Statistical Guidelines on Clinical Studies of Drugs for Rare Diseases

(Trial Version)

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1. Overview

Compared with common diseases, rare diseases and their drug development have the following characteristics: (1) many rare diseases are serious or life-threatening disorders, many of which are congenital genetic diseases and commonly originate in childhood; (2) for rare diseases, there are usually limited data on epidemiology and natural history, insufficient medical information, and may be a lack of recognized efficacy evaluation methods and clinical endpoints; (3) the patient population is small, with limited opportunity to carry out clinical research, and the experience in drug development is insufficient ; (4) a rare disease may have multiple subtypes, for which the symptoms, signs, prevalence and disease progression patterns may be heterogeneous; (5) small sample clinical research methods have special characteristics. As a result, challenges are often faced in the design, conduct, and interpretation of clinical studies for rare diseases, and there is a widespread unmet medical need for patients with rare diseases.

During drug development for rare diseases, appropriate study design and analysis are needed to ensure the quality of studies and the reliability of results. The clinical study design is one of the most important factors in determining the success of drug development. A good study design can help to achieve the objective of research and improve the research quality and the efficiency of drug development. Sound statistical analysis helps to interpret the results. This guideline addresses key statistical issues in clinical research on drugs for rare

diseases and are intended to provide guidance for sponsors to conduct clinical studies of drugs for rare diseases. This guideline applies primarily to clinical studies that support the registration and marketing of drugs, and can also be used as a reference for clinical studies for non-registration purposes.

2. Design and Analysis for Clinical Studies of Drugs for Rare Diseases

2.1 General considerations

In the study design phase, given the purpose of the study, the sponsor should determine the appropriate estimand, inclusion/exclusion criteria, study and treatment duration, data collection frequency, and other key elements related to the clinical study.

Natural history studies are very important in drug development for rare diseases. The natural history of a disease is defined as the course a disease takes in the absence of intervention in individuals with the disease, from the disease's onset, development, until the outcome (either the disease's resolution or the individual's death). A natural history study is a preplanned observational study intended to track the course of the disease, which aims to identify demographic, genetic, environmental, and other factors (e.g., treatment modalities, concomitant medications, etc.) that correlate with the development and outcome of the disease. Therefore, collecting the natural history data is an important way to obtain information on disease diagnosis, progression, transformation, outcome, etc., and plays a critical role in all stages of drug development for rare diseases, especially in the identification of patient populations, selection of study endpoints, determination of efficacy thresholds, identification and development of biomarkers, selection of controls, etc. For rare diseases, the natural history data provide important guidance for the development and post-marketing use of relevant drugs. Early clinical study data should be combined

with natural history data to scientifically establish substantial and logically sound chain of evidence to support the later development of the drug.

For the target population of clinical studies, on the one hand, due to the small population of patients, a clinical study of drugs for rare diseases may appropriately relax the inclusion/exclusion criteria to allow a relatively larger number of patients to participate the study. This helps patient recruitment and allows for a more adequate evaluation of the benefits and risks of drugs in the target treatment population. On the other hand, for rare diseases with high heterogeneity, a reasonable enrichment strategy can also be considered in clinical studies to reduce non-drug-related heterogeneity in patients and to enhance the ability of the study to demonstrate a potential treatment effect.

If the target population of the study is a subgroup of the population with the rare disease, sponsors should consider evaluating the drug in other subgroups to determine whether the study results can be generalized to the broader patient population.

Sponsors should obtain evidence of effectiveness of the target population from adequate and scientifically soundly designed studies, and should use concurrent controls (e.g., placebo, standard of care, active treatment, and different dose groups, etc.) to the extent ethical and practically feasible. The selection of control groups may affect the recruitment and dropout of subjects, and sponsors may consider the use of sound study designs such as dose-response design, delayed start design, randomized withdrawal design, crossover design, adaptive design with interim analysis, and hybrid control arm using both trial and external data. These designs retain the advantages of placebo-controlled trials

and include features that minimize placebo exposure and enhance access to experimental therapies.

