age should be obtained first. If the woman is not pregnant...

If safety data for pregnant women indicates specific safety risks, then further investigation is needed.

Further large-scale studies will be conducted within the group before a decision is made on whether to conduct clinical trials in pregnant women.

test.

Despite the hope that vaccination can protect the mother/fetus as early as possible and prevent maternal transmission.

To maximize antibody levels, but to ensure the safety of the mother/fetus, it is recommended to have appropriate antibody levels at enrollment.

The gestational stage of the pregnant subjects should be taken into consideration. At the same time, other stages of pregnancy should also be considered.

The impact of relevant factors on safety and efficacy, such as cautious enrollment of patients in early pregnancy,

Those with severe pregnancy complications, multiple pregnancies, etc.

Clinical trials involving pregnant women whose primary objective is to protect young infants.

The study should consider measuring antibody levels in the umbilical cord blood of the pregnant woman at the time of delivery.

And assess the impact of the time interval between vaccination and delivery on infant maternal antibody levels.

Impact. Furthermore, a comparative analysis should be conducted on deliveries from vaccinated and unvaccinated mothers.

Differences in infant antibody levels and persistence.

Safety considerations for pregnant participants, in addition to following the general guidelines for vaccine clinical trials...

In addition to the principles, attention should also be paid to pregnancy complications, duration of pregnancy, pregnancy outcome, and infant mortality.

An evaluation of the infant's health status at birth is conducted, taking into account both the pregnant/postpartum woman and the infant.

Conduct long-term safety follow-up.

If a vaccine clinical trial is planned to include breastfeeding women, in addition to conducting [treatment/testing] on the participants...

In addition to appropriate assessments, long-term safety follow-ups should be conducted on the breastfed infants.

It is necessary to monitor for antibodies acquired from the mother through breast milk (such as secretory IgA antibodies).

wait).

(ii) Elderly people

Due to factors such as weakened immune function and underlying diseases in the elderly, vaccination...

The level of immune response after vaccination may be low, and safety characteristics may also be unique.

Special characteristics. Therefore, if the target population for experimental vaccines includes the elderly, attention should be paid to the research and development process.

To ensure the representativeness of the study population, such as stratifying the enrollment by age and health status, and to reasonably design the study population...

Determine the sample size and proportion of each group; conduct adequate immunization programs for the elderly population.

Preface, dosage exploration; attention to the effects of underlying diseases or combined medications on immune response,

Impact on security.

(III) Immunocompromised individuals

Immunodeficiency can be caused by factors such as congenital developmental abnormalities or acquired damage.

Individuals with immunodeficiency have weakened or absent immune function, and therefore require vaccination.

In addition to the potential impact of the subsequent immune response, there may also be additional safety concerns.

Sexual risks. Therefore, given the limited accumulation of data on the safety and efficacy of vaccines.

In such cases, caution should generally be exercised when directly conducting large-sample clinical trials in this population.

Testing is necessary. Attention should be paid to the safety characteristics of vaccines using different technological approaches; for example, careful consideration should be given to...

Consideration is being given to conducting clinical trials of attenuated live vaccines in immunocompromised individuals.

Because clinical trials cannot cover all types of immunodeficiency, therefore...

When exploring immunization procedures and dosages for this population or subgroup, attention should be paid to population type.

Representativeness of the type, such as selecting people most likely to influence the immune response to a specific vaccine.

In the absence of a clearly defined threshold for immune-protective association, it is recommended to prioritize [treatment/treatment].

Choose an immunization schedule and dosage that are comparable to the immune response of healthy individuals. For clinical purposes...

Immunization schedules and dosages for immunodeficiency types not covered in the trial can be based on...

The accumulated validity and security data are taken into account.

VIII. Vaccines urgently needed to respond to public health emergencies

Vaccines urgently needed to respond to major public health emergencies (referred to as emergency vaccines)

(Vaccines) should follow the basic principles of vaccine research and evaluation; however, issues surrounding clinical "urgent" [vaccines] remain.

