Provisional Translation (as of May 2025)*

Points to consider for externally controlled 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 "drug") is to conduct a randomized controlled clinical trial that compares the test treatment with a control treatment within the same study. However, in cases where it is difficult to conduct randomized controlled clinical trials due to the small number of patients, for example, in the development of orphan drugs, an open-label single-arm clinical trial may be conducted for the test treatment. In such cases, the results of the trial may be evaluated by comparing them with the results of an external group that did not receive the treatment, known as a comparison with an external control. In this document, clinical trials conducted with the intention of comparing with an external control are referred to as externally controlled trials. Also, it is assumed that such externally controlled trials will be used to evaluate the efficacy and safety of the drug, and that the results may be utilized as part of the documentation for applications for marketing approval and related purposes.

As for the external control group for an externally controlled trial, it may consist of patients who were treated prior to the conduct of the trial (historical controls), or patients who are treated under different conditions during the same time period as the externally controlled trial. However, since none of these groups are randomized concurrently, they do not constitute a population drawn from the same population as the group receiving the test treatment. Bias arises from the fact that the comparison group is not randomized and that the clinical trials conducted as externally controlled trials are generally open-label. The inability to control for such bias is one of the main limitations of externally controlled trials. This document outlines key considerations for conducting externally controlled trials in light of these limitations. Additionally, the ICH guideline titled “Choice of Control Group and Related Issues in Clinical Trials” (ICH E10)[1] may also serve as a useful reference regarding the characteristics of control groups.

Various data sources can be considered for the external control group, such as the placebo group

* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

and an active drug group in other clinical trials for the same disease, and data obtained in actual medical settings (Real World Data, hereinafter "RWD") such as registry data. All of these are covered in this document. Regarding the use of RWD obtained from registries as external controls, this is also mentioned in "Basic Principles on Utilization of Registry for Applications" (March 23, 2021, PSEHB/PED Notification No.0323-1, PSEHB/MDED Notification No.0323-1) [2], and this document includes supplementary information on the contents outlined in that guideline. This document does not address the reliability of RWD used as an external control. Please refer to the relevant notifications, such as "Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications" (March 23, 2021, PSEHB/PED Notification No.0323-2, PSEHB/MDED Notification No.0323-2) [3], as appropriate. In addition, this document assumes that individual participant/patient-level data are available for use as an external control, regardless of the data source, and does not apply to cases where the results of an open-label single-arm clinical trial are compared against a specific threshold.

This document does not address the use of so-called hybrid controls, in which external control data are combined with the control arm of a randomized controlled trial for comparison with the test treatment group. However, even in such cases, this document can serve as a reference for considerations regarding issues that arise from using external controls in addition to concurrently randomized controls—such as the similarity and poolability between the external control and the control group of the randomized controlled trial, as well as the comparability between the test treatment group and the combined control group.

Whether the results of an externally controlled trial, rather than a randomized controlled trial, can be used as evidence of the efficacy and safety of a drug in an application for marketing approval depends on various factors, including the characteristics of the target disease and drug, the reliability of the data used as an external control, and the overall information obtained from the entire development program, including the externally controlled trial. Therefore, it is strongly recommended to consult with the Pharmaceuticals and Medical Devices Agency in advance through clinical trial consultation meetings. Likewise, if it is considered difficult to address certain principles described in this document, clinical trial consultation meetings should be sought in advance.

2. Basic principles

In randomized controlled trials, randomization ensures comparability between groups, and when combined with blinding, it enables comparisons that minimize the potential for bias. When feasible, randomized controlled trials should be conducted as the clinical trials providing the main evidence of efficacy and safety for applications. The use of externally controlled trials should be considered in situations where the conduct of a randomized controlled trial is difficult, the disease or condition has a predictable course based on available knowledge, and sufficient information is available regarding factors and their characteristics that may influence the progression of the disease.

