药物临床试验方案提交与审评工作规范

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1. Background

In July 2018, the State Drug Administration issued the “Notice on Adjusting

Announcement on the Review and Approval Procedures for Drug Clinical Trials (No. 50, 2018)

The review and approval of drug clinical trials has been adjusted to clarify that the 60-day implied approval

While it is allowed, it also puts forward clear regulations on communication and clinical trial applications.

Preparation of communication meeting materials and submission of clinical trial application materials

The requirements clearly specify the submission and evaluation of clinical trial plans.

Clinical trial protocol is a document that contains the purpose, design, methodology,

The document with detailed information on statistical considerations and organizational implementation is the National Drug Administration

The Drug Evaluation Center of the Administration (hereinafter referred to as the Drug Evaluation Center) reviews clinical trial applications

Conduct review and core information exchange based on clinical trial plans,

Clinical trial design is related to the quality of drug clinical trials and is also a guarantee

The safety of subjects and obtaining high-quality data are key issues.

According to the Drug Administration Law of the People's Republic of China and the

In order to improve the applicants’

The quality of writing clinical trial protocols and standardizing communication on clinical trial protocols

improve the quality of clinical trial program review and strengthen

Provide technical guidance to applicants to ensure that the review process is in compliance with laws and regulations, open and transparent,

Formulate this work specification.

II. Scope of application and basic requirements

According to the relevant laws and regulations, applicants may

In the stage, through communication application, clinical trial application, supplementary application, etc.
Submit clinical trial plan. In chronological order, it is generally divided into clinical trial application
Pre-clinical communication, clinical trial application, clinical trial period, especially confirmatory clinical
Communication before clinical trials and communication on protocol changes during clinical trials
or supplementary application and clinical trial program registration, etc. This work specification applies to
Clinical trials involved in clinical trial applications, supplementary applications and communication applications
Submission and review of protocol materials, especially for confirmatory clinical trials (or
Key clinical trial) program.

The applicant shall be responsible for the clinical research and development of the drug and shall submit
When applying for clinical trial and supplementary application and communication application related to clinical trial,
Submit a complete clinical research and development overall plan and clinical trial plan.
When drafting a clinical trial plan, relevant laws and regulations should be followed.
Consider the ICH series of guidelines and the technical guidance on clinical trials issued by my country
Principles, relevant indications and individual drug guidelines, etc. If there is no relevant guidance in China
Principles, please refer to the stringent regulatory agencies abroad (Stringent Regulatory
guidelines issued by the SRA, clinical trials of similar products, and
Market review experience, etc.

The Drug Evaluation Center shall review the application in accordance with relevant laws, regulations, technical guidelines, etc.
The scientificity, completeness, feasibility and risks of the clinical trial plan submitted by the applicant
For those who only submit the clinical trial program framework without providing a complete
The clinical trial plan or clinical trial plan has major defects or cannot guarantee the subjects
The Center for Drug Evaluation shall not approve clinical trial applications or supplementary applications that are not safe for patients.

Clinical trials; for those who only submit the clinical trial protocol framework without providing a complete clinical trial

The test plan or clinical trial plan has major defects or cannot guarantee the safety of the subjects.

The communication application will be returned to the applicant by the Drug Evaluation Center, requiring the applicant to re-

Please resubmit after reorganizing and improving the information.

3. Submission and response of clinical trial plans during communication

1. Communication before clinical trial application

1. Application for communication

According to the "Administrative Measures for Communication and Exchange of Drug Development and Technical Review",

In principle, before applying for the first clinical trial of a new drug, the applicant should submit a

Submit a communication request.

When proposing such communications, the applicant should submit an overall clinical development plan.

plan, a complete first clinical trial plan, a risk management plan, and subsequent clinical trials

Trial protocol or protocol framework (if applicable), review of nonclinical studies, pharmaceutical studies

If the applicant does not provide supporting documents,

The applicant does not have the necessary information to communicate with the applicant and is unable to provide any consultation information.

