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Points to Consider for Small Clinical Trials
(Early Consideration)

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1. Introduction

The fundamental approach to obtaining evidence of the efficacy and safety of medicinal products, etc. (hereinafter simply referred to as a "drug") is to conduct a randomized controlled clinical trial (RCT). In such trials, the test treatment is compared with a control treatment within the same study. When planning an RCT, it is necessary to set a sufficient number of participants so as to ensure adequate statistical power for the statistical hypothesis testing that is generally used for the between-group comparison in the primary analysis. However, even in situations where the conduct of such RCT would ordinarily be expected, it may be infeasible to initiate and complete the trial within a reasonable timeframe. Such circumstances may arise, for example, in the development of orphan drugs, where the number of patients with the target disease is limited, or where enrollment of study participants is difficult due to various factors.

In this document, “small clinical trials” are defined as follows. These are clinical trials intended to constitute the primary evidence of efficacy and safety of drugs, but conducted with a sample size smaller than that required to ensure adequate statistical power for hypothesis testing in the primary analysis. These trials are expected to be used to evaluate the efficacy and safety of drugs and to support applications for marketing authorization.

This document addresses situations in which an RCT is considered desirable; however, the statistical power for between-group comparisons is insufficient, or is extremely limited, thereby necessitating the conduct of a single-arm clinical trial. Regardless of the trial design employed, it is essential to predefine success criteria aligned with the study objectives and to ensure that the trial can yield meaningful conclusions. In addition, taking feasibility into account, it is important to plan and conduct small clinical trials in a manner that ensures scientific validity and maximizes the interpretability of the results. This document outlines the fundamental considerations for planning small clinical trials, key elements to be considered, and the explanations required to justify the

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appropriateness of such trial designs in the context of clinical trial consultation meetings with the Pharmaceuticals and Medical Devices Agency (PMDA), as well as during regulatory submissions for marketing approval.

When planning a small clinical trial, the trial design and statistical methods should be selected after thoroughly reviewing all information available at the time of planning, including the characteristics of the target disease and the clinical pharmacological background of the drug. Whether a small clinical trial can be used as major evidence for the efficacy and safety of a drug in a marketing approval application depends on various elements, such as the characteristics of the target disease and the drug, and the information obtained from the overall development program, including the small clinical trial. With regard to the planning of an induvial small clinical trial and the composition of the clinical data package to demonstrate sufficient evidence of efficacy and safety for marketing approval, it is strongly recommended to seek advance consultation through PMDA clinical trial consultation meetings.

2. Basic principles

If a planned clinical trial is expected to be a small clinical trial, it is important to adequately assess the number of participants who can be enrolled. Specifically, investigations should be conducted on the planned study regions, the number of patients with the target disease in those regions, the availability of medical institutions that treat the disease and can participate in the trial, and the number of patients who are actually eligible for enrollment based on the inclusion and exclusion criteria. Based on this information, it is necessary to determine whether a sufficient number of participants can be secured and to assess the feasibility of conducting the trial. Available disease registries may serve as useful sources of information for this evaluation[1).]

When considering the feasibility of conducting small clinical trials, the following situations should be assumed in sequence. However, this assumes that an investigation of the number of participants that can be enrolled has been conducted and the anticipated scale of the number of participants will be taken into consideration.

- Situations in which an RCT is expected to be conducted but there is insufficient power for the between-group comparison

  There are situations in which an RCT is expected and considered feasible, yet enrolling a sufficient number of participants is challenging, leading to anticipated underpowering relative to conventional targets. In such cases, consideration of elements such as those described in Chapter 3, including trial design and statistical analysis, may help increase statistical power and enable the generation of interpretable results.
- Situations in which implementation of an RCT is difficult because the power for the between-group comparison is extremely insufficient

There are also situations in which, even after careful consideration of elements such as those described in Chapter 3, statistical power remains substantially insufficient to conduct an RCT and demonstrate efficacy through between-group comparison, and therefore a single-arm clinical trial may be required. If the disease course can be predicted with sufficient accuracy based on available information on the disease and its symptoms, and if there is adequate information on responses to placebo or standard of care, it may be possible to conduct a single-arm clinical trial to evaluate efficacy. In such cases, it may be appropriate in practice to compare the results of a single-arm clinical trial with an external control or a clinically meaningful threshold. For considerations regarding comparisons with external controls, "Points to consider for externally controlled trials (Early Consideration)" may serve as a useful reference[2]. When comparing efficacy results with a threshold, it is essential to define a clinically meaningful threshold based on prior clinical trials, natural history studies, disease registries, and related sources, such that the drug's efficacy can be appropriately demonstrated against that benchmark. For example, if a certain level of efficacy is expected in a placebo group, the threshold should be set to demonstrate that the efficacy of the investigational treatment exceeds that level. It should also be noted that single-arm clinical trials lack randomized control and are, in principle, open-label clinical trials, which may introduce bias.