Due to the limited number of patients, it is recommended to maximize the use of data from each subject as much as possible, such as conducting expansion cohort studies and randomization in the early stage of development, etc. If necessary, properly stratified randomization can be used to improve comparability of groups and to increase statistical power with pre-specified stratified analyses.

Blinding is one of the important means of controlling bias. Proper justifications should be provided for unblinded designs, and all possible measures should be taken to control potential biases.

The overall type I error rate should be strictly controlled at a certain level. If the primary purpose of the study involves hypothesis testing of multiple populations (e.g., biomarker-positive population and overall population), multiple endpoints, or planning to perform interim analysis that may stop the study early due to efficacy, an appropriate multiplicity control strategy should be adopted and pre-specified in the protocol and statistical analysis plan. When planning to stop the study early due to efficacy, considerations should be given to whether the data for safety reviews are sufficient.

For many rare diseases, well-recognized efficacy endpoints are currently not available, and it is recommended to establish new endpoint assessment methods or improve existing methods at the early stage of drug development. For composite endpoints with multiple components, each component should also be analyzed separately to ensure that the overall result does not rely too much on selected components; If hypothesis testing will also be performed for certain

components, the method for controlling the overall type I error rate should be pre-specified.

When choosing the endpoint, it is important to note that clinical studies of rare diseases may include a broader range of disease stages (e.g., severity of manifestations, development of manifestations secondary to long-standing primary disease manifestations) or phenotypes than studies of common diseases. For patients with different stages or phenotypes, there may be disparities in the validity, sensitivity, reliability, or interpretability of an endpoint. In addition, endpoints may differ between pediatric and adult patients.

2.2 Study designs

Typically, randomized controlled trials (RCT) minimize the impact of factors affecting the estimation of drug efficacy by randomized grouping, leading to high reliability of study conclusions, and are the most effective and accurate "gold standard" for evaluating drug efficacy and safety. In fact, most approved drugs for rare disease are based on RCTs. This guideline will not elaborate on designs with regular RCT components that may be applicable to drug development for rare diseases, such as dose-response design, delayed start design, randomized withdrawal design, and crossover design, etc., but primarily describe methods with additional design elements to conventional RCTs (e.g., sequential design, response-adaptive design, n-of-1 design, adaptive seamless design, basket trial design, and Bayesian methods, etc.), single-arm trials, and real-world studies, etc. If a single-arm trial design or a real-world study, etc. is used as the key evidence for registration filing, the sponsor should justify its rationale.

It is important to note that any kind of study design has its own unique advantages and limitations. Therefore, in practice, the sponsor should choose the appropriate design according to the purpose of the study and the specific situation, and communicate with the regulatory authority in advance.

2.2.1 Sequential design

Sequential design utilizes interim analyses based on cumulative data while controlling the overall type I error rate, evaluating efficacy and determining whether to continue the trial by pre-specified proper boundaries and sample sizes. The sequential design is suitable for clinical trials where the endpoints of studies can be observed quickly (relative to patient recruitment rates). This approach is applicable to clinical trials of rare diseases with small populations and slow recruitment rates.

2.2.2 Response-adaptive design

Response-adaptive design changes the probability of random treatment allocation for new subjects based on the treatment outcome for enrolled subjects. There are many specific forms of this design, commonly the "play-the-winner" design. In a blinded clinical trial, patients newly enrolled in the study are more likely to be assigned to the treatment group with better efficacy assessed based on the response of enrolled subjects. Such designs increase patient exposure in potentially relatively effective treatment groups while reducing the overall sample size during dose selection and confirmatory trial phases. As with the sequential design, this design is suitable for trials that achieve clinical outcomes relatively quickly (relative to patient recruitment rates). However, this design is not based on the standard assumption of fixed randomization allocation probability, and attention needs to be paid to maintaining blinding, statistical analyses, and other related issues.