In externally controlled trials, in addition to the treatments, various factors that may influence study outcomes—such as baseline characteristics including demographic factors and concomitant diseases, diagnostic criteria, disease-related factors such as disease duration and severity, concomitant treatments, and observational conditions such as evaluation methods and the expectations of those involved—can differ between the test treatment group and the external control group. As a result, ensuring comparability between groups is challenging, and imbalances in known or unknown confounding factors can introduce bias into the evaluation. Moreover, externally controlled trials are generally conducted as open-label single-arm clinical trials, and due to the lack of blinding, bias may arise in participant selection and outcome evaluation as a result of the expectations of those involved in the test treatment. Bias may also arise during the selection of the external control group itself, for example, due to retrospective data selection. Even when efforts are made to enhance comparability between groups in externally controlled trials, it remains difficult to strictly control for such biases. Consequently, when the observed difference between groups is small, it cannot be ruled out that the difference may be due to potential biases, making it difficult to determine whether a treatment effect has been demonstrated. Therefore, the use of external controls should be considered in cases where, based on already available information about the test treatment, a certain degree of treatment effect is reasonably expected—so that, even when considering the presence of bias, a certain conclusion regarding the treatment effect can still be drawn from the study results.

Based on the above considerations, if the implementation of an externally controlled trial is deemed appropriate, measures should be taken in the trial planning to minimize various types of biases as much as possible. This includes planning and specifying in advance the selection of the external control group and appropriate statistical analysis methods, ensuring that the population of the external control should be one for which detailed individual patient data are available and that is similar to the test treatment group in terms of factors—particularly confounding factors, and adopting similar observation periods and evaluation methods between comparison groups. Further details are described in the following sections.

Furthermore, based on these considerations during the planning stage of the trial, if it is deemed that biases in the evaluation cannot be sufficiently minimized, alternative trial designs should be considered.

3. Data sources for external controls

Various data sources, such as other clinical trials and RWD, may be considered for use as external controls. It is important to note that points to consider apply depending on the data source.

When using data from other clinical trials (for example, data from the placebo group of a previously conducted clinical trial) as an external control, it is generally possible to understand the specifications for data collection—such as inclusion/exclusion criteria, treatment details, and

definitions of endpoints —because clinical trials are typically conducted rigorously in accordance with the trial protocols. Since other clinical trials may differ from the externally controlled trial to be conducted in terms of objectives, evaluations, and interpretations, it is important to assess the comparability between the test treatment group in the externally controlled trial and the external control group, taking into account the information available from the trial protocols. When using data from previously conducted clinical trials as an external control, attention should be paid to the fact that the timing of those trials differs from that of the externally controlled trial to be conducted, which may result in differences in disease assessment, management, etc. Additionally, there is a potential for bias when using clinical trials for which results are already available or have been published. When using clinical trial data as external controls, it is necessary to explain that the selected trial is appropriate and was not chosen arbitrarily, taking into account the above considerations.

When using RWD, such as registry data, as external controls, it is necessary to refer to existing guidelines for general considerations such as the protection of personal information, the reliability of RWD, the appropriateness for the intended purpose, and early consultation with registry holders when using registry data[2), 3)]. It is also strongly recommended to use clinical trial consultation meetings with the PMDA regarding the use of RWD for purposes such as applications. Much of the RWD is not necessarily collected for the purpose of evaluating the efficacy and safety of drugs or for inclusion in dossiers submitted for applications. In addition, due to the nature of data typically derived from routine clinical practice, attention should be paid to the fact that the timing and frequency of data collection, the data items collected, and how much of the data are actually collected may differ from what is expected in clinical trials. In particular, situations where information on key confounding factors is not collected or is subject to a high degree of missingness may pose a serious challenge, making it difficult to reduce bias in between-group comparisons for externally controlled trials. Additional considerations specific to the use of RWD as a data source will be discussed in the following sections.

4. Consideration in trial planning

As with conventional clinical trials, careful consideration at the planning stage is essential in externally controlled trials to minimize potential sources of bias. The trial plan for an externally controlled trial should be specified and clearly described in the trial protocol and related documents prior to trial initiation (i.e., before the first participant is enrolled in the test treatment group). This should include the selection of the population to serve as the external control group, or the method for selecting the population, for example, in cases where the external control group is constructed from RWD, as well as the statistical analysis plan with methods for adjusting for confounding factors and the criteria for trial success based on statistical analysis. Given the inherent lack of blinding in externally controlled trials, changes to the trial plan during the trial should be avoided. If changes become necessary due to unavoidable reasons, the timing, rationale, and content of the changes must

be clearly documented and appropriately justified.

