Guiding Principles for Comprehensive Analysis of Effectiveness in Drug Clinical Research

(Trial)

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I. Introduction

When applying for drug registration and marketing, in order to better understand the overall risks of the drug To evaluate the risk-benefit situation, the sponsor needs to submit additional information related to the drug In addition to evidence of efficacy and safety from all individual clinical studies, this is usually required Integrate research data from different sources related to the drug to formulate a comprehensive Possible complete chain of evidence and in accordance with ICH M4E (R2) General Technical Document (CTD) Module 5 Section 5.3.5.3 requires submission of multiple study data analysis reports tell.

Research from various sources including non-clinical studies, dose-response relationships, drug Interactions with drugs and drugs and diseases (e.g. effects of renal metabolism drugs on the kidneys) Clinical pharmacology research on the effects, research on drug-device combinations related to human factors research, in vitro studies of drug activity, and exploratory studies conducted nationally and internationally and confirmatory clinical studies, etc. Comprehensive analysis of clinical study data is the responsibility of the sponsor An important part of the data analysis report submitted for multiple studies, usually including comprehensive analysis of efficacy and safety. Comprehensive analysis of effectiveness is a Conduct all clinical effectiveness research data for the same indication to be applied for registration Systematic analysis, comparing the strengths and weaknesses of different research data to describe the overall effectiveness effectiveness characteristics, and conduct research on the reasons why some important research data were not included in the analysis. explain. Comprehensive safety analysis is a comprehensive clinical safety study of the drug Conduct a systematic analysis of the data to describe the overall safety profile and identify drugs that should be included

Risk statement in the product manual.

This guideline is intended to provide sponsors with guidance on the effectiveness of clinical studies of drugs.

Comprehensive analysis provides technical guidance to demonstrate the effectiveness of the drug as comprehensively and systematically as possible.

effectiveness characteristics. A meta-analysis in this guideline refers to an individual study of independent studies.

Individual-level or group-level data are combined for analysis.

In principle, all clinical trials related to the same indication for which the drug is proposed to be registered

All clinical effectiveness studies should be included in a comprehensive analysis of effectiveness, including but not limited to the following

content:

1. Present all clinical studies in tabular form regardless of whether they are accredited

Efficacy results, including studies completed, according to a pre-specified research plan

And studies that were terminated early (for example, because the effectiveness results reached the preset during the interim analysis)

premature termination due to certain conditions), ongoing research, terminated but unfinished research

research and legacy research, etc.; and provide a brief summary of all clinical studies in the list

key design information and effectiveness results, regardless of whether the effectiveness results are consistent

accounting significance.

2. Review key design information and statistical analysis methods for all clinical studies.

A comparison is made and its impact on the effectiveness results is discussed.

3. Compare and meta-analyze the effectiveness results of all clinical studies.

4. All clinical trials can be conducted as needed (for example, to observe the efficacy of subgroups of people).

Effectiveness results were compared and meta-analysed across study subgroups.

5. For clinical trials assessing the relationship between exposure (dose or plasma concentration) and effect.

Comprehensive analysis of clinical pharmacology research data and combined with the effectiveness of clinical research

results to support the usage and dosage stated in the drug package insert.

6. The long-term efficacy, tolerability and

Discontinuation data are compared, summarized and discussed.

2. Overview of individual clinical studies

(1) Key research information

Extract key research information from each individual clinical research report and list it

The form is briefly presented. Key research information includes: drug indications, research code

number, research status (such as ongoing or completed), research area, research

The purpose of the study, the stage of the study (e.g., phase II or phase III), the type of comparison (e.g., superiority or

non-inferiority), trial group, type of comparison (such as placebo or active drug pair)

photos), sample size (such as the preset and actual number of enrollments and the number of group allocations),

Randomization method and randomization stratification factors, blinding method (such as single-blind, double-blind or open

design), key inclusion criteria, medication regimens, and standard definitions of effectiveness endpoints

and effectiveness results, etc. Regardless of whether the effectiveness results of a single clinical study are achieved

The purpose of the study should list at least its primary and key secondary efficacy endpoints.

Estimate, interval estimate, and *P* value (if applicable).

For individual clinical studies that are not included in the comprehensive analysis of effectiveness, the original

because.

(2) Research design elements

Compared to the brief content in the above list, this section should provide a more detailed

The design elements of each clinical study are described, compared, and discussed, especially

Clinical studies included in the comprehensive analysis of effectiveness. Research design elements include, but are not limited to

to the following:

1. Key entry criteria for subjects, such as disease status, demographic characteristics, and Concomitant medication status, etc.; or subject selection methods, such as enrichment strategy and design Methods such as calculation and placebo lead-in period.