2.2.3 n-of-1 design

The n-of-1 trial is also known as a structured within-patient randomized controlled multi-crossover trial design, referred to as a self-multi-phase RCT. A typical n-of-1 trial consists of multiple treatment cycles (generally ⩾3), and each cycle consists of several periods, and within each period the subject receives a treatment. The sequence of treatments within the first treatment cycle (e.g., experiment-control, or control-experiment) is determined randomly, and the order of treatments in each subsequent treatment cycle is determined randomly or by a systematic balanced design (e.g., assuming the trial has two treatments, if the first randomly determined treatment sequence is control-experiment, then the subsequent treatment cycles are directly assigned to the treatment sequence of experiment-control and then control-experiment, and so on). The main goal of this design is to find the optimal treatment plan for the subject through observing the subject's response to the experimental drug and the control drug by performing multi-cycle crossover treatment with the same subject. When multiple subjects have performed n-of-1 trials of the same design, the results of multiple n-of-1 trials can be combined in a manner similar to both a crossover study and a meta-analysis. A series of n-of-1 trials usually better show an efficacy trend favoring one treatment. Taking three cycles of two treatments (A and B) as an example, the schematic diagram of the n-of-1 trial design of a single subject is shown in Figure 1.

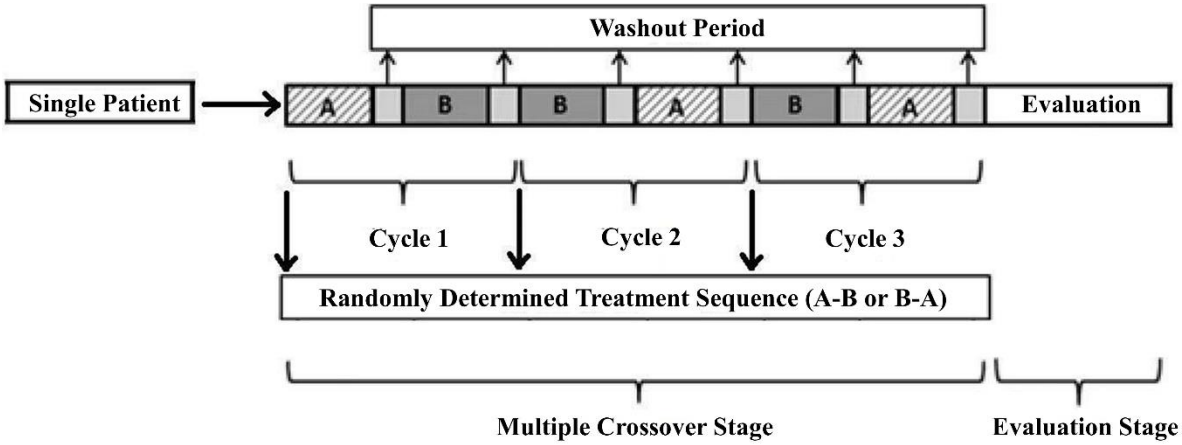

Figure 1: Diagram of the n-of-1 design

The advantage of n-of-1 design is that the use of self-control design can improve statistical efficiency and reduce sample size. Meanwhile, it can ensure that each subject can receive positive treatment. The n-of-1 design also has limitations, such as being more suitable for fast-acting symptomatic treatments and diseases that quickly return to a stable baseline value after treatment ends. The n-of-1 design should not be used for diseases with long course of treatment or slow-acting drugs, as well as self-limiting diseases.

It should be noted that, similar to a general crossover design, there may be a delayed effect in different periods (early vs. late) of the n-of-1 design. Therefore, the washout period needs to be considered between treatment periods of the trial. In addition, the follow-up time of the subjects is longer than the parallel design, so the likelihood of dropouts is higher. Other issues such as randomization of treatment sequences and maintenance of blinding need to be considered as well in the study design.

2.2.4 Adaptive seamless design

The adaptive seamless design suitable for rare diseases is primarily the inferentially seamless design, which allows for the use of data from early part

of the clinical trial and may be applicable in the case of a limited patient population. For example, the adaptive inferentially seamless dose-finding phase II/III design can often shorten the time interval from the end of phase II trial to the start of phase III trial, reduce the total sample size of the trial, and shorten the length of the trials, etc. In addition, participants enrolled in phase II trial have a longer follow-up time, which helps earlier observation of the long-term efficacy and safety of the drug. When using adaptive seamless design, it is necessary to consider controlling the overall type I error rate and maintaining trial integrity (e.g., preventing the disclosure of interim analysis results that affect subsequent investigator actions and subject enrollment).

