Technical Guiding Principles for Protocol Changes During Drug Clinical Trials (Trial)

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I. Overview

Plan changes during drug clinical trials refer to changes during drug clinical trials because

For various reasons, it is necessary to review drugs that have been approved by the drug review agency or approved by communication and exchanges.

Modify or improve the content of the clinical trial protocol.

The sponsor should bear the main responsibility for changes to the clinical trial plan, comprehensively and in-depth

Into the evaluation of the necessity and scientific rationality of protocol changes during clinical trials, and

Impact of protocol changes on subject safety.

To guide sponsors to better implement the safety of protocol changes during clinical trials

conduct sexual evaluation and related work, control clinical trial risks, and protect the safety of subjects,

Develop these guidelines.

This guiding principle applies to registration-related traditional Chinese medicines, chemical drugs, and biological products.

(Including vaccines) related clinical trial protocol changes. These guidelines do not apply to

During clinical trials, changes in dosage forms, routes of administration, new indications, and additional

Combination use of other drugs, etc., the above situations do not fall within the scope of protocol change management

Category 1, a new clinical trial application should be submitted in accordance with relevant requirements.

2. Common situations and evaluation points of plan changes

(1) Common situations

During drug clinical trials, clinical changes may need to be made due to various reasons.

relevant content in the clinical trial protocol. It mainly includes the following aspects:

1. During clinical trials, new safety issues or potential safety issues of the drug are discovered

Risks, such as new safety data and information from clinical or non-clinical studies, need to

It is necessary to modify or improve the relevant content of clinical trial safety research in a timely manner;

2. During clinical trials, relevant content needs to be studied on the effectiveness of clinical trials

make modifications or improvements;

3ÿ During clinical trials, in order to improve the efficiency of clinical trial implementation, it is necessary to revise

Modify relevant content in the test plan;

4. Others, such as changing contact persons, contact information, etc., generally do not involve testing

Changes in program design.

(2) Key points of assessment

During drug clinical trials, a comprehensive and in-depth evaluation should be conducted before the protocol is changed.

Evaluate the necessity and scientific rationality of program changes. Should combine non-clinical safety and

Effectiveness research, pharmaceutical technology, quality standards, stability research, etc., as well as clinical

Different stages and nature of clinical trials, such as first-in-human trials, exploratory trials,

Confirmatory trials, etc., and the overall design, implementation, and implementation of clinical trials after protocol changes.

Expected effectiveness results, statistical analysis, risk control, risk-benefit trade-off, etc.

Conduct a new assessment to determine whether there may be significant impact. The key points of the assessment include:

1. Safety risks for clinical trial subjects (including risk-benefit balance);

2. Scientific nature of clinical trials;

3. Reliability of clinical trial data generation.

3. Change classification

According to changes in the clinical trial protocol, the safety risks of subjects and the scientific nature of the trial and the extent of the impact on data reliability, especially the possible adverse effects, Such as increasing the safety risks of subjects, reducing the scientific nature of clinical trials, reducing the Based on the reliability of experimental data, etc., protocol changes during clinical trials can be classified as substantial changes. Updates and non-substantive changes.

(1) Substantive changes

Substantial changes refer to the safety of clinical trial subjects and the science of the trial. Changes that may have a significant impact on the reliability of scientific properties and test data.

1. Confirmatory clinical trials require special attention and focused evaluation,

Examples of possible substantive changes are as follows:

(1) Change the main purpose;

(2) Changing the primary endpoint may have an important impact on the safety and scientific nature of the trial secondary endpoints;

(3) Change the measurement methods or evaluation criteria of the primary endpoint and important secondary endpoints. allow;

(4) Changes that may have a significant impact on the scientific nature and safety of the test Selection criteria or exclusion criteria, such as significantly changing the characteristics or scope of the subject population;

(5) Change the dosage;

(6) Change the administration method, such as administration time, administration interval, administration cycle etc.;

(7) Change, add or delete the control group/comparison drug (including placebo);

(8) Changes in diagnosis and treatment that may have an important impact on the safety and scientific nature of the trial

Medical monitoring methods or procedures;

(9) The basis for changes that may have an important impact on the safety and scientific nature of the test

treat;

(10) Reduce safety indicators or the number of visits or follow-up time;

(11) Change the definition of test end, test suspension criteria, and terminate test

Criteria (including termination of individual subjects and termination of the entire clinical trial);

(12) Change bias control methods, such as randomization methods, blinding settings, etc.;

(13) Change the statistical analysis method of the primary endpoint or important secondary endpoint,

analysis plan;

(14) Cancellation of the Data Security Monitoring Committee/Data Monitoring Committee/Independence

Data Monitoring Committee;

(15) Others.

When changing the specific clinical trial protocol, the sponsor should make changes based on the specific trial

Plan design, combined with non-clinical and pharmaceutical and other related research results, based on changes

An in-depth analysis of specific projects, extent and scope of changes was conducted to evaluate the

Whether the change does have significant impact on trial safety, scientific quality or data reliability?

