Guideline on Integrated Summary of Efficacy for Clinical Trials

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Contents

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1. INTRODUCTION

To better evaluate the overall risks and benefits of a drug at the time of registration and marketing application, sponsors are required to submit data on efficacy and safety from all individual clinical studies related to the drug, and they should also usually integrate other sources of data relevant to the drug to provide substantial evidence. Reports of analyses of data from more than one study are submitted as required by ICH M4 Common Technical Document (CTD) Module 5, Section 5.3.5.3.

Data sources include nonclinical studies; clinical pharmacology studies that describe dose-response, concentration-response, and drug-drug and drug-disease (e.g., renal dysfunction) interactions; human factor studies for drug-device combinations; in vitro studies that clarify drug activity; and exploratory and confirmatory clinical studies conducted locally and internationally, etc. The integrated analysis of clinical data is an important part of the analysis of data from multiple studies submitted by the sponsor, and usually includes an Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS). ISE provides systemic analyses of data across all studies that characterize efficacy of the drug, compares the strengths and weaknesses of the data from different studies to describe the

overall efficacy results, and explains why data from certain important studies are not included in the analysis. ISS provides systemic analyses of data across all studies that characterize safety of the drug, describes the overall safety results, and identifies risk statements that should be included in the package insert. This guideline is intended to provide technical guidance for sponsors to conduct integrated analysis of clinical efficacy data, so as to show the efficacy characteristics of a study drug as comprehensively and systematically as possible.

In principle, all clinical studies should be included in ISE, which should normally consist of the following:

1) A tabular listing of all studies should be provided, irrespective of whether the data support or do not support a conclusion of efficacy, including completed studies, studies that were terminated early according to a prespecified study plan (e.g., early termination because efficacy results met prespecified conditions at the time of interim analysis), ongoing studies, terminated but incomplete studies, and legacy studies; and critical design features and efficacy results should be briefly summarized, irrespective of whether the efficacy results were statistically significant.
2) Critical design features and statistical methods should be compared across all studies, and the corresponding efficacy results should be discussed.
3) Comparison and meta-analyses should be conducted on the efficacy results of all studies, with a focus on clinical trials for the same or

related indications.

4) Comparisons and meta-analyses of efficacy results for subgroups across all studies may be performed as needed (e.g., to observe the efficacy of subgroups or to provide subgroup information in the package insert).
5) A comprehensive analysis of clinical pharmacology data that pertain to the relationship between exposure (dose or blood concentration) and response (especially dose-response relationships) should be performed in conjunction with the efficacy results of clinical studies, supporting the dosage and administration section of the labeling.
6) Long-term effectiveness, tolerance and discontinuation data from all clinical studies should be compared, summarized and discussed.

2. OVERVIEW OF INDIVIDUAL STUDIES

2.1 Critical Information

A tabular listing of critical information for individual studies should be briefly described. Critical information includes: drug indication, study number, study region, study objectives, study phase such as Phase II or Phase III, types of comparison (e.g., superiority or non-inferiority), study groups, types of controls (e.g., placebo or active control), sample size (e.g., number of predefined and actual enrollments and number assigned to groups), method of randomization and randomization stratification factors, blinding (e.g., single- and double-blind or open label), key inclusion/exclusion criteria, dosing regimen, standard definitions of

clinical response, adverse event categories, pharmacokinetics, in vitro testing, and efficacy results. Point estimates, interval estimates, and P-values for the primary and key secondary efficacy endpoints must be listed, irrespective of whether the efficacy results of individual studies meet the study objectives.

For individual studies that are not included in ISE, the reasons should be provided.

2.2 Study Design

In contrast to the brief overview in the above section, this section should include the description and critique of the design features of all studies, especially those that are incorporated into ISE. Examples of common design features are as follows:

1) Inclusion and exclusion criteria, for example: disease characteristics, demographic characteristics, prior and concomitant medications; or subject selection methods, such us use of enrichment strategy and design, or use of placebo run-in.
2) Dosage selection, including fixed-dose, flexible dose, and forced titration.
3) Types of comparison, such as superiority, equivalence or non-inferiority designs etc. When using non-inferiority design, special attention should be paid to the justification of the non-inferiority margin and the constancy assumption.
4) Selection of control group

① Concurrent control, where the control group and test group are chosen

from the same population and treated concurrently, such as placebo control, no-treatment/blank control, active control, and dose-response control. When an active control is used, the rationale for the selection of the active drug should be specifically stated.

② External control, such as historical control and synthetic control using real-world data, etc.