2.2.5 Basket trial design

The master protocol design suitable for rare diseases is mainly the basket trial design. The basket trial design aims to evaluate the therapeutic effects of a drug simultaneously for multiple types of disease with the same biological characteristics, and each sub-protocol targets one or more types of disease.

2.2.6 Bayesian method

The Bayesian method is a method of synthesizing a priori information with the sample information of the trial to obtain a posterior distribution, and then making statistical inferences based on the posterior distribution. That is, the results of the study are adjusted using prior information. Sources of prior information include, but are not limited to, historical studies and expert experience; or a non-informative prior can be used. Using evidence from a variety of reliable sources as prior information can reduce the sample size of the present trial, shorten trial length, improve statistical power, and may be applicable for rare diseases with recruitment difficulty.

In order to obtain sufficient statistical evidence and ensure the quality, validity and integrity of the study, sponsors should fully assess the rationality of the prior information and the possible impact on statistical results and the final conclusion. It is recommended to use other reasonable prior distributions in sensitivity analyses to ensure that the findings do not heavily rely on prior information.

2.2.7 Single-arm trial

When the number of patients with rare diseases is very small, the conduct of clinical trials is difficult, especially for those major life-threatening diseases that lack effective treatment currently, RCTs may have medical ethical risks. In these cases, if the single-arm trial design is considered, the sponsor needs to provide rationalities and clarify the bias control measures.

Single-arm trials usually use external controls, which can be either objective performance criteria (OPC) or external individual-level data. For single-arm trials with OPC as the control, the OPC should be determined with good grounds, which can be derived from the effect size of previous study (e.g., meta-analysis or a study with the best reference value), or it can be a widely recognized effect in the industry. The OPC will be used as the target effect, which should be the minimum effect achieved for the experimental group. OPC-controlled single-arm trials must control selection bias during study design and implementation, ensure representativeness of enrolled patients and their comparability with historical controls, and consider possible biases (e.g., selection bias, and survivorship bias, etc.) in the statistical analysis. Due to the lack of concurrent parallel controls, the results of the study should be interpreted with caution.

For single-arm trials with external individual-level data as control, there are parallel controls and historical controls, and parallel controls are recommended. The use of historical control is a case of real-world studies. The relevant study using historical control can be carried out only when the historical data is curated and meets the applicability requirements. The choice of endpoints for externally controlled studies should be consistent with the experimental group, and if the measurement of certain clinical endpoints is not exactly consistent with the experimental group in the external control, the impact needs to be assessed first and the countermeasures should be proposed in the study design phase. The sample size estimate of the experimental group still needs to be based on statistical hypothesis or estimation precision. Since the sample size estimation of the external control needs to consider factors including matching, the sample size of the external control is usually larger than that of the experimental group.

2.2.8 Real-world study

A real-world study refers to the research process of collecting data related to the health of subjects (real-world data) or aggregated data derived from these data in a real-world environment for pre-specified clinical questions, and obtaining clinical evidence regarding the usage and potential benefits and risks (real-world evidence) through analyses.

If the sponsor considers the use of real-world studies as key evidence to support the marketing of a drug for rare diseases, it is recommended to conduct scientific and rigorous design with reference to the relevant guidelines, and communicate and align with regulators on the protocol, data curation/management plan, and statistical analysis, etc.

