Guideline on Integrated Summary of Efficacy for Clinical Trials

(Trial Version)

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Guideline on Integrated Summary of Efficacy for Clinical Trials

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 typically integrate other sources of data that are relevant to the drug to provide substantial evidence. Reports of analyses of data from more than one study are submitted as required by ICH M4E (R2) 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. Additionally, other sources can include human factor studies for drug-device combinations, *in vitro* studies that clarify drug activity, and exploratory and confirmatory clinical studies that are locally and internationally conducted. 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 all of the clinical efficacy data of the same indication for which the drug is to be applied for registration; additionally, ISE 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 all of the clinical safety data 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 an integrated analysis of clinical efficacy data to demonstrate the efficacy characteristics of a study drug as comprehensively and systematically as possible. A meta-analysis in this guideline refers to the pooled analyses of individual subject-level or group-level data of independent studies.

In principle, all of the clinical studies that are relevant to the same indication of the drug that is applied for registration should be included in ISE, which should include (but not be limited) to the following.

1) A tabular listing of all of the clinical studies should be provided, irrespective of whether the data support or do not support a conclusion of efficacy. These studies include completed studies, studies that were terminated early according to a prespecified study plan (e.g., early termination of the study because efficacy results met prespecified conditions at the time of the interim analysis), ongoing studies, terminated but incomplete studies, and legacy studies. Additionally, 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 analysis methods should be compared across all of the clinical studies, and the corresponding efficacy results should be discussed.

3) Comparisons and meta-analyses should be conducted on the efficacy results of all of the clinical studies.

4) Comparisons and meta-analyses of efficacy results for subgroups across all of the clinical studies may be performed as needed (e.g., to observe the efficacy of the subgroups).

5) A comprehensive analysis of clinical pharmacology data that pertain to the relationship between exposure (dose or blood concentrations) and responses should be performed in conjunction with the efficacy results of the clinical studies, thus supporting the dosage and administration section of the labeling.

6) Long-term effectiveness, tolerance, and discontinuation data from all of the clinical studies should be compared, summarized, and discussed.

2. OVERVIEW OF INDIVIDUAL STUDIES

2.1 Key Study Information

A tabular listing of key study information from individual clinical study reports should be briefly presented. Key study information includes drug indication, study number, study status (e.g., ongoing or completed), study region, study objectives, study phase (such as Phase II or Phase III), types of comparison (e.g., superiority or noninferiority), study groups, types of controls (e.g., placebo or active control), sample size (e.g., number of

predefined and actual enrollments and number of individuals assigned to the groups), method of randomization and randomization stratification factors, blinding (e.g., single-blind, double-blind, or open label), key inclusion/exclusion criteria, dosing regimen, standard definitions of efficacy endpoints, and efficacy results. Point estimates, interval estimates, and P-values (if applicable) for the primary and key secondary efficacy endpoints must be listed, irrespective of whether the efficacy results of the individual studies meet the study objectives.

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

2.2 Study Design Elements

In contrast to the brief overview in the previous section, this section should include the description and critique of the design elements of all of the studies, especially those that are incorporated into ISE. Common design elements include (but are not limited to) the following.

1) Key inclusion and exclusion criteria, such as disease characteristics, demographic characteristics, prior and concomitant medications, or subject selection methods, such as enrichment strategy and design or placebo run-ins, among other criteria.

2) Dosage selection, including fixed-dose, flexible dose, and forced titration.

3) Types of comparisons, such as superiority, equivalence, or noninferiority designs, among other comparisons. When using a

noninferiority design, special descriptions should be made to justify the noninferiority margin and the constancy assumption.

4) Selection of control group

①. Concurrent control, wherein the control group and test group were chosen from the same study population and treated concurrently, including 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 controls, such as historical control, parallel control, target value control, and synthetic control, originate from the study population.

③. Multiple controls, such as uses of both placebo and active control, or uses of several doses of the test drug and several doses of the 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 the choice of the endpoint should be discussed, and its validity as a predictor of clinical outcomes should be supported. If the efficacy claim is based on a new clinical outcome assessment (e.g., a patient-reported outcome or clinician-reported outcome), justification should be provided.

6) Treatment duration and study 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 block randomization, adaptive randomization, minimization methods, and random assignment systems, such as interactive web response systems (IWRSs).

9) Blinding methods, such as single-blind, double-blind, and open label, as well as methods of simulation of the study drug in odor and color (e.g., use of simulants).

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

11) Adaptive design features, such as sample size re-estimation, group sequential design, drops or additions of treatment arms, and changes in patient enrollment criteria. Special attention should be given to whether the modifications of the study design are predefined and whether the overall Type I error rate is controlled, among other considerations.

2.3 Statistical Analysis Methods

This section should describe, compare, and discuss the statistical analysis methods for the primary and key secondary efficacy endpoints for each study; in particular, this section should compare (in detail) the similarities and differences in the statistical analysis methods of the clinical studies that are included in ISE. It should include (but not be limited to):

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

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

3) If necessary, a discussion of the post hoc analyses in individual studies.