③ Multiple controls, such as use of both placebo and active control, or use of several doses of test drug and several doses of active control in a single study.

5) Choice of endpoints, such as primary and key secondary efficacy endpoints. If an efficacy claim is based on a surrogate endpoint, the basis for choice of the endpoint should be discussed and its validity as a predictor of clinical outcome should be supported. If the efficacy claim is based on a new patient-reported outcome or clinician-reported outcome, justification should be provided.

6) Study duration and treatment duration, e.g., 1 month for treatment duration and 3 months for follow-up.

7) Sample size determination, such as parameters used for sample size estimation, estimation methods, and test group allocation ratios.

8) Randomization methods, such as simple randomization, block randomization, stratified blocked randomization, adaptive randomization, minimization methods, and random assignment systems, such as Interactive Web Response Systems (IWRS).

9) Blinding methods, such as single-blind, double-blind, and open label;

and methods of simulation of the study drug in odor and color, etc.

10) Use of independent committees in the study, such as data monitoring committees, event adjudication committees, etc.

11) Adaptive design features, such as sample size re-estimation, group sequential design, dropping or adding treatment arms, and changes in patient enrollment criteria. Special attention should be paid to whether the modifications of study design are pre-defined, whether the overall Type I error rate is controlled, etc.

2.3 Statistical Methods

This section should describe, compare, and discuss the statistical methods for the primary and key secondary efficacy endpoints for each study, and in particular, should compare in detail the similarities and differences in the statistical analysis methods of the clinical studies included in ISE. Also, the meta-analyses method in the statistical analysis plan for ISE should be briefly described in this section. The following should normally be included:

1) Compare the similarities and differences in statistical methods for the primary and key secondary efficacy endpoints in each individual study, such as analysis of covariance with different covariates.

2) Compare the handling of dropouts and missing data in each individual study.

3) Describe briefly meta-analyses method for analyzing the efficacy results of individual studies in the statistical analysis plan.

4) If necessary, post-hoc analysis in individual studies can also be

discussed.

3. OVERALL ANALYSIS OF EFFICACY RESULTS

3.1 Comparison of Results of Individual Studies

Tables should be provided to show number of subjects, number of dropouts, demographic characteristics, and baseline characteristics. Efficacy results of each individual study should be presented and compared, using tables or figures (such as forest plots). Comparisons of efficacy results across individual studies should be based on primary and key secondary efficacy endpoints and discussed in relation to demographic and baseline characteristics (e.g., disease severity), inclusion or exclusion criteria, types of control, exposure dose, durations of exposure, and statistical methods. In addition, the consistency of efficacy results in subjects from different regions (if any) should be analyzed.

If an efficacy endpoint appears in multiple studies with different level of importance, though the individual result is not statistically significant, it can be analyzed and compared across the studies as an important assessment of drug efficacy. For example, in studies for the treatment of coronary heart disease, the primary efficacy endpoint is a composite endpoint of mortality and other events. A comparison and analysis of occurrence of death events across such comparable studies will provide insight into whether the drug has a true benefit in reducing mortality.

The efficacy results of individual studies with the same or similar design features (e.g., the same or similar control groups) should usually be

compared and discussed together. When heterogeneity is observed, these findings should be thoroughly discussed. Clinical studies (e.g., bridging studies) that confirm efficacy in Chinese populations on top of data from foreign studies should be specifically noted in the discussion, along with additional supporting information for extrapolation of data from foreign studies to Chinese populations.

3.2 Meta-analyses of Each Individual Study

The rationality of the methods used in the meta-analyses of the efficacy results for individual studies should be described. Sponsors are encouraged to use individual subject-level data for meta-analysis.

Individual studies should be carefully selected during the meta-analysis to minimize selection bias to ensure the reliability of the meta-analysis results. It should be noted that individual studies of different study types should not be used for meta-analysis, for example, a single-armed study should not be lumped with a study with controlled group for meta-analysis.

4. ANALYSIS FOR SUBPOPULATIONS

Similar to the analysis of overall population, the analysis of efficacy results for subgroups of interest also include comparisons and meta-analyses of the efficacy results across individual studies. The purpose of subgroup comparisons is to assess the consistency of efficacy results among subgroups across individual studies. In most cases, subgroup meta-analysis is more likely to provide adequate statistical power to assess differences in efficacy results between subgroups, which can suggest hypotheses for

further clinical studies.