As noted above, comparability between the test treatment group and the external control group is a major issue in externally controlled trials. Therefore, during the planning stage, it is essential to thoroughly examine differences between the groups, as well as the information necessary to construct a comparable external control group. This includes understanding the characteristics of the data sources to be used and identifying potential confounding factors and sources of bias.

During the planning of the trial, the estimand—which is a precise description of the treatment effect reflecting the clinical question posed by the trial objective—should be clearly defined. By designing the externally controlled trial in accordance with the estimand framework, it becomes possible to thoroughly examine potential differences between the test treatment group and the external control group that are related to the attributes of the estimand, and to clearly define the treatment effect that the trial is intended to estimate.

The following elements of the trial should be given particular attention during the planning stage, as they are primarily related to the comparability between the test treatment group and the external control group.

- Population

  In externally controlled trials where randomization is not implemented, it is important to ensure, to the extent possible, that the baseline and disease characteristics of participants/patients in the test treatment group and the external control group are comparable. To achieve this, potential confounding factors that may affect the estimation of treatment effects should be carefully examined, and it should be investigated whether relevant information on these confounding factors is available in the external control data source, as well as how such factors are measured and assessed. Based on this assessment, it is important to construct the external control group to be as similar as possible to the test treatment group, for example, by applying the inclusion and exclusion criteria of the externally controlled trial to the external control population. The trial protocol or related documents should clearly describe the method for selecting the external control group, including details of any matching techniques used, to demonstrate that an appropriately similar population to the test treatment group has been selected and that the selection was not arbitrary.

  With respect to baseline characteristics related to geographic region, if the externally controlled trial is conducted as a multiregional clinical trial—meaning that either the test treatment group and/or the external control group includes participants from outside of Japan—consideration of the comparability between the test treatment group and the external control group should take into account the following documents: ICH guidelines titled “Ethnic Factors in the Acceptability of Foreign Clinical Data” (ICH E5) [5] and “General Principles for Planning

and Design of Multi-Regional Clinical Trials" (ICH E17) [6].

- Treatment

In externally controlled trials, the details of the treatment used in the external control group are important for the interpretation of the treatment effect of the test treatment. In addition to the treatment being investigated in the externally controlled trial, it is necessary to examine aspects such as the dosage, treatment duration, adherence to treatment, and the use of concomitant therapies. Potential imbalances between the groups in these aspects should be carefully considered for their potential impact on the interpretation of results. If the external control data source is from a clinical trial, information related to these factors can typically be obtained from the trial protocol or related documents. On the other hand, if the data source is from RWD, such information may not be recorded or may be incomplete. Furthermore, differences in the medical care that participants/patients receive, due to the differing environments of clinical trials and routine clinical practice, may also influence treatment outcomes. When planning an externally controlled trial, it is important to consider the limitations of the external control data source and ensure that sufficient information on treatment is available for interpreting the results based on group comparisons.

- Timing of data collection

Definitions and diagnostic criteria, standard of care and concomitant therapies, and methods of disease assessment for the disease under investigation in the externally controlled trial may change over time. Therefore, if there is a difference in the timing of data collection between the test treatment group and the external control group, the comparability between groups may be affected by these temporal changes. When planning an externally controlled trial, differences in the timing of data collection and their potential impact on various trial elements and the interpretation of results should be carefully considered in advance. If it is feasible to prospectively collect data for the external control group using sources such as RWD, it is recommended to consider using data collected during the same period as that of the test treatment group. However, in such cases, it should be noted that the external control group may differ from the test treatment group in terms of patient background and other characteristics, as the patients/participants in the external control group did not participate in the externally controlled trial. This should be taken into account when evaluating comparability.