If effective communication is not carried out, the Drug Evaluation Center may inform the applicant to reorganize and improve the information.

Submit again.

2. Review and respond to communication issues

After receiving the communication application, the project manager of the Drug Evaluation Center will review the application.

The information provided by the applicants shall be preliminarily reviewed according to relevant requirements, and any incomplete information shall be

If the requirements are met, communication will be terminated and the applicant will be informed to make improvements.

If requested, it will be delivered to the relevant professional review team.

The review team should focus on the scientificity, completeness, and operability of the clinical trial plan.
The drug's operability, risk controllability, etc. are reviewed, with a focus on the drug's title,
Safety and risk management measures support the conduct of clinical trials.
In addition to the specific questions raised by the applicant, the review should be based on the principle of subject protection.
Submit clinical trial plans and make comments or suggestions on clinical trial plans
Proposal, list the contents that should be modified and paid attention to.

The review team can hold meetings (face-to-face or online)
or written reply to the applicant and submit the communication
The meeting minutes or written reply shall include:
Including but not limited to: basic information on drug development; clinical trial data submitted by the applicant
The title, number, version number and date of the test plan; the applicant's explanation of the problem
The Center for Drug Evaluation's response to the applicant's questions;
Revision comments, etc.

2. Communication before confirmatory (or pivotal) clinical trials

1. Application for communication

The Drug Clinical Trial Approval Notice requires the applicant to “complete the exploratory
Clinical trials: Before conducting confirmatory (or pivotal) clinical trials,
The Center has submitted a communication application to evaluate the subsequent clinical trial plan.
Applicants should submit a communication application.

The applicant should conduct a preliminary analysis of the results of the early clinical trials that have been conducted.
Based on the existing clinical trial data, we design scientific, reasonable, complete and feasible
A confirmatory (or pivotal) clinical trial plan.

When submitting a communication application, the applicant should also submit a completed

Preliminary summary of clinical trials, complete plan for clinical trials and risk management

Plan, non-clinical research review, pharmaceutical research review, etc.

2. Review and respond to communication issues

The Center for Drug Evaluation conducts reviews based on the proposed confirmatory clinical trial plan.

The review team first reviews the preliminary summary of the early clinical trials submitted by the applicant.

Evaluate the results and their support for subsequent clinical trials, and clarify the current

Are the safety and efficacy results of early clinical trials sufficient to support the development of

Conduct confirmatory clinical trials. For confirmatory (or pivotal) clinical trial plans,

Focus on the suitability of the target population, dosage and cycle, and primary endpoints.

The scientific nature of the target, the acceptability of statistical assumptions, the rationality of sample size estimation,

The feasibility of the risk management plan and the assessability of the benefit/risk assessment elements

The scientificity, completeness and feasibility of the overall clinical trial plan

A comprehensive evaluation will be conducted on the feasibility, controllability of risks, etc.

In addition to answering the applicant's questions about the confirmatory clinical trial plan, the review team

In addition to the problems in the clinical trial protocol, the problems and revision suggestions should also be clarified.

Do you agree to conduct clinical trials according to this plan or the revised plan?

Applicants are required to complete the clinical trial plan and communicate again.

The review team can hold meetings (face-to-face or online)

or written reply to communicate with the applicant, and the communication meeting

Minutes or written response to the applicant. The meeting minutes or written response includes

But not limited to: basic information on drug development; clinical trials submitted by the applicant

Protocol title, number, version number and date; clarify whether the clinical trial is using

The key clinical trial for registration; whether to agree to follow the clinical trial plan

Conduct clinical trials based on the proposed or revised plan; whether the questions raised by the applicant are relevant to the

The applicants reach a consensus and clarify the common views and differences of opinion between the two parties;

The center's suggestions for revising the clinical trial protocol.