2.3 Sample size

For clinical studies of rare diseases, the sample size should be sufficient to adequately assess the benefits and risks of the drug. Traditional estimation methods are commonly used to determine the sample size, that is, the sample size required for obtaining statistically significant results under certain statistical power and significance level is estimated based on the clinical study objective, type of design, null hypothesis, alternative hypothesis, target treatment effect, and individual variation. The biggest challenge for rare disease clinical studies is the low prevalence and not enough patients to be included in the study. Sponsors may adopt a flexible design that reduces the sample size required for the study to some extent. If a non-traditional method is used to determine the sample size (e.g., using Bayesian and other methods), the rationality of the sample size estimation method (e.g., the setting of a priori distribution, or parameter estimates, etc.) needs to be fully demonstrated, and if necessary, different methods and/or different parameters for simulations can be used, and the selection of relevant parameters need to be fully communicated and agreed with regulatory authorities. The sample size should be determined after comprehensive consideration. Sample size estimation should be fully documented in detail, including but not limited to relevant bases, documentation, codes and results, to support regulatory review and validation as necessary. In addition, the determination of sample size should also consider the availability of sufficient data for safety evaluation. For international multicenter clinical studies, it is recommended to reference ICH E17 for sample size allocation.

2.4 Statistical analysis

2.4.1 Assumptions of statistical models

Rare disease studies typically have small sample sizes and may require consideration of sophisticated, efficient, and informative statistical analysis

methods. Many of these approaches involve statistical modelling, and it is worth noting that inferences about treatment effect using clinical study data are only reasonable if the assumptions of statistical models are met. In the case of a small sample, it is difficult to test whether the assumptions of the pre-specified statistical model is correct in practice. Therefore, sensitivity analysis should be fully considered during the design stage to check the robustness of the conclusions under different assumptions and with different analysis methods.

It is important to judge whether the model is suitable and to verify the model assumptions. The sponsor should fully explain the key statistical issues such as the model assumptions, covariate selection, and rationality of analytical methods used in the protocol or statistical analysis plan, and communicate with the regulators to reach an agreement.

2.4.2 Statistical distributions

Assumptions of statistical distributions are prerequisites for using statistical models, and nonparametric methods can be considered when it can not be determined whether the data come from a particular statistical distribution (e.g., normal distribution).

The standard asymptotic method is based on the assumption that when the sample size is large enough, the hypothesis test statistic is assumed to follow a specific distribution. This may not be applicable in the case of small sample sizes in rare disease studies. When it is uncertain whether the asymptotic assumption holds, a suitable method should be used to assess the small sample nature of the method or consider using an exact method.

2.4.3 Covariates

Including important covariates in the model may improve the precision and statistical power of treatment effect estimates. However, it should be noted that the number of covariates should not be excessive. Stratification factors for randomization should be considered in statistical analysis, but their interaction terms are usually not included in the primary analytical model.

2.4.4 Repeated measurements

The use of repeated measurements at multiple time points (or different parts of the body) of the subject can improve the efficiency of the test. It is important to note that in a repeated measurement design, the observations of the same subject are not independent of each other. Ignoring this non-independence can lead to the use of wrong statistical methods or drawing wrong conclusions. In this case, statistical analysis methods for non-independent data such as hierarchical linear models and mixed-effects models can be used.

3. Considerations in the Execution of Clinical Studies on Rare Diseases

Compared with the clinical studies of drugs for common diseases, the clinical studies of drugs for rare diseases often faces problems such as difficulty in enrollment or long enrollment time, limited sample size, high heterogeneity of enrolled subjects, and lack of effective treatments, so there are higher requirements for the quality of clinical study execution.

First, investigators often lack sufficient clinical study experience for rare diseases. Sponsors need to carefully select clinical study centers to ensure that (1) the study centers meet the corresponding requirements; (2) investigators and researchers have a full understanding of the protocol and conduct the study in strict accordance with the protocol and good clinical practice (GCP); (3) investigators and study staff have relevant experience and have sufficient capability to deal with emergencies that may arise during study operation.

Second, patients with rare diseases, especially those with childhood diseases and maternal-infant diseases, often have little understanding of the relevant knowledge of clinical studies, resulting in patients' low acceptance of clinical studies and weak willingness to participate in clinical studies. Therefore, it is necessary to increase the patients' perception of participation, make patients fully understand the process of clinical studies and the possible benefits and risks fully informed, and follow up to the greatest extent in order to minimize the dropout rate. Participants who discontinue their medication should be encouraged to continue to stay in the study and be followed up to maximize the integrity and interpretability of the study information.