2. Drug dose selection, such as fixed dose, flexible dose, forced titration, etc.

3. Type of comparison, such as superiority, equivalence or non-inferiority design, etc. Pick When using a non-inferiority design, special explanation should be given as to whether the non-inferiority margin is reasonable and constant. Determine whether the hypothesis is true.

4. Selection of control group

(1) Contemporaneous control refers to the experimental group and the control group drawn from the same research population. Select and administer drugs simultaneously, such as placebo control, no drug/blank control, active drug substance control and dose-effect control, etc. When using positive drug controls, special care should be taken Explain the rationale for selecting this positive drug.

(2) External controls, such as historical controls outside the study population, parallel controls, Target value control or synthetic control, etc.

(3) Multiple controls, such as using both placebo controls and Positive drug control, or the simultaneous use of several doses of the test drug and several agents amount of positive drug control.

5. Selection of efficacy endpoints, such as primary or key secondary efficacy endpoints. If the efficacy endpoint is a surrogate endpoint, the rationale for selecting the endpoint should be discussed to and support its rationality in predicting clinical outcomes. If the efficacy endpoint is the first use Clinical outcome evaluation indicators used (such as patient-reported outcomes, clinician-reported outcomes

bureau, etc.), the rationality of its use should be explained.

6. Treatment duration and study duration, if treatment duration is 1

months, and the follow-up duration was 3 months.

7. Sample size determination, such as sample size estimation parameters, estimation methods, experimental groups

Don't assign ratios.

8. Randomization methods, such as simple randomization, block randomization, and stratified block randomization

etc., or adaptive randomization, such as minimization methods, etc.; and random assignment systems,

Such as interactive response system.

9. Blinding methods, such as single-blind, double-blind and open design, as well as the identification of experimental drugs

Methods of simulating smells or colors, etc. (such as using simulating agents).

10. Use independent committees in the study, such as data monitoring committees, final

Click on the Adjudication Committee, etc.

11. Adaptive design features, such as sample size re-estimation, group sequential design

planning, abandonment or addition of treatment groups, changes in patient inclusion criteria, etc. Special attention should be paid to

Whether the changes to research measures are preset and whether the overall Type I error rate is effectively controlled

System etc.

(3) Statistical analysis methods

This section addresses the primary and key secondary efficacy endpoints of each clinical study.

Describe, compare and discuss statistical analysis methods for points, especially detailed comparisons

Similarities and differences in statistical analysis methods for clinical studies included in comprehensive analyzes of effectiveness. Bag

Including but not limited to the following:

1. Compare the primary and key secondary efficacy endpoints of each individual clinical study

Similarities and differences in statistical analysis methods, such as covariance analysis using different covariates

wait.

2. Compare the situation of subject dropout and missing data in each single clinical study

management method.

3. If necessary, non-preset statistical scores in each individual clinical study can also be analyzed

Analysis methods are discussed.

3. Overall analysis of effectiveness results

(1) Comparison between individual clinical studies

A list showing the number of subjects, dropouts, and people in each single clinical study

Oral characteristics, baseline characteristics, etc. Lists or graphs (such as forest plots) to display and compare

Compare effectiveness results from individual studies. Comparison of effectiveness results from individual studies,

It should focus on the primary and key secondary efficacy endpoints, combined with subject demographics.

and baseline characteristics (e.g., disease severity), inclusion or exclusion criteria, control type,

Exposure dose, exposure duration, and statistical analysis methods are discussed. also,

The consistency of effectiveness results among subjects across different regions (if available) should also be analyzed.

If an efficacy endpoint is not important in multiple individual clinical studies

The same but repeated occurrences can also be compared and analyzed (even without statistics

scientific significance) as an important evaluation content of drug effectiveness. For example, in treatment

In similar studies of coronary heart disease drugs, a frequently observed effectiveness endpoint is death.

The same or different composite end points of death events. Deaths in these similar studies

By comparing and analyzing what happened, you can know whether the drug really has

benefit from reducing mortality.

Generally, the same or similar research design characteristics (such as the same or similar
The effectiveness results of individual clinical studies (control group) are put together to compare
and discussion. If there is heterogeneity in these results, this should be fully discussed. right
Clinical research to confirm the effectiveness of the Chinese population based on foreign research data
(e.g. bridging research), should be specifically noted during the discussion and provide a link to the study abroad
Additional supporting information for extrapolation of data to the Chinese population.

(2) Meta-analysis of individual clinical studies

A meta-analysis of the effectiveness results of each individual clinical study should be described.
the rationality of the methods used. It is recommended to use individual-level data for meta-analysis
analysis, but heterogeneity between individual studies should be taken into account.