If only the clinical trial protocol framework is provided, which makes it impossible to evaluate,

If necessary, the applicant may be asked to improve the plan in the meeting minutes or written reply.

Submit the communication application again.

(III) Other communications during the clinical trial

During the clinical trial, if the applicant considers it necessary to

Communicate with the Center for Drug Evaluation on issues encountered in the trial plan or clinical trial

You can apply at any time to clarify the issues you want to communicate.

The relevant contents of Sections 3(1) and 3(2) of this Standard shall be implemented.

(IV) Communication on Application for Conditional Listing Approval

Communication regarding application for conditional marketing approval can be conducted during the clinical trial period.

The relevant contents shall be in accordance with the Technical Requirements for Conditional Approval of Drugs for Marketing

The specific application and review requirements are the same as those in Part 3 (II).

Of particular concern is the replacement of confirmatory (or pivotal) clinical trial protocols.

Whether the endpoint or intermediate clinical endpoint or interim analysis is appropriate.

In the communication before the listing application, the “attached conditions” should also be

Review clinical trial plans for the indicated population, especially those based on early

In the case of applying for conditional marketing approval with clinical trial data or surrogate endpoints, the

Carefully review the confirmatory clinical trial protocols that support routine approval and report them in the form of meeting minutes

Or confirm in the form of a written reply.

(V) Writing of meeting minutes or written responses

Communication meeting minutes or written responses are the communication between CDE and the applicant.

The results of the discussion on the issues raised during the communication and the importance of the subsequent technical review

For reference, each piece of information should be written carefully. The minutes of the communication meeting should be complete.

Present and reflect the situation of the communication meeting and encourage both parties to complete the meeting minutes on the spot

For those that cannot be completed on the spot, the review team should

Complete the revision and confirm with the applicant. The meeting minutes should not include any additional information that was not discussed at the meeting.

The content of the discussion.

The language used in meeting minutes or written responses should be accurate, concise, and clear.

The content should be complete and the conclusion should be clear. Ambiguous or misleading language should not be used.

For example, the applicants can discuss and consult with the researchers on the key issues in the proposal.

Improve after approval, reserve opinions on key issues, etc. The response to the question should be

Carefully choose whether the two parties have reached an agreement. If no agreement is reached, the two parties should

Clearly list your respective views and basis.

Further communication can be conducted through communication meetings.

The basis or conditions for the trial should make it clear that the current R&D situation does not support the development of a confirmation test.

Confirmatory (or pivotal) clinical trials or confirmatory (or pivotal) clinical trials

The defects in the trial protocol clearly indicate that clinical trials cannot be conducted using this clinical trial protocol.

After the clinical trial plan is completed, the Center for Drug Evaluation should be consulted again to confirm the

Clinical trials can only be carried out after approval.

For communication before confirmatory (or pivotal) clinical trials of innovative drugs,

Since it involves clinical, statistical and clinical pharmacology disciplines, the disciplines should be as close as possible to each other.

Coordinate and organize face-to-face meetings (or online meetings); if written replies are received,

The applicants will be reviewed by the principal on the basis of individual and timely feedback from each major.

The review report department coordinates and summarizes the opinions of various professionals and then gives unified feedback to the applicant.

Invite someone.

IV. Submission and Review of Trial Protocols in Clinical Trial Applications

1. Submission of clinical trial plan

When submitting a clinical trial application, the applicant should

and Application Materials Requirements, "Chemical Drug Registration Classification and Application Materials Requirements", "

"Registration Classification and Application Materials Requirements for Pharmaceutical Products" submit a complete clinical development plan,

A complete clinical trial protocol (at least the first clinical trial protocol), risk factors,

Risk management plan and subsequent clinical trial protocol framework (if applicable).

2. Review of clinical trial protocols

The review team should review the key elements of the submitted clinical trial protocol.

Evaluation of scientificity, completeness, operability, and risk controllability. If necessary,

Expert consultation meetings may be held.