Third, the enrollment of clinical studies on rare diseases is often difficult and takes a long time, which results in a longer clinical study cycle. Over a relatively long period of time, the development of disease diagnostic techniques may lead to changes in the characteristics of enrolled subjects, resulting in selection bias, or it may be difficult to select the control group due to changes in standard therapy. These can lead to additional difficulties for the execution and analysis of clinical studies, which require the necessary consideration at the study design stage.

Fourth, to ensure the representativeness of the study population and adequate sample size, clinical studies of drugs for rare diseases sometimes have relatively broad inclusion/exclusion criteria. This requires that the enrollment process strictly follows the subject's screening criteria to avoid unnecessarily enrolling non-target population in the study.

Fifth, the number of patients with rare diseases is limited, and data from clinical studies may come from multiple sources. This requires that the collection and collation of data must be scientifically standardized. Standardized operating procedures (SOP), quality control, and data quality assurance are all essential. In addition, a scientific, rational, and standardized evaluation of the treatment effect is necessary.

4. Evaluation of Evidence

As with drugs for common diseases, the overall goal of drug development for rare diseases is to confirm the effectiveness and safety of a drug for a given disease, to assess the benefits and risks of the drug, and to provide a basis for the development of drug labels. Therefore, the development and evaluation of drugs for rare diseases should also be based on a solid assessment of the safety and efficacy of the drug.

4.1 Evaluation of evidence for effectiveness and safety

Under the regulatory standards aligned with the evaluation of drugs for common diseases, in view of the characteristics of rare diseases, the evaluation of related drugs has a certain flexibility. In particular, the establishment of evidence for drug development for rare diseases may require consideration of evidence in multiple forms, from multiple aspects, or combined evidence from multiple data sources, and drug evaluation will also be based on the analysis of the totality of evidence, including the clinical relevance to the treatment effects cross different endpoints, the persistence of treatment effects, and the assessment of safety.

All forms of evidence provide some information and should be included in the final comprehensive analysis. For example, in extremely rare diseases, the combined evaluation of single-case studies may be the only way to provide evidence. Such studies should be prospectively planned and described in the

study protocol. A systematic review and meta-analyses of all data (including data from other sources) will increase the strength of the evidence, such as a combined analysis of individual case reports or observational studies.

There is often a lack of well-recognized primary efficacy endpoints and evaluation approach in drug development for rare diseases, so it is recommended that reasonable or possible endpoints (including surrogate endpoints, patient-reported outcomes, etc.) should be considered when possible at the design stage, and all data should be presented in the final study report in order to provide stronger evidence. At the same time, the rationality of efficacy measurements can be explored during the clinical study, providing evidence for the rationality of the selection of efficacy measurements. It is encouraged to develop new measurement tools and endpoint that are appropriate for rare diseases during clinical studies. There should be a clear relationship between a reasonable surrogate endpoint and clinical efficacy before the surrogate endpoint can be accepted. Otherwise, further evidence should be used to support the evaluation of clinical efficacy, safety, and benefit-risk, based on a pre-specified plan.

The statistical design, data collection and analysis, and the interpretation of results of clinical studies of rare disease drugs should follow ICH E9 and E9(R1), taking into account the estimands and the impacts of intercurrent events. The application package should generally include pre-planned statistical analysis, such as primary analysis, sensitivity analysis, supplementary analysis, subgroup analysis, etc. For studies on rare disease, complex statistical analysis methods may be needed due to the small number of patients, and care needs to be taken to conduct sufficient and reasonable sensitivity analyses to ensure the robustness of conclusions. In addition, it is necessary to pay attention to the impact of related issues in the conduct of clinical studies on the results of the

study, such as missing data, heterogeneity, etc., and to quantify the potential impact of these issues on the results as much as possible.