If there is any adverse impact, it should be judged as a substantial change. For example: increase

The dosage does not exceed the results of non-clinical safety studies and existing clinical studies.

If the safety window indicated is a non-substantive change; it has exceeded the non-clinical safety research

If there is a safety window suggested by research or clinical research results, it is a substantial change.

2. For clinical pharmacology research and exploratory clinical trials, the nature of the trial,

The purpose, design and confirmatory trials are quite different, including dosage, dosage regimen, etc.

It is in the process of exploratory research. Therefore, at this stage of clinical trials, substantial changes

The focus of the evaluation is more focused on changes that significantly impact subject safety risks.

(2) Non-substantive changes

Non-substantive changes refer to the safety of clinical trial subjects and the nature of the trial.

Changes that will not have a significant impact on the scientific nature and reliability of experimental data.

Examples of possible substantive changes that require special attention and focused evaluation

, if based on the specific clinical trial plan, after comprehensive evaluation, it is deemed that the change

The safety of clinical trial subjects, the scientific nature of the trial, and the reliability of the trial data

If it does not have a significant impact on reliability, it is considered a non-substantive change.

Examples of other common non-substantive changes are as follows:

1. Text printing errors;

2. Minor adjustments to the text to clarify unclear statements in the plan

content;

3. File format or content (non-substantive content) of recorded test data

Appropriate adjustments;

4. Change the exploratory endpoint or its detection method;

5. Increase safety based on preventive purposes rather than emergency risk control situations

Sexual indicators or number of visits (other than invasive tests);

6. Change the contact persons and contact information of all relevant parties;

7. Others.

4. Security risk assessment

Before implementing changes to the clinical trial protocol, the sponsor should first ensure the safety of the subjects
Conduct a comprehensive and in-depth study on the risks, as well as the scientific nature of changing the experimental plan.
and evaluation, scientifically and reasonably judge the nature of plan changes, and distinguish substantive changes
or non-substantive changes.

For substantive changes, further clarification is needed as to whether they will significantly increase clinical
Safety risks to trial subjects.

The assessment of subject safety risks after the change should focus on the subject population
Characteristics and scope, investigational drug dosing regimen, drug exposure, and safe dosage
scope, nonclinical safety studies, and known clinical safety study results for the purpose
Carry out in-depth analysis on the support level of the previous safety research design, and evaluate the changes in the plan.
Whether the safety risks of clinical trial subjects have increased significantly or new risks have emerged.
risk. On this basis, combined with non-clinical effectiveness research and known clinical effectiveness
The results of this study will be used to further evaluate the expected risks-benefit of the subjects.

Examples are as follows:

Delete "people with abnormal liver and kidney function" in the exclusion criteria, but not for clinical safety
The research results indicate that this product has obvious hepatotoxicity or nephrotoxicity.
Therefore, the safety risks of clinical trials after changing the protocol will significantly increase.

Revise the inclusion criteria and change the severity of the disease from "severe" to "mild".
However, the results of non-clinical safety studies and/or the results of known clinical safety studies provide
It indicates that this product has a relatively large toxic reaction, and the expected risks to the subjects after the change outweigh the benefits.

This guideline cannot list safety risk assessment aspects of trial protocol changes.

All situations. Sponsors should conduct comprehensive and in-depth analysis and evaluation based on specific circumstances.

research, scientifically and rationally evaluate the impact of protocol changes during clinical trials on the safety of subjects

full risk impact.

5. Ethical review

If the protocol changes during drug clinical trials, the sponsor must conduct a full risk assessment

On the basis of the evaluation, the relevant regulations and requirements of ethical review should also be strictly observed.

When necessary, the researcher's handbook, informed consent form and other relevant documents should also be updated and submitted to the ethics report.

Committee review.

6. Change management and data requirements

(1) Before the implementation of protocol changes, in addition to submitting ethical review, the sponsor should also

Depending on the different nature of the change and its impact on subject safety risks, the following

Requests for work to be carried out:

1. Substantive changes that may significantly increase the risk to subject safety should be

Submit a supplementary application in accordance with the requirements of the "Drug Registration Management Measures" and other relevant laws and regulations.

2. For other substantive changes (that will not significantly increase the risk to subject safety,

However, it may significantly affect the scientific validity of the test and the reliability of the data), if it is confirmatory

For changes in the clinical trial plan, the sponsor should submit a communication application to the Center for Drug Evaluation

Please; if the sponsor deems it necessary to change the clinical trial plan for other stages,

Applications for communication and exchange can be submitted to the Center for Drug Evaluation.

3ÿ Non-substantive changes can be implemented after ethics review approval or filing.

(2) After the plan is changed, the sponsor still needs to follow the relevant requirements on the drug

Clinical trial registration and information disclosure platform updated information.