In any of these situations, because small clinical trials are characterized by a limited number of participants, particular attention must be paid during trial planning to minimizing, while maintaining scientific validity, situations in which data necessary for evaluation cannot be obtained from enrolled participants (e.g., occurrence of intercurrent event(s) or situations in which data corresponding to the estimand[3] are not collected).

The choice of design—such as whether to conduct an RCT despite insufficient power or whether a single-arm clinical trial can support a meaningful conclusion—depends on the characteristics of the target disease, the characteristics of the drug including the anticipated magnitude of effect, and the information required for an application for marketing approval, in the individual situation. Therefore, it is important to discuss the matter with PMDA in advance.

3. Elements that may be considered at the planning stage

The following lists elements and methods that have been discussed to date for specific situations encountered in small clinical trials; however, these are not limited to those described below.

- Primary endpoint

  The primary endpoint should be one that provides the most clinically relevant and convincing evidence directly related to the primary objective of the trial[4]. However, there may be situations in which the achievable sample size is insufficient to provide adequate power for the originally intended primary endpoint; in such cases, sufficient power may be attained by

using a surrogate endpoint, a closely related endpoint, or by evaluation using biomarkers. When planning a small clinical trial, if it is reasonably likely —based on epidemiological and pathological knowledge of the disease, as well as the pharmacological mechanism of the drug— that efficacy can be evaluated using such an endpoint, and if its surrogacy can be clinically justified, it may be acceptable to designate it as the primary endpoint. In this case, however, attention should be paid to the possibility that the endpoint may not be a true predictor of the clinical outcome of interest and that it is not an endpoint that can be weighed directly against safety, potentially making benefit–risk assessment difficult[4]. In addition, even endpoints that would originally be the primary endpoint may be included as secondary endpoints to allow data collection and support interpretation of efficacy, while taking into account the limitations due to the small number of participants. Particularly in the development of orphan drugs, it may be difficult to determine an appropriate endpoint that should be the primary endpoint at the time of planning stage; however, in principle, it is necessary to prioritize endpoints appropriately based on the information available at that time, and the primary endpoint should be prespecified.

With respect to the characteristics of the primary endpoint, particularly when it is difficult to conduct an RCT and a single-arm clinical trial is conducted, given the potential for bias in the results of subjective endpoints due to expectations regarding the drug under development, the primary endpoint should be objective.

For primary endpoints that are continuous variables, using the measured values directly, rather than dichotomizing outcomes (e.g., effective vs. ineffective) or categorizing them based on certain criteria, may retain more information and enable evaluation with a smaller sample size. However, such approaches should be selected with careful consideration of what magnitude of change or state in the endpoint is clinically meaningful.

- Use of longitudinal data

By utilizing data repeatedly measured at multiple time points for a participant (longitudinal data), it becomes possible to incorporate a greater amount of information into the evaluation. In such case, it is important to prespecify how the obtained data will be selected and analyzed.

- Analyses accounting for factors

When conducting an RCT, stratified randomization by factors considered to influence efficacy, and analyses accounting for factors considered to influence efficacy including those used for stratified randomization, may increase power. However, when the number of participants is small, stratified randomization may not sufficiently achieve its purpose; therefore, when considering implementation, it is important to take into account the extent to which the factors influence efficacy and the anticipated number of participants in the clinical trial.

- Adjustment of the significance level for statistical hypothesis testing

In general, for statistical hypothesis testing for the between-group comparison that constitutes the primary analysis of an RCT, the significance level is set to 5% or less for a two-sided test to control the probability of a Type I error to 5% or less. In small clinical trials, however, there may be situations in which it is desired to conduct an evaluation of efficacy based on the results of statistical hypothesis testing after setting the significance level to a larger value, such as 10%. However, when there is limited evidence on efficacy beyond the small clinical trial being conducted, and the overall assessment of efficacy is expected to rely heavily on its results, it is, in principle, not recommended to set the significance level above 5%.