Subgroup analyses can be presented using tables or figures (especially forest plots), and statistical inference is generally not required. Stratification can be performed by subgroups of each individual study to minimize bias introduced by differences in study design. Subgroup analysis should typically include the following:

1) Evaluate the effect of major demographic factors (e.g., age and sex) and other relevant intrinsic and extrinsic factors (e.g., disease severity, prior treatment, concomitant drugs, renal or hepatic dysfunction) on efficacy results.
2) Evaluate the differences in efficacy results across countries and regions.
3) If a subgroup is planned to claim an effectiveness benefit in the package insert, it should be assessed whether a subgroup analysis has been predefined in individual studies with appropriate multiplicity adjustments, etc., so that an inferential conclusion on the efficacy results for the subgroup can be obtained.

5. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

Clinical information relevant to dose recommendations includes clinical pharmacology data that evaluate the relationship between exposure (dose or blood concentration) and response (especially dose-response relationships) and that evaluate the relationship between dose and blood concentration. These data usually cover the following: a) recommended

dose range, including starting and maximal doses; b) upper dose limits beyond which safety has not been established or beyond which increasing the dose would not result in an increase in effectiveness; c) doses for each indication and subpopulation; d) dose schedule; e) the method of dose titration; e) dose recommendations based on clinical pharmacology data (e.g., food effects); f) modification of dosage needed because of drug interactions or in special patient populations (e.g., children, elderly, groups defined by genetic characteristics, patients with renal or hepatic insufficiency); g) important considerations regarding compliance with the dosing regimen; and h) any other recommendations related to individualized dosing.

Integrated analysis of clinical pharmacology data across individual studies focuses on the following:

1) The analysis results of each individual study, and any cross-study analyses supporting the dose recommendation, should be included in the integrated analysis.
2) If the drug product used in the study is not identical to the one commercially available in the market, their equivalence should be established.
3) Deviations due to, for example, nonlinear characteristics of pharmacokinetics and possible causes (e.g., delayed effects, tolerance, or enzyme induction) and their impact on clinical use should be described.
4) Limitations of the data (e.g., titration designs were used instead of

fixed-dose designs) should be described and assessed.

5) The dosing instructions in each study (e.g., once daily in the morning or before a meal), the dose administered for each treatment group, information on relevant dosing changes due to adverse events, and information on relevant dosing changes when any key measures specified in the study protocol affect the dosing regimen (e.g., dose level titration) should be clearly described.
6) The methods used to assess differences in dose-response relationships (even when no differences were found) should be described, including specific studies conducted for subgroups, analysis of efficacy results by subgroup, and determination methods of blood level of the study drug.

6. ANALYSIS FOR PERSISTENCE OF EFFECT, TOLERANCE, AND DISCONTINUATION

Long-term effectiveness, tolerance, and discontinuation of the drug should be analyzed in a comprehensive manner. In general, drug effectiveness and tolerance are observed over time, but the observation period for pivotal clinical studies is usually short (e.g., 6–12 months). Therefore, all available information for long-term observations should be collected if at all possible, and presented in a study list with descriptions of long-term observations such as dose usage, duration of exposure, and reasons for discontinuation. Changes in effectiveness and tolerance over time should be analyzed, and effectiveness, tolerance, and discontinuation should be summarized and

discussed. Integrated analyses of long-term efficacy should focus on the efficacy results of studies with controls, and should clearly distinguish between well-controlled studies and those with relatively poor design.

7. REGULATORY CONSIDERATIONS

7.1 Develop and Submit Statistical Analysis Plan for ISE

Before conduct of an ISE, a corresponding statistical analysis plan should be developed to describe its analysis strategy and analysis methods. Unlike statistical analysis plans for individual studies, those for ISE do not need to be developed prior to the end of the study. The statistical analysis plan for ISE should be submitted to the regulatory authorities together with the ISE report. Full communication with regulatory authorities is recommended prior to or during the development of a statistical analysis plan for ISE.

7.2 Meta-analysis of Efficacy Results only as Supporting Evidence

While meta-analyses of the efficacy results of individual studies (including meta-analyses of the study population and subpopulations) can provide regulatory authorities with more adequate and relevant information about the effectiveness of study drugs, they cannot replace the confirmatory role of individual studies. Irrespective of the statistical significance of efficacy results from the total population and subpopulation in each individual study, and irrespective of the statistical significance of relevant meta-analysis results, the efficacy results derived from meta-analysis can only be considered as supporting evidence of effectiveness and cannot be

considered as confirmatory evidence.