During meta-analysis, individual studies should be carefully selected to minimize
Reduce selection bias to ensure the credibility of meta-analysis results. Attention should be paid to research
Single studies with different design characteristics are generally not suitable for meta-analysis, e.g.
Meta-analyses should not be performed on arm studies and studies with parallel controls.

4. Subgroup analysis

Similar to the analysis of the total population, effectiveness is performed on subgroups of interest
The overall analysis of the results also includes the subgroup effectiveness of each individual clinical study.
Comparison and meta-analysis between results. The purpose of subgroup comparisons is to assess
Consistency of effectiveness results across subpopulations across individual studies. In most cases
In this case, meta-analysis of subgroup populations is more likely to accurately assess the relationship between subgroup populations.
The differences in effectiveness results between the two groups can provide hypotheses for further clinical research.

The subgroups in each individual study and their definitions are presented in tabular form.

Subgroup population analysis can be displayed in lists or graphs (especially forest plots), but is generally not

Statistical inference is required. can be divided according to the subgroup definition of each individual study.

layers to minimize bias introduced by differences in study design. subgroup of people

Group analysis includes but is not limited to the following:

1. Evaluate key demographic characteristics (such as age, gender) and other relevant internal

internal and external factors (eg, disease severity, previous treatments, concomitant medications, renal

functional or hepatic impairment) on effectiveness results.

2. Evaluate differences in effectiveness results across countries and regions.

5. Analysis of clinical information related to recommended drug dosage

Clinical information related to recommended drug dosing includes assessment of exposure (dose or

the relationship between plasma drug concentration) and effect and the relationship between estimated dose and blood drug concentration

clinical pharmacology data. These data typically cover the following:

ÿ Recommended dose range, including starting dose and maximum dose; ÿ Do not increase dose

The lower limit of dose that will lead to increased effectiveness; ÿ Dosage for each indication and subgroup population

amount; ÿ frequency of administration; ÿ method of titrating dosage; ÿ based on clinical pharmacology data

According to medication recommendations (such as food effects); ÿ Due to drug interactions or special populations

(e.g. children, elderly, genetically defined groups, renal insufficiency or

patients with liver dysfunction) and need to adjust the dose; ÿ Regarding compliance with the medication regimen

Important precautions regarding sex; ÿ Any other suggestions related to individualized medication.

When performing a comprehensive analysis of clinical pharmacology data from individual studies, it is important to

Pay attention to the following aspects:

1. Analyzes of individual studies supporting dose recommendations and any cross-sectional studies

The analysis results of cross studies should be included in the comprehensive analysis.

2. If the preparation used in the study is inconsistent with the preparation to be commercialized, it should be stated

Demonstrate its comparability.

3. Bias caused by nonlinear characteristics of pharmacokinetics should be described.

separation and possible causes (e.g. delayed effects, tolerance effects or enzyme induction) and their effects on

Implications for clinical use.

4. Limitations of the data should be described and assessed (e.g. the study used a titration design

rather than a fixed dose design).

5. The method of administration for each study should be clearly described (e.g. once daily in the morning or

before meals), the dosage of each treatment group, and the occurrence of adverse events

Information on medication changes and any critical measures specified in the study protocol that affect

Information related to medication changes in medication regimens (e.g., dose level titration).

6. The method used to assess differences in dose-response relationships should be described (even if

when no differences are found), including specific studies in subgroups of populations,

Analysis of effectiveness results and study drug blood concentrations by subgroups

Detection methods, etc.

6. Long-term effectiveness, tolerability and discontinuation analysis

Information on long-term drug effectiveness, tolerability, and discontinuation should be comprehensively analyzed.

analysis. Generally speaking, effectiveness and tolerability require long-term observation, but key clinical

Studies typically have shorter observation periods (e.g. 6-12 months) and therefore, whenever possible

Collect all available information on long-term observations and describe doses used, duration of exposure

Long-term observation information such as time and reasons for discontinuation, and analyze the effectiveness and

Changes in tolerance and the impact of other concomitant medications on effectiveness may have

Efficacy, tolerability, and discontinuation are summarized and discussed. Comprehensive long-term effectiveness

The combined analysis should focus on the effectiveness results of controlled clinical studies and should clearly state

Be sure to distinguish between well-controlled studies and relatively loosely designed studies.

7. Regulatory considerations

(1) Develop and submit a statistical analysis plan for comprehensive effectiveness analysis

Before conducting a comprehensive analysis of effectiveness, a corresponding statistical analysis plan should be developed.

plan to describe its analytical strategies and methods, including analysis of each individual clinical study

A method for meta-analysis of effectiveness results. Integration with single clinical studies

Unlike the statistical analysis plan, the statistical analysis plan for the effectiveness comprehensive analysis does not need to be

developed before the conclusion of each individual study. Statistical analysis plan for comprehensive effectiveness analysis

This should be submitted to the regulatory agency together with a comprehensive analysis of effectiveness. Suggestions are being formulated

Statistical analysis of comprehensive analyzes of effectiveness before or during planning with regulatory agencies

Communicate fully.