- N-of-1 trials

An N-of-1 trial is a clinical trial in which a single patient receives an investigational treatment and placebo or other control treatment in a random order, and the results are evaluated. The results from multiple patients for whom similar investigations have been conducted may also be integrated for evaluation. N-of-1 trials have limitations similar to those of crossover trials and can generally be used in situations where symptoms are stable, the effects of the treatment are observed within a relatively short time, and the effects disappear promptly after treatment ends.

- Adaptive designs

An adaptive design is a clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on interim analysis of accumulating data from participants in the trial. It can address uncertainties at the planning stage by incorporating information obtained during the trial and may increase statistical power for a given expected sample size. In the context of small clinical trials, the aspects of the trial that can be prospectively planned to be modified should be determined based on the specific efficacy information required from the clinical trial. When using an adaptive design, reference should be made to discussions on E20 in the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)[5].

- Bayesian approach

In contrast to conventional statistical hypothesis testing commonly used in clinical trial analyses, the Bayesian approach refers to a broad range of statistical methods in which a prior distribution—representing pre-existing information—are combined with the data from the clinical trial to derive a posterior distribution of the treatment effect for evaluation. The use of Bayesian approaches in clinical trials may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust[4]. In small clinical trials, the Bayesian approach may enable information outside the planned clinical trial to be explicitly incorporated into the analysis and used effectively. For example, it may be considered for use in various adaptive designs, for reducing the number of participants in the concurrent control group by using

existing data for the control group in an RCT, and for quantitative evaluations to support interpretation of results of a single-arm clinical trial.

Because the use of a Bayesian approach involves multiple considerations, such as the rationale for its use, the appropriateness of the prior distribution, the suitability of success criteria based on posterior probabilities, the adequacy of evaluating operating characteristics (including simulations), and the robustness of the results, it is important to discuss the planned use in advance through PMDA clinical trial consultation meetings.

4. Explanation of clinical trial planning

When planning and conducting a small clinical trial, it is important to be able to provide a detailed explanation of the design ultimately selected and the reasons for selection, among other matters. This explanation is particularly important when discussing clinical trial design through PMDA clinical trial consultation meetings.

Based on the contents described in Chapter 2, the explanation should, in principle, be organized in the following order.

- Anticipated number of participants

  Explain the number of participants anticipated to be enrollable in the planned clinical trial, including details of the considerations. Specifically, provide concrete information on the planned trial regions, the number of patients with the target disease in those regions, the clinical sites that manage the target disease and are capable of participating in the clinical trial, the number of patients who would be eligible based on the inclusion and exclusion criteria, and the anticipated enrollment period.

- Feasibility of conducting an RCT

  Explain the number of participants that would be required for an RCT with sufficient power for the statistical hypothesis testing that is expected to be conducted, and, after considering the anticipated number of participants and the individual elements described in Chapter 3, explain the feasibility of conducting an RCT.

  ✧ When an RCT is considered feasible

  When an RCT is considered feasible, explain the selected design and the individual elements considered in the design. Also explain what conclusion can ultimately be obtained from the trial from the perspective of statistical power and the precision of the results.

  ✧ When an RCT is considered difficult

  When it is concluded, after consideration of various elements, that conducting an RCT is difficult, it is necessary to explain whether efficacy can be evaluated using an alternative trial design and to provide details of the considerations for each relevant

element, as well as the rationale and the process leading to the conclusion that an RCT is not feasible. Then describe the characteristics and limitations of the selected trial design and clarify the conclusion that can ultimately be drawn from the trial. In addition, when conducting a single-arm clinical trial with comparisons to an external control or a predefined threshold, it is necessary to justify the appropriateness of the chosen external control or threshold.

In the process of these considerations, it may also be useful to compare and explain the advantages and limitations of multiple designs assumed.

References

1) Ministry of Health, Labour and Welfare, Basic principles on Utilization of Registry for Applications, PSEHB/PED Notification No.0323-1, PSEHB/MDED Notification No.0323-1, March 23, 2021. https://www.pmda.go.jp/files/000240810.pdf

2) Points to consider for externally controlled trials (Early Consideration), March 24, 2025. https://www.pmda.go.jp/files/000275337.pdf

3) ICH Harmonised Guideline: Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials (E9(R1)), November 20, 2019. https://www.pmda.go.jp/files/000269157.pdf

4) ICH Harmonised Guideline: Statistical Principles for Clinical Trials (E9), February 5, 1998. https://www.pmda.go.jp/files/000156905.pdf

5) ICH E20 Adaptive Designs for Clinical Trials. https://www.pmda.go.jp/int-activities/int-harmony/ich/0100.html (in Japanese)