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Administrative Notice
June 20, 2024

To: Appended Parties

Pharmaceutical Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare

Considerations for the Utilization of Master Protocol Trials in Drug Development

Research on Regulatory Science of Pharmaceuticals and Medical Devices "Examining of regulatory, statistical and practical issues regarding the conduct of domestic master protocol clinical trials and creating guidelines for their proper use" (led by Dr. Akihiro HIRAKAWA, Tokyo Medical and Dental University, Graduate School of Medical and Dental Sciences, Department of Clinical Biostatistics, Professor) supported by Japan Agency for Medical Research and Development (AMED) have been compiled as shown in the Appendix, entitled "Considerations for the Utilization of Master Protocol Trials in Drug Development."

We ask you to understand and inform related parties.

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

(Appended Parties)

The Federation of Pharmaceutical Manufacturers's Association of Japan

Japan Pharmaceutical Manufacturers Association

Pharmaceutical Research and Manufacturers of America

European Federation of Pharmaceutical Industries and Associations

Pharmaceuticals and Medical Devices Agency

The Biometric Society of Japan

Japanese Society of Computational Statistics

Japan Society of Clinical Trials and Research

The Japanese Association of Pharmaceutical Medicine

Japanese Society of Medical Oncology

Japan Society of Clinical Oncology

The Japanese Association for Infectious Diseases

Japanese Society of Chemotherapy

Japanese Society for Pediatric Infectious Diseases

Appendix

Considerations for the Utilization of Master Protocol Trials in Drug Development

1. Background

In conventional drug development, the efficacy and safety of a single drug for a single disease are evaluated in a single clinical trial. However, due to recent changes in the clinical trial environment, this approach has become increasingly challenging. In particular, developing drugs efficiently for rare diseases or rare fractions as well as development of therapeutic and preventive medications during pandemics have become urgent issues.

The master protocol is a comprehensive protocol designed to evaluate the multiple objectives of several drugs and diseases in a single trial. This protocol includes execution plans for multiple sub-studies conducted concurrently (the studies under the master protocol are sometimes referred to as cohorts; however, in this document we refer to these studies as sub-studies). Clinical trials using a master protocol (hereinafter referred to as "master protocol trials") can evaluate multiple drugs and/or diseases simultaneously or sequentially through various sub-studies. Based on the purpose and design of each sub-study, master protocol trials are classified into basket, umbrella, and platform trials. By implementing multiple sub-studies under a common, comprehensive protocol and infrastructure, master protocol trials can enhance the efficiency of clinical development. However, planning and executing master protocol trials are more complex than standard clinical trials, necessitating careful consideration when appropriately evaluating the efficacy and safety of drugs. Additionally, clear communication with trial participants and their families is essential to convey the risks and benefits of participating in a master protocol trial and deepen their understanding.

Master protocol trials are becoming increasingly prevalent, particularly in oncology. For example, the number of basket trials evaluating the efficacy of targeted drugs by cancer type (or across cancer types) for various cancers with specific genetic abnormalities has increased. During the coronavirus disease (COVID-19) pandemic, platform trials have been conducted to expedite the development of therapeutics. Compared to planning and conducting randomized controlled trials for each drug individually, platform trials using a master protocol allow for the efficient evaluation of each drug's efficacy and safety by sharing a common control group. The use of master protocol trials is expanding beyond oncology and infectious diseases and is expected to be a particularly effective approach for rare diseases and other conditions in which patient recruitment is challenging and where multiple investigational drugs are being developed for a single disease.

However, several challenges specific to master protocol trials have been identified. Because most of these challenges do not occur in conventional clinical trials, sponsors should

understand and appropriately address them. This document outlines the basic considerations and key points for utilizing master protocol trials. Reference should also be made to other guidelines, such as “ICH E8(R1) General Considerations for Clinical Studies” (December 23, 2022, PSEHB/PED Notification No. 1223-5) and “Guidelines for clinical evaluation of anti-cancer drugs” (March 31, 2021, PSEHB/PED Notification No. 0331-1). This document aims to promote the development of pharmaceutical products in Japan.