When using real-world evidence, the scientific rigor of the research methods, the quality and relevance of the data, and the reliability of the results should be fully evaluated. The focus should be placed on the analysis of potential selection bias, information bias, confounding bias in the study, and elaborating on the relevant control measures for bias at the stage of study design, conduct, and statistical analysis. The limitations of the study results should be explored and sufficient sensitivity analyses should be undertaken to test the robustness of the study conclusions.

The goal of safety evaluation during drug development is to describe the safety of a drug with intended use in a reasonable number of subjects over a reasonable period of time.

For drugs for rare diseases, the possible challenges posed by the limited number of patients with the disease should be taken into account. To increase the amount of pre-marketing safety data as much as possible, sponsors should consider using some approaches to enhance safety assessment, such as using natural history data, dose selection studies, setting up control groups, and auxiliary safety cohorts. Adequate and reliable natural history data can help distinguish drug-related adverse effects from underlying disease manifestations. Whenever it is ethical and practically feasible, the use of concurrent control group designs can assist in the interpretation of causalities of adverse events. Auxiliary safety cohorts (e.g., safety cohorts parallel to efficacy studies, studies of other indications for drugs, and studies of similar drugs) can enrich pre-marketing safety databases and provide more information on drug safety. Sponsors should

propose specific strategies to address potential challenges in drug development programs.

4.2 Benefit-risk assessment

Although data on rare disease development may not be rich enough, there is still a need to present a clear benefit-risk profile. Sponsors should follow the requirements of ICH M4 E(R2) to provide a succinct, integrated, and clearly explainable benefit-risk assessment for the drug with the intended use. Benefit-risk analysis should take into account rare disease characteristics, such as whether there is currently an effective treatment, the severity of the disease (whether it is serious or even life-threatening), the clinical urgency, and the patient's tolerance of the risk in the absence of unmet medical needs. Benefit-risk analysis should begin with a clear definition of benefits and risks, provide data related to key benefits and risks, and fully assess the limitations and uncertainties of the data. Appropriate risk management plans should be proposed for identified or potential risks. Both of statistical significance and clinical relevance should be considered when interpreting the results of data analysis, and patient-reported outcomes and physician clinical perspectives can be incorporated into the benefit-risk analysis to serve as an important complement.

In view of the limitations of clinical studies of drugs for rare disease, it is usually required to further collect relevant safety and efficacy data after the drug is marketed, so as to provide more adequate evidence and information for the benefit-risk evaluation of drugs.

5. Communication with Regulatory Authorities

Due to the peculiarities of rare diseases in study design, conduct, analysis and reporting, sponsors are encouraged to communicate with regulators on key statistical issues in design and implementation. Prior to communication, the sponsor should provide the regulator with detailed information on the protocol and key statistical issues in advance.

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Appendix: Chinese-English Glossary

Chinese	English
n-of-1 设计	n-of-1 Design
贝叶斯方法	Bayesian Method
层次线性模型	Hierarchical Linear Model
单臂设计	Single-arm Design
非独立	Non-independent
辅助安全队列	Auxiliary Safety Cohort
个体层面数据	Individual-level Data
混合合成对照组	Hybrid Synthetic Control Arm
混合效应模型	Mixed-effects Model
疾病自然史研究	Natural History Study
剂量效应	Dose Response
渐进方法	Asymptotic Method
交叉设计	Crossover Design
精确方法	Exact Method
可解释性	Interpretability
可靠性	Reliability
扩展队列研究	Expansion Cohort Study
篮式设计	Basket Trial Design
灵敏度	Sensitivity
平行设计	Parallel Groups Design
适应性Ⅱ/Ⅲ期推断无缝剂量选择设计	Adaptive Phase II/III Inferential Seamless Dose-selection Design
适应性无缝设计	Adaptive Seamless Design
随机撤药设计	Randomized Withdrawal Design
随机对照试验	Randomized Controlled Trial (RCT)
速效对症治疗	Fast-acting Symptomatic Treatment

Chinese	English
完整性	Integrity
消退	Resolution
幸存者偏倚	Survivorship Bias
序贯设计	Sequential Design
延迟启动设计	Delayed Start Design
应答适应性设计	Response-adaptive Design
阈值	Threshold