- Index date and observation period

Because externally controlled trials are not randomized, differences in the definition of the index date—the start date of the observation period—between the test treatment group and the external control group may introduce bias into the results. In clinical trials, the index date is typically defined as the enrollment date, the treatment initiation date, or the date of randomization. Therefore, if the external control data source is also a clinical trial, this is generally not a major

concern. However, when the external control group is derived from RWD, the index date may be defined in various ways, and aligning the definition of the index date between the test treatment group and the external control group may be difficult. Special caution is needed when the endpoint of the trial is time-to-event. A well-known issue in this context is immortal time bias. For example, in a trial comparing a test treatment group with an untreated external control group using RWD, where death is the event of interest, if the index date is defined as the time of failure of a prior therapy, the time from failure of the prior therapy to the initiation of the test treatment is counted as immortal time for the test treatment group. In contrast, because the external control group is untreated, this period is not counted, and the time from failure of the prior therapy to death is observed directly. When defining the index date, care should be taken to avoid evaluating one group in a way that includes immortal time, as illustrated in this example.

The length of the observation period should also be consistent between comparison groups. Therefore, it is necessary to ensure that the external control data source contains sufficient data to support the observation period required for the externally controlled trial.

- Endpoints

Externally controlled trials are generally conducted as open-label single-arm trials, and therefore, there is a potential for bias in the evaluation arising from the fact that investigators and other involved parties are aware of the treatment being administered. Additionally, differences between clinical trials, or between clinical trials and routine clinical practice, may affect evaluations and in turn influence comparative results. Therefore, endpoints used in externally controlled trials should be appropriate for addressing the trial objective and the clinical question, and should also be objective and clearly defined. In some cases, blinded evaluation or evaluation by an independent review facility may be useful.

Endpoints and their evaluations must be consistent between the test treatment group and the external control group. In particular, when the data source for the external control group is RWD, the endpoints collected may not be clearly defined, or the evaluation methods may not be standardized, making comparisons with the test treatment group difficult. It is essential to carefully examine the endpoints in the external control data source, including the timing and frequency of evaluations, as well as the specific evaluation criteria and methods used. The selected endpoints must allow for valid comparisons between groups, and their appropriateness should be clearly justified both at the planning stage and when evaluating the results.

- Intercurrent events

Addressing intercurrent events, such as discontinuation of the assigned treatment or the use of an alternative treatment, that affect either the interpretation or the existence of the measurements is important for defining the treatment effect to be estimated. Such intercurrent events should be anticipated and appropriate strategies should be considered during the planning

stage of the trial. In externally controlled trials, the absence of randomization may lead to greater differences in the types and frequencies of intercurrent events between comparison groups than in randomized controlled trials. While it is desirable that intercurrent events be observed with similar rigor in both the test treatment group and the external control group, this may not always be possible— particularly when the data source for the external control group is RWD. For example, the addition or modification of concomitant treatments may not be accurately recorded. Therefore, based on the characteristics of the external control data source, it is important to consider in advance the extent to which information on the occurrence of intercurrent events can be captured, the potential impact of differences from the test treatment group on the evaluation, and the limitations of the evaluations.

- Number of participants/patients (sample size)

When conducting an externally controlled trial, the sample size for both the test treatment group and the external control group must be sufficient to achieve the primary objective of the trial. In externally controlled trials, the external control group is often constructed by selecting a population similar to the test treatment group from the external control data source, using common inclusion/exclusion criteria and matching methods. As a result, it may be difficult to secure a sufficient number of participants/patients in the external control group. Therefore, when planning an externally controlled trial, a feasibility study of the external control data source should be conducted in advance to evaluate how large an external control group can be constructed, based on the available number of patients and the status of data collection. While such a feasibility study is useful for understanding the characteristics of the external control data source, detailed investigation of results of the endpoints or closely related variables should be avoided in order to prevent bias that may arise from prior knowledge of the external control group outcomes. If a feasibility study is conducted, the timing and content of the study should be documented and made available for explanation in the context of regulatory submissions, such as applications for marketing approval.

5. Considerations for statistical analysis

This document does not recommend any specific statistical method for externally controlled trials. Appropriate analysis methods should be selected based on factors such as the trial design, the data source of the external control group, and the characteristics of the data, and the appropriateness of the selected method should be clearly explained. Key considerations for the statistical analysis methods and the implementation of the analysis of externally controlled trials include the prespecification of the statistical analysis plan, the statistical methods used in the trial, and strategies to address the limitations of the data and the comparability of groups.