"Needs", and its research, clinical trial design and implementation, evaluation, etc., have special characteristics.

Due to their unique characteristics, emergency vaccines should be developed and evaluated in full consideration of these specificities.

price.

Emergency vaccines are typically based on prior experience and platforms in related vaccine development, and are developed quickly.

To accelerate research and development, it is proposed to simplify or reduce the complexity of the platform technology.

If a study is exempted, the basis and reasons should be explained.

The development of emergency vaccines should prioritize those that can provide rapid protection.

The vaccination program and convenient vaccination routes; due to the potential need for large-scale vaccination...

To achieve herd immunity, clinical trials should ideally cover all ages of the target population.

The overall development time can be shortened if necessary through clinical trial design. Furthermore,

The clinical development of emergency vaccines is typically characterized by phased and gradual processes, requiring continuous improvement as needed.

Knowledge of diseases and pathogens, epidemiological characteristics of diseases, and non-pharmacological interventions

The implementation and clinical trial environment are constantly being dynamically adjusted.

The evaluation of emergency vaccines needs to take into account the transmission and mutation of pathogens and the epidemic situation.

The situation, existing prevention and treatment methods, and public health emergency needs should be taken into account.

Applicants are encouraged to consult with regulatory agencies regarding trials in emergency situations, based on their specific circumstances.

We will communicate and exchange ideas on design and evaluation standards, safety monitoring, and other related matters.

IX. List of Abbreviations

full name of abbreviation	Chinese translation
GCP Good Clinical Practice	Good Clinical Practice for Drug Clinical Trials
I The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
DMC Data Monitoring Committee	Clinical Trial Data Monitoring Committee
GMT Geometric Mean Titer	Geometric mean titer
GMC Geometric Mean Concentration	Geometric mean concentration
GMFR Geometric Mean Fold Rise	Geometric mean growth factor
ICP Immune Correlate of Protection	Immunogenicity indicators that are correlated with protective efficacy
EAC Endpoint Adjudication Committee	Endpoint Determination Committee
ADE Antibody Dependence Enhancement	Antibody-dependent enhancement effect
VED Vaccine Enhanced Disease	Vaccine-enhanced diseases
SAE Serious Adverse Event	Serious adverse events
AESI Adverse Event of Special Interest	Adverse events of special concern

X. Glossary

Monovalent vaccine: Used to prevent disease caused by a single pathogen; may be a single-valent vaccine.

The vaccine may also be a multivalent vaccine.

Multivalent vaccines: vaccines containing two or more groups or types of the same pathogen.

A vaccine composed of antigenic components.

Multivalent vaccines: vaccines containing antigens from two or more different pathogens, formulated according to specific conditions.

They are mixed in specific proportions to create a vaccine that prevents a variety of diseases.

Antibody protection rate: the percentage of subjects whose antibodies are above the defined ICP threshold level.

Ratio.

Antibody seroconversion rate: The percentage of antibodies reaching the defined level after vaccination, compared to pre-vaccination levels.

The percentage of subjects who received an increase (e.g., at least a 4-fold increase).

Antibody positivity rate: The percentage of subjects with antibodies above the predetermined level.

The level is usually related to the detection method.

Summarized adverse events: within the predetermined time period after vaccination (i.e., the predicted adverse events)

The observation and prediction of clustered adverse events (generally 7 or 14 days) are...

First, clearly list the adverse events in the clinical trial protocol or diary card.

Non-soliciting adverse events: During the monitoring period for solicited adverse events, excluding solicited adverse events...

Any adverse event other than the initial adverse event, and the monitoring period for solicited adverse events.

All adverse events observed externally.

Serious adverse events (SAEs) refer to deaths that occur in subjects after vaccination.

Death, life-threatening, permanent or severe disability or loss of function, subject

Those requiring hospitalization or extended hospital stay, as well as those with congenital abnormalities or birth defects.

Adverse medical events such as defects.

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