For clinical trials that are considered to be approved after comprehensive review, the technical review

The indications, clinical trial methods and

The title, number, version number, version date, etc. of the case, and if necessary, the clinical

The revision opinions or suggestions of the trial plan should also be noted:

Before conducting an exploratory clinical trial of a drug, a corresponding clinical trial plan should be formulated.

After the exploratory clinical trial is completed,

Before conducting confirmatory (or pivotal) clinical trials, communicate with the Center for Drug Evaluation

Application for communication meeting, evaluation of subsequent clinical trial plans (if applicable);

Clinical trials of drugs should be carried out within 3 years from the date of approval.

If the participant signs the informed consent form, this document will automatically become invalid.

For clinical trial plans that require revision after review,

Communicate with applicants through professional inquiry letters and clearly inform them of the problems existing in the current plan.

The applicant is required to follow the “Supplementary

Submit the revised clinical data within the prescribed 5 days.

To ensure that the clinical trial plan approved by the review is scientific and feasible.

Action nature.

The clinical trial plan submitted by the applicant is deemed by the reviewer to be unsatisfactory.

feasibility, or defects that make it impossible to ensure the safety of the subjects, or other

Serious defects and other problems, and the applicant cannot make corrections within the time limit specified in the inquiry letter

If the application is not improved, the clinical trial application should not be approved.

The "Notification of Clinical Trial Approval" should clearly inform the applicant that the current information is temporarily unavailable.

The reasons for not supporting the clinical trial, the title of the clinical trial protocol, and

Identify specific deficiencies in the clinical trial protocol (e.g., incomplete, unscientific, inconsistent

laws and regulations, relevant guidelines, uncontrollable risks, etc.), and submit an application

The person re-submitted and suggested revisions or concerns.

V. Changes to Clinical Trial Protocol

With the development of science and the progress of clinical trials, there is a need for

When the plan is changed, the applicant may

The relevant requirements of the Technical Guidelines for Protocol Changes during Clinical Trials are first

Conduct self-assessment of the changes and carry out further work based on the results of the self-assessment.

Changes to the protocol during a clinical trial are classified into the following three situations:

(1) The sponsor assesses that the risk to subject safety may be significantly increased

A supplementary application shall be submitted for any substantial changes.

(2) The sponsor assesses that it will not significantly increase the safety risk to the subjects,

However, other factors that may significantly affect the scientific nature of the test and the reliability of the test data generated

Substantial changes, if it is a confirmatory (or pivotal) clinical trial protocol, apply for

The person should submit a communication application to the Center for Drug Evaluation.

If the sponsor deems it necessary to change the plan, he or she may also communicate with the Center for Drug Evaluation.

Exchange application.

(III) If the sponsor considers that the change is not substantial, the change shall be subject to ethical review.

It can be implemented after approval or filing.

For the first two situations, the sponsor should refer to the

The review team will submit materials in accordance with the relevant requirements of the Technical Guidelines for Changes in Clinical Trials.

The review of the supplemental application for protocol change/communication review should focus on the changes

Matters, clearly state whether you agree to the plan change item by item, for matters that you do not agree to change,

The statement should be clear and the reasons should be stated.

VI. Clinical Trial Registration and Information Disclosure

According to the Drug Registration Management Measures, the applicant should

Before clinical trials of drugs,

The sponsor should refer to the Drug Registration Platform to register the drug clinical trial plan and other information.

The Center for Drug Evaluation shall submit materials according to the current laws and regulations.

Laws and regulations, drug clinical trial license documents, registration platform filling guide, communication

The minutes of the communication meeting require the applicant to register the drug clinical trial information.

Conduct normative and logical review. If the registered clinical trial plan involves changes,

If necessary, it can be made public after confirmation by the review team.

The time limits specified in this work specification are calculated in working days.

Any inconsistency with the requirements of published documents shall be implemented in accordance with this work specification.

This work specification shall be implemented from the date of publication.