7.3 Distinguishing between Integrated Summary of Efficacy and Summary of Clinical Efficacy

Both the ISE and Summary of Clinical Efficacy (SCE) are reports of overall efficacy data for clinical studies required for the Common Technical Document (CTD) or electronic CTD (eCTD), and both should conform to the format requirements of that dossier. However, ISE is a comprehensive analysis of the efficacy results of all studies, while SCE is only a summary of ISE report and should not contain any analysis or conclusions that do not belong to ISE. ISE should be included in Section 5.3.5.3 "Reports of Analyses of Data from More than One Study" of CTD/eCTD Module 5, and the SCE should be included in Section 2.7.3 "Summary of Clinical Efficacy" of Module 2. When data available from clinical studies are very limited, for example, in clinical studies of orphan drugs, or when only one clinical study is available, or only a few small clinical studies are included, the main part of the ISE can be used as the SCE. In this case, the ISE report can be split between module 2 and module 5 of CTD/eCTD, with the main part in module 2, section 2.7.3, and the tables, figures and datasets as appendices in module 5, section 5.3.5.3. A clear explanation is required in the corresponding sections of module 2 and module 5.

7.4 Impact of Application of ICH E9 (R1) on the Implementation of this Guideline

ICH E9 (R1) introduces the concept of estimand and establishes a new

framework that goes from the trial objectives, estimand (including intercurrent events and their addressing strategies), method of estimation (including sensitivity analysis) to estimates. Following the application of ICH E9 (R1), these new concepts and frameworks will inevitably affect the implementation of this guideline. Therefore, this guideline will be further revised after more practical experience has been gained in applying these new concepts and frameworks.

REFERENCES

[1] NMPA. Biostatistics Principles for Clinical Trials of Drugs. 2016

[2] NMPA. Guidelines for Real-World Evidence to Support Drug Development and Review (Interim). 2020

[3] NMPA. Guideline on Non-Inferiority Clinical Trials for Drugs. 2020

[4] NMPA. Guideline on Multiplicity Issues in Clinical Trials of Drugs (Interim). 2020

[5] NMPA. Guideline on Subgroup Analysis of Clinical Trials of Drugs (Interim). 2020

[6] NMPA. Guideline on Data Monitoring Committee of Clinical Trials of Drugs (Interim). 2020

[7] NMPA. Guideline on Adaptive Designs for Clinical Trials of Drugs (Interim). 2021

[8] FDA. Guidance for Industry on Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document. 2009

[9] FDA. Guidance for Industry on Integrated Summary of Effectiveness. 2015

[10] ICH. E3: Structure and Content of Clinical Study Reports. 1995

[11] ICH. E9: Statistical Principles for Clinical Trials. 1998

[12] ICH. E9(R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. 2019

[13] ICH. E10: Choice of Control Group and Related Issues in Clinical Trials. 2000

[14] ICH. M4/M4(R4): Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use. 2016

Appendix 1: GLOSSARY

Integrated Summary of Efficacy (ISE) provides systemic analyses of data across all studies that characterize efficacy of the drug, compares the strengths and weaknesses of the data from different studies to describe the overall efficacy results, and explains why data from certain important studies are not included in the analysis.

Integrated Summary of Safety (ISS) provides systemic analyses of data across all studies that characterize safety of the drug, describes the overall safety results, and identifies risk statements that should be included in the package insert.

Common Technical Document (CTD) is a standard dossier for drug marketing applications with a common organization and format that has been agreed upon among global regulatory authorities, and which can simultaneously meet the requirements of global regulatory authorities for filing information.

Synthetic control is used in clinical trials where no parallel controls are available, but rather data collected outside of the study are used as controls, including historical data, real-world data, or data from other sources.

Appendix 2: Chinese-English Vocabulary

Chinese	English
安全性综合分析	integrated summary of safety, ISS
伴发事件	intercurrent event
电子通用技术文档	electronic common technical document, eCTD
复合终点	composite endpoint
估计方法	estimator
估计目标	estimand
估计值	estimate
合成对照	synthetic control
恒定假设	constancy assumption
患者报告结局	patient-reported outcome, PRO
剂量-效应关系	dose-response relationship
历史遗留研究	legacy study
临床医生报告结局	clinician-reported outcome
临床有效性总结	summary of clinical efficacy, SCE
桥接研究	bridging study
森林图	forest plot
事后分析	post hoc analysis
适应性设计	adaptive design
通用技术文档	common technical document, CTD
同期对照	concurrent control
无给药对照	no treatment control
有效性综合分析	integrated summary of efficacy, ISE
安全性综合分析	integrated summary of safety, ISS