3. OVERALL ANALYSIS OF EFFICACY RESULTS

3.1 Comparison of Results of Individual Studies

Tables should be provided to show the number of subjects, number of dropouts, demographic characteristics, and baseline characteristics. Efficacy results of each individual study should be presented and compared by using tables or figures (e.g., forest plots). Comparisons of efficacy results across individual studies should be based on primary and key secondary efficacy endpoints and should be discussed in relation to demographic and baseline characteristics (e.g., disease severity), inclusion or exclusion criteria, types of control, exposure doses, 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 levels of importance, and although 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 commonly used primary efficacy endpoint is a composite endpoint of mortality and other events. A comparison and analysis of the 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 typically 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 (in addition to data from foreign studies) should be specifically noted in the Discussion section, along with additional supporting information for the 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. It is recommended to use individual subject-level data for meta-analyses; however, the heterogeneity between individual studies should be taken into consideration.

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 design characteristics should not be used for the meta-analysis; for example, a single-armed study should not be included with a study with a control group for the meta-analysis.

4. ANALYSIS FOR SUBPOPULATIONS

Similar to the analysis of the 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, a subgroup meta-analysis is more likely to provide precise assessments of differences in efficacy results between subgroups, which can suggest hypotheses for further clinical studies.

A tabular listing should be provided to present the subgroups and their definitions in the respective individual studies. Subgroup analyses can be presented by using tables or figures (especially forest plots), and statistical inference is generally not required. Stratification can be performed by definitions of subgroups of each individual study to minimize any biases introduced by differences in study designs. A subgroup analysis should include (but not be limited to) the following.

1) Evaluation of the effects 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 dysfunction, or hepatic dysfunction) on efficacy results.

2) Evaluation of the differences in efficacy results across countries and regions.

5. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

Clinical information that is relevant to dose recommendations includes clinical pharmacology data that evaluate the relationship between exposure (dose or blood concentrations) and responses, as well as data that evaluate the relationship between dose and blood concentrations. These data usually encompass the following factors: a) recommended dose range, including starting and maximal doses; b) lower dose limits 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; f) dose recommendations based on clinical pharmacology data (e.g., food effects); g) modifications of dosage needed because of drug interactions or in special patient populations (e.g., children, elderly individuals, groups defined by genetic characteristics, and patients with renal or hepatic insufficiency); h) important considerations regarding compliance with the dosing regimen; and i) any other recommendations related to individualized dosing.

An 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 recommendations should be included in the integrated analysis.

2) If the drug product that was used in the study is not identical to the product that is commercially available in the market, their comparability should be established.

3) Deviations due to factors such as 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 drug usage in each study (e.g., usage at 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 that are specified in the study protocol affect the dosing regimen (e.g., dose level titration) should be clearly described.

6) The methods that are used to assess differences in dose–response relationships (even when no differences were found) should be described, including specific studies conducted for subgroups, an analysis of efficacy results by subgroup, and determination methods of blood levels 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 possible, with descriptions of long-term observations, such as dose usage, duration of exposure, and reasons for discontinuation. Changes in effectiveness and tolerance over time and the impact of other concomitant medications on effectiveness 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 studies with relatively poor designs.

7. REGULATORY CONSIDERATIONS

7.1 Develop and Submit Statistical Analysis Plan for ISE

Before conducting the ISE, a corresponding statistical analysis plan should be developed to describe its analysis strategy and analysis methods, including meta-analysis methods for the efficacy results of each individual clinical study. Unlike statistical analysis plans for individual studies, those plans for ISE do not need to be developed prior to the end of each individual 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

Although 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 a meta-analysis can only be considered to be supporting evidence of effectiveness and cannot be considered to be 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 reports should conform to the format requirements of that dossier. However, the ISE is a comprehensive analysis of the efficacy results of all studies, whereas the SCE is only a summary of ISE reports and should not contain any analysis or conclusions that do not belong to the ISE. The 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 the data available from clinical studies are very limited (for example, in

clinical studies of orphan drugs, when only one clinical study is available, or when 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 located in module 2, Section 2.7.3, and the tables, figures, and datasets included 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 progresses from the trial objectives, estimand (including intercurrent events and their addressing strategies), and 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.

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Appendix 1: GLOSSARY

Integrated Summary of Efficacy (ISE) provides systemic analyses of all clinical efficacy data of the same indication for which the drug is to be applied for registration, 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.

The integrated summary of safety (ISS) provides systemic analyses of all clinical safety data of the drug, describes the overall safety results, and identifies risk statements that should be included in the package insert.

The summary of clinical efficacy (SCE) provides a brief summary and contains the same scope as the ISE. SCE does not contain any analyses or conclusions that are out of scope of the ISE.

Common technical documentation (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 that 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; rather, data that are collected outside of the scope 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
临床结局评价	Clinical Outcome Assessment, COA
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 Diagram
适应性设计	Adaptive Design
通用技术文档	Common Technical Document, CTD
同期对照	Concurrent Control
无用药对照	No Treatment Control
有效性综合分析	Integrated Summary of Efficacy, ISE

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