2. Scope of Application

This document summarizes the basic considerations and key points for planning, conducting, analyzing, and evaluating master protocol trials (basket, umbrella, and platform trials) as clinical trials defined under the “Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices” (Act No. 145 of August 10, 1960, Article 2), based on current scientific knowledge.

3. Communication with PMDA

Master protocol trials represent a new approach, with a limited number of applications. Appropriate designs for new drug applications (NDAs) must be considered individually based on the characteristics of the target diseases and drugs. Therefore, consultation in advance with the Pharmaceuticals and Medical Devices Agency (PMDA) is recommended when using the results of a master protocol trial or its sub-studies to confirm the efficacy and safety of an investigational drug for NDAs. The PMDA recognizes that the primary purpose of using master protocol trials is to streamline the clinical trial implementation system, standardize data collection and management, improve data quality, and introduce efficient trial designs for multidrug development. Notably, PMDA consultations typically focus on the development of individual drugs, making it challenging to discuss the appropriateness of an entire master protocol unrelated to specific drugs or diseases. If discussions about the appropriateness of the master protocol itself are necessary during the individual drug development plan discussions with the PMDA, it is recommended that the master protocol, sub-study protocols, statistical analysis plans, consultation materials with foreign regulatory authorities, and related literature be submitted.

4. Master Protocol Trials

(1) Definitions and purposes of master protocols

The master protocol is a comprehensive protocol designed to evaluate the multiple objectives of several drugs and diseases in a single trial. By creating a master protocol, multiple sub-studies can be conducted using a common clinical trial implementation system and infrastructure. A master protocol should be developed to plan and conduct sub-studies efficiently

in line with the objectives of the trial.

(2) Clinical trial protocol preparation considerations

When preparing master and sub-study protocols, the scope and content necessary to efficiently conduct sub-studies should be considered. For example, common trial elements across sub-studies should be included in the master protocol, whereas drug-specific elements should be documented in separate sub-study protocols. This approach can streamline planning and implementation processes. Master protocol trials generate various related clinical trial documents, including master and sub-study protocols. The extent to which parts are shared among the sub-studies varies depending on the master protocol. These documents should be easily understood to avoid confusion and management complexity. For instance, sub-study protocols can be created as appendices for the master protocol with consistent descriptions of elements across sub-studies, facilitating the understanding and initiation of new sub-studies. If there are a few unique elements in each sub-study, they can be incorporated into the master protocol without creating separate sub-study protocols, while maintaining clear identification. In cases where sequential addition of sub-studies is allowed, considerations for planning sub-studies, trial designs, evaluation endpoints, efficacy and safety evaluation methods, statistical analysis plans, and monitoring systems can be predocumented in the master protocol to expedite the initiation of new sub-studies during the trial.

(3) Establishment of common infrastructure

When conducting screening evaluations to select trial participants for sub-studies under a master protocol, establishing a common screening platform (e.g., types and methods of tests for patient enrollment) is recommended. This enables efficient and consistent quality checks of the eligibility of all study candidates to participate in the sub-studies, including sequentially added sub-studies. Consequently, redundant screening evaluations and eligibility confirmations, typically performed for each trial, are eliminated, thereby enhancing participant enrollment efficiency. However, if simultaneous registration in multiple sub-studies and participants meeting the eligibility criteria for multiple sub-studies is expected, the assignment method should be specified in the master protocol. Participants who do not meet eligibility criteria for any sub-study can be included in an observational cohort as part of the master protocol trial and followed up to collect natural history data. When using registry data for NDA, the “Basic Principles on Utilization of Registry for Applications” (March 23, 2021, PSEHB/PED Notification No. 0323-1, PSEHB/MDED Notification No. 0323-1) should be referred to.

Providing a common data management system for sub-studies can facilitate smooth data collection and sharing and improve data quality. Master protocol trials often require frequent interim analyses, necessitating a data management system that can handle the data obtained in a

timely manner during the trial.