(3) After the plan is changed, the sponsor should also follow the relevant requirements in the "R&D

Periodic Security Update Report (DSUR).

(4) The sponsor submits supplementary applications or communicates with the drug review agency

When applying, at least the following technical information should be provided:

1. Describe in detail the specific content of the change. Provide clinical trials before and after changes

Compare the test plan and change list.

2. Detail the necessity, scientific justification, and subject safety of the changes

Risk control and other related basis and provide relevant research information.

3ÿ When necessary, non-clinical, pharmaceutical and other related research materials should also be provided.

4. If necessary/if revised, provide informed consent form and researcher's manual.

5. If necessary/revised, provide clinical trial review data, pharmacology and toxicology

Physiological review information and pharmaceutical review information.

7. Communication

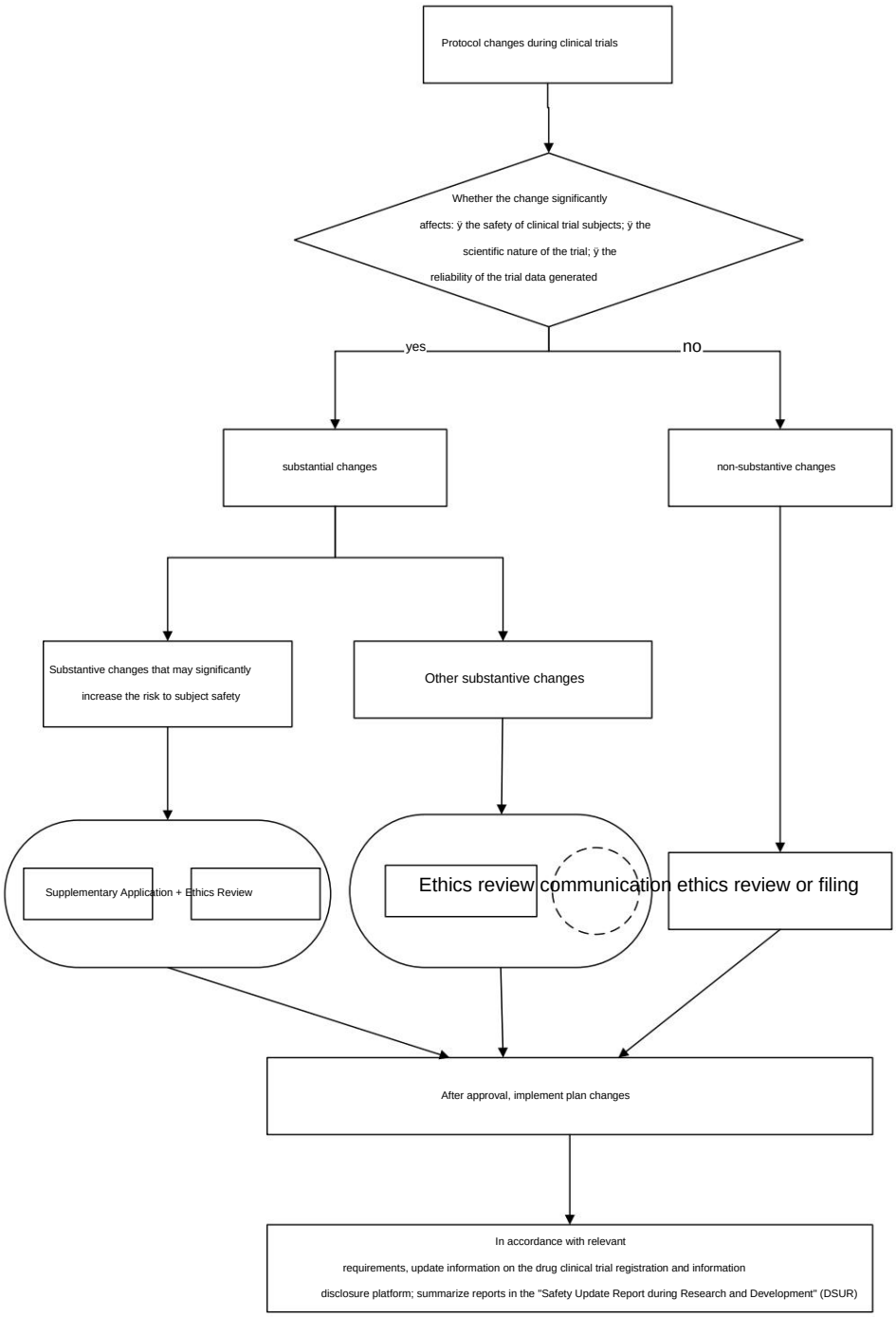
For complex or difficult program change situations not covered by this guideline,

On the basis of risk assessment, the sponsor can follow the "Drug Research and Technology

According to the relevant provisions of the Measures for the Management of Review Communication and Exchange, relevant provisions shall be submitted to the Center for Drug Evaluation.

Application for communication by category.

8. Schematic diagram of route change



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