- Prespecification of the statistical analysis plan

The statistical analysis plan for an externally controlled trial should be defined prior to the initiation of the trial and clearly described in the trial protocol and/or the statistical analysis plan, depending on the content. When using historical data for the external control group, measures should be taken to avoid arbitrary selection of statistical methods, for example, by ensuring that the individuals responsible for planning are not exposed to the outcomes of the external control group when defining the analysis plan. Modifications to the statistical analysis plan during the course of the trial should be avoided. In principle, the results obtained using the statistical analysis methods prespecified before trial initiation are considered to have the highest level of scientific credibility for interpretation. If changes to the analysis plan are made due to unavoidable circumstances, the timing, reasons, and details of the changes must be clearly documented and justified.

- Statistical methods used in externally controlled trials

Statistical analyses conducted in externally controlled trials may include the selection of a population from the external control data source that is similar to the test treatment group to ensure comparability between groups, evaluation of the similarity between the test treatment group and the constructed external control group, and adjusted comparisons between groups to minimize the impact of confounding factors. For each analysis, the necessary assumptions and methodological details should be clearly described in the statistical analysis plan or related documents. Potential biases that are difficult to address through analysis should be considered in advance. Where appropriate, sensitivity analyses and supplementary analyses should be planned and conducted to assess the impact of such biases.

A propensity score may be used as a method for comparing groups with adjustment for confounding factors. In such cases, because propensity score values can influence the results of group comparisons, if the individuals responsible for the analysis are aware of the outcome data for the external control group at the time of propensity score estimation, it may raise concerns that the scores were derived post hoc to yield favorable results. Therefore, the covariates for estimating the propensity scores and details of the estimation methods used should be prespecified. In addition, if the plan includes re-estimating the propensity scores in cases where the prespecified method does not adequately balance patient characteristics between groups, the criteria for determining imbalance and the detailed procedures for re-estimation should also be defined in advance.

- Addressing limitations of data and comparisons

In externally controlled trials, in addition to missing data due to the reasons typically encountered in conventional clinical trials, such as the end of participant observation, there is a higher likelihood of missing data that are necessary for analysis but are not available—

particularly when the external control group data are historical or derived from RWD. Based on the estimand of the trial, such missing data should be identified and statistical methods for appropriately handling them should be planned in advance, and the impact of the missing data on the results should be carefully assessed. Particular attention should be paid to situations in which the external control data source is RWD, where missing data may arise due to events (e.g., intercurrent events) for which no information is available, making proper handling difficult. Attention should also be given to the possibility that a high proportion of missing data may affect the robustness of the results and make their interpretation more difficult, in addition to the concerns regarding the comparability inherent in externally controlled trials.

Confirming the robustness of the trial results—through sensitivity analyses that examine the impact of deviations from the statistical assumptions underlying the methods, including the assumptions about the missing data mechanism used to handle the missing data, as well as through supplementary analyses under varying conditions—plays a crucial role in externally controlled trials, which often rely on various assumptions to account for potential biases. Planning these analyses in advance and conducting them are essential for the appropriate interpretation of trial results.

References

1） ICH Harmonised Guideline: Choice of Control Group and Related Issues in Clinical Trials (ICH E10), July 20, 2000. https://www.pmda.go.jp/files/000156803.pdf

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3） Ministry of Health, Labour and Welfare, Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications, PSEHB/PED Notification No.0323-2, PSEHB/MDED Notification No.0323-2, 23 March, 2021. https://www.pmda.go.jp/files/000240811.pdf

4） 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

5） ICH Harmonised Guideline: Ethnic Factors in the Acceptability of Foreign Clinical Data (E5(R1)), February 5, 1998. https://www.pmda.go.jp/files/000156836.pdf

6） ICH Harmonised Guideline: General Principles for Planning and Design of Multi-Regional Clinical Trials (E17), November 16, 2017. https://www.pmda.go.jp/files/000224562.pdf