Conducting centralized reviews by a central institutional review board (IRB) rather than individual reviews at each participating institution can save time in responding to the issues highlighted. Typically, the committees involved in trial operations, such as steering committees or independent data monitoring committees, are established for each trial. In master protocol trials, establishing a common committee across sub-studies can enable decision making based on common principles regarding trial continuation, discontinuation, or modifications.

Additionally, a common infrastructure for monitoring, efficacy and safety evaluation can be constructed according to the content of a master protocol trial. Even in master protocol trials, including sub-studies of both investigational and non-investigational drugs, a common infrastructure should be established. Compliance with regulatory requirements and ensuring trial quality are essential for each type of sub-study.

(4) Type of sub-studies

Generally, clinical trials conducted during drug development are classified as exploratory or confirmatory, based on their objectives. The distinction between exploratory and confirmatory trials is described in the "ICH E9 Statistical Principles for Clinical Trials," with the stringency of considerations varying according to trial type. In master protocol trials, sub-studies are classified as either exploratory or confirmatory, and their nature remains consistent with those of traditional exploratory and confirmatory trials. The considerations presented in this document are intended to improve the validity and integrity of master protocol trials, regardless of the type of sub-study, and are common in exploratory and confirmatory trials.

5. Classification of Master Protocol Trials

(1) Basket trials

Basket trials evaluate the efficacy and safety of a single drug against multiple diseases. Basket trials in drug development are generally conducted as exploratory trials aimed at a proof-of-concept (POC) evaluation early in development, although they may also be conducted as confirmatory trials. If a high clinical utility is observed for a specific disease during a trial, enrollment in that population may be expanded to gather further data.

In basket trials with hypotheses for statistical testing, the statistical hypotheses of the primary endpoint should be determined by considering trial objectives, the plausibility of drug effects across multiple diseases, and the feasibility of participant enrollment. The PMDA should be consulted in advance regarding the appropriateness of statistical hypotheses. Statistical hypotheses may be set for each disease individually, or one for all diseases or a combination of several diseases, or both. When integrating all or some diseases, the assumption of a uniform drug

effect across multiple diseases must be reasonably predictable, and the homogeneity of drug effects should be evaluated using statistical analysis. If a uniform drug effect cannot be assumed, hypotheses should be formulated for each disease. In safety evaluations, it may be useful to assess safety data for all diseases or some diseases together, in addition to the data for individual diseases.

(2) Umbrella trials

Umbrella trials evaluate the efficacy and safety of multiple drugs for the treatment of a single disease. Sub-studies may be conducted as single-arm or randomized controlled trials. The considerations for individually conducted single-arm and randomized controlled trials as sub-studies are the same as those for traditional clinical trials.

(3) Platform trials

Platform trials are designed to target single or multiple diseases, allowing for the addition or exclusion of drugs during the trial and the long-term evaluation of multiple drugs on an ongoing basis. Basket and umbrella trials can also be viewed as specific types of platform trials, if they permit the inclusion or exclusion of drugs during the trial. Although various forms of platform trials exist, this discussion focuses on those that establish a common control group for a single disease and evaluate multiple drugs simultaneously. In this type of platform trial, interim analyses are repeatedly conducted to assess the efficacy and futility of each drug. Based on the results, enrollment in certain drug groups may be halted. In such cases, it is necessary to provide sufficient explanation to trial participants and their families and make efforts to minimize any disadvantages caused by the discontinuation of enrollment in this drug group. In this type of platform trials, where the primary objective is to compare the effectiveness and safety of multiple drugs with those of a common control group, each comparison may be performed for either exploratory or confirmatory purposes. Given that platform trials are likely to be large-scale and long-term, managing and operating them poses a significant burden, necessitating the establishment of robust trial implementation systems and infrastructure for sustained execution.