(2) Meta-analysis of effectiveness results can only be used as supporting evidence.

Although the meta-analysis of the effectiveness results of each single clinical study (including

meta-analysis of the total population and subgroups) can provide regulatory agencies with more

Sufficient relevant information on the effectiveness of the study drug, but not a substitute for each individual item

The confirmatory role of research. Regardless of the total population and subgroups of each individual study,

Whether the effectiveness results are statistically significant, regardless of meta-analysis results

Whether there is statistical significance or not, meta-analysis of effectiveness results can only be used as a

Supportive evidence of effectiveness cannot be regarded as confirmatory evidence.

(3) Comprehensive analysis of discriminant effectiveness and summary of clinical effectiveness

Comprehensive analysis of effectiveness and clinical effectiveness summary are both CTD or electronic communication

Information on the overall effectiveness of clinical studies required using technical documents (eCTD)

All reports must comply with the format requirements of the document. But the comprehensive analysis of effectiveness is

Comprehensive analysis of effectiveness results from all clinical studies, and clinical effectiveness summary

It is only a summary of the comprehensive effectiveness analysis report and should not include comprehensive effectiveness

Any analysis or conclusion other than analysis. Comprehensive analysis of effectiveness should be placed in

Section 5.3.5.3 “Multiple Study Data Analysis Report” of CTD/eCTD Module 5

, the clinical effectiveness summary should be placed in Module 2, Section 2.7.3 “Clinically Effective

Safety Summary. When very limited data are available from clinical studies, e.g., orphan

Clinical studies of drugs, or only one clinical study, or only a few small clinical studies

Clinical studies, the main part of the comprehensive effectiveness analysis report can be used as clinical effectiveness

Sexual summary. At this point, there can be split between CTD/eCTD module 2 and module 5

Comprehensive effectiveness analysis report, the main part of which is placed in Section 2.7.3 of Module 2.

The tables, figures and data sets as appendices are placed in Section 5.3.5.3 of Module 5,

And need to be clearly explained in the corresponding chapters of Module 2 and Module 5.

(4) Impact of applying ICH E9(R1) on the implementation of this guideline

ICH E9(R1) proposes the concept of estimation targets and establishes the

Goals, estimated goals (including accompanying events and their handling strategies), estimation methods (including

A new framework for layer-by-layer in-depth analysis of sensitivity analysis) to estimated values. Applicable to ICH E9

(R1), these new concepts and new frameworks will inevitably affect the implementation of this guideline.

Give. Therefore, after accumulating more mature experience in applying these new concepts and new frameworks,

These guidelines will be further revised following practical experience.

8. References

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Appendix 1: Glossary

Integrated Summary of Efficacy (ISE): Yes

Systematize all clinical effectiveness research data of a drug to be registered for the same indication

Analyze, compare the strengths and weaknesses of data from different studies to describe overall effectiveness characteristics, and

Explain the reasons why some important research data were not included in the analysis.

Integrated Summary of Safety (ISS): the right medicine

Systematically analyze all clinical safety research data of the drug to describe the overall safety characteristics,

and identify risk statements that should be included in drug package inserts.

Summary **of Clinical Efficacy (SCE):** Yes

A brief summary of the comprehensive analysis of effectiveness, the scope of which is consistent with the comprehensive analysis of effectiveness,

Any analysis and conclusions other than a comprehensive analysis of effectiveness are not included.

Common Technical Document (CTD): refers to

A common organizational structure and format agreed upon among global regulators for

A standard document for drug marketing applications that can simultaneously meet the requirements of regulatory agencies around the world.

Information requirements.

Synthetic Control : There is no parallel control in clinical research, but

It uses data collected outside the study as a control, including historical research data.

data, real-world data, or data from other sources.

Appendix 2: Chinese and English comparison table

Chinese	English
Integrated Summary of Safety, ISS	Electronic Common Technical Document,
Intercurrent Event	eCTD
Composite endpoint	Composite Endpoint
estimation method	Estimator
estimate target	Estimand
estimate	Estimate
synthetic control	Synthetic Control
Constant Assumption	Constancy Assumption
Patient-reported Outcome, PRO	Dose-response Relationship
Legacy Study	Clinical Outcome Assessment, COA
Clinician-reported Outcome	Summary of Clinical Efficacy, SCE
Bridging research	Bridging Study
Forest Map	Forest Diagram
Adaptive Design	Adaptive Design
Common Technical Document, CTD	Integrated Summary of Efficacy, ISE
Concurrent Control	No Treatment Control