(i) Sharing a common control group

By sharing a single control group across multiple drug groups, it is possible to maintain sufficient statistical power for comparisons between each drug and the control group, while reducing the overall number of participants required for the trial. However, caution must be exercised when using all data from the control group for comparison. When evaluating the effectiveness of a specific drug, data from participants enrolled in the control group before that drug is added in the platform trial or after patient enrollment in that drug group has been completed are considered non-concurrent control data. As these data may not ensure

comparability between the two groups, issues similar to those encountered in external control comparisons arise. For example, if there are changes in the trial execution environment or standard treatments over time, analyses including non-concurrent control data may introduce bias, leading to increased type I error rates or decreased power in statistical testing. The decision to use nonconcurrent control data should be made considering the trial objectives, disease area, and timing of control data collection. Generally, it is recommended to use concurrent control data registered during the same period as the drug group for the primary analyses of primary endpoint for this drug in confirmatory trials.

(ii) Interim analysis

In platform trials, interim analyses may be conducted repeatedly to decide whether to continue or stop allocation to the enrolled drug groups, or add new drug groups. For considerations regarding interim analyses, including the need for interim analyses not initially planned, reference may be made to the "ICH E9 Statistical Principles for Clinical Trials". Occasionally, based on the interim analysis results, adaptive designs such as sample size re-estimation are implemented. Incorporating such design changes (adaptations) can complicate trial execution, raise concerns about maintaining trial integrity, and increase type I error rates. This may ultimately complicate the interpretation of the trial results owing to design changes during the trial. When conducting interim analyses, the master and/or sub-study protocols should detail the timing and frequency of the interim analyses and the conditions for design changes based on the interim analysis results. It is particularly important to consult the PMDA in advance regarding the appropriateness of the adaptive designs.

(iii) Type I error rate control

In platform trials in which multiple comparisons with a common control group are conducted for each drug group, multiple hypothesis tests are performed within the same trial. Consequently, the overall type I error rate for the trial exceeded the nominal value (generally one-sided type I error rate of 2.5% in confirmatory trials), leading to multiplicity issues. However, when evaluating each drug separately, the type I error rate for comparisons between each drug group and the control group does not increase even when a common control group is used. Consequently, it is usually not required to adjust the multiplicity for the entire trial in such circumstances. Nevertheless, if the drugs evaluated in a platform trial are similar compounds, or include combination therapies with various drugs, adjustments for multiplicity may be necessary. The need for methods to adjust for multiplicity in platform trials should be discussed in advance with the PMDA, considering the characteristics of each drug and the overall objectives of the trial.

(iv) Publishing results

In platform trials, the efficacy and safety of each drug are evaluated sequentially as data collection for each drug is completed. If the comparative results between a specific drug group and the control group are published during the trial, the interim data of the control group may be known to clinical trial stakeholders, which may potentially affect subsequent trial plans, the background of enrolled participants, trial dropout rates, and outcome assessments. Therefore, careful consideration is required regarding who has access to trial results, the information to be published, and the method of publication.

6. Statistical Analysis

For the statistical analysis of each objective in a master protocol trial, it is necessary to refer to the "ICH E9 Statistical Principles for Clinical Trials" and appropriately plan and execute the analysis according to the trial design, similar to traditional clinical trials.

The frequentist approach, which evaluates the magnitude and presence of drug effects based on observed data, is a mainstream and generally recommended method for evaluating drug efficacy and safety in clinical trials. However, as stated in the "ICH E9 Statistical Principles for Clinical Trials," Bayesian methods can also be considered if there is a clear rationale for their use and if the conclusions remain sufficiently stable under different assumptions. When employing Bayesian methods in master protocol trials, it is important to demonstrate their necessity based on individual designs and to ensure that the results are stable and can be appropriately interpreted. In particular, during trial planning, it is necessary to evaluate the information and extent used to specify prior distributions, as well as the operating characteristics of the Bayesian method (e.g., type I error rate, power, and degree of consistency of trial results with frequentist methods). If it is challenging to evaluate operating characteristics analytically, a clinical trial simulation should be used.

Regardless of the statistical analysis method used, when evaluating drug effects across different diseases, validity should be considered not only from the perspective of statistical analysis methods but also from biological rationality, considering the differences in diagnostic methods, efficacy evaluation methods, and drug mechanisms of action for each disease.

7. Independent Data Monitoring Committee

In master protocol trials, changes to the trial plan, decisions on trial continuation, and addition or exclusion of drug groups may occur during the trial. To ensure the safety of trial participants and guarantee the validity and integrity of the trial, an Independent Data Monitoring Committee (IDMC) should be established as necessary. The IDMC may provide recommendations for preplanned evaluations of efficacy and/or futility, trial plan changes, and

unplanned issues necessary for the proper conduct of the trial such as protocol modifications or other relevant measures. When selecting members of the IDMC in master protocol trials involving multiple sponsors and evaluating multiple drugs, it is essential to ensure their independence from sponsors and other stakeholders to provide neutral recommendations for trial continuation for individual drugs. For the establishment and operation of the IDMC, please refer to the "Guidelines on Data Monitoring Committees" (Notification No. 0404-1, April 4, 2013, issued by the Director of the Office of New Drug Evaluation, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour, and Welfare).

8. Preparation of Regulatory Documents

(1) Points to consider when preparing documents for new drug applications

Because master protocol trials involve multiple drugs and diseases, when evaluating the efficacy and safety of drugs intended for approval based on the results of sub-studies, it may be necessary to refer to the background of trial participants and information from other related sub-studies (e.g., allocated treatment groups, reasons and timing for treatment discontinuation or dropout). Information from related sub-studies may be requested during the PMDA review process. Therefore, it is essential to thoroughly discuss among stakeholders the sub-studies related to those intended for application, considering aspects such as the availability of this information, specific procedures, and contractual rights issues.

(2) Clinical Trial Notification

Regarding the notification of clinical trial plans for master protocol trials, please refer to “Handling of Information in Clinical Trial Notifications for Drugs Referencing Other Clinical Trial Notifications (in Japanese)” (June 30, 2022, PSEHB/PED Notification No. 0630-1) and “Revision of Questions and Answers (Q & A) on Notification of Clinical Trial Plan and Implementation of Clinical Trial for Drugs” (August 31, 2022, PFSB Notification No. 0831-1).

9. Considerations in Specific Disease Areas

This section introduces considerations for basket trials in the development of anticancer drugs and platform trials in the development of treatments for emerging and reemerging infectious diseases during pandemics. The contents and considerations introduced here are examples that should not be generalized to all cases in related fields or other disease areas.

(1) Basket trials for anticancer drug development

Basket trials are often used to develop anticancer drugs that target genetic abnormalities. Specifically, these trials evaluate the efficacy of targeted drugs against multiple cancer types that

share a specific genetic abnormality, with the objective response rate (ORR) as the primary endpoint, both by cancer type and across cancer types. Examples include:
Basket trial of larotrectinib: for patients with advanced or recurrent solid tumors positive for the *NTRK* fusion gene (Review Report – Larotrectinib, January 19, 2021, Pharmaceuticals and Medical Devices Agency (Japanese only)).

Basket trial of dabrafenib and trametinib combination therapy: for patients with malignant neoplasms harboring a *BRAF V600E* mutation and no standard treatment options (Review Report - Dabrafenib Mesilate, October 12, 2023, Pharmaceuticals and Medical Devices Agency (Japanese only)). Formulation of a plan that considers the specific characteristics and development strategies of a drug is crucial. This example should be used solely as a reference, and is not intended as a recommendation for trial planning.

When a basket trial is conducted as a single-arm sub-study, the target sample size is typically determined to ensure a high probability that the lower bound of the confidence interval for the ORR exceeds a predetermined threshold. A statistical analysis of the ORR is decided based on the establishment of the statistical hypotheses, for example, for each cancer population, for combined populations of some cancer, or for the combined population of all cancer.

To evaluate the effectiveness of anticancer drugs for individual or different cancer types in basket trials, frequentist methods are commonly used to estimate ORRs and confidence intervals. However, Bayesian methods can provide different quantitative evaluations such as posterior or predictive distributions of ORRs, which can aid in interpreting drug effects. For example, hierarchical Bayesian models, if their assumptions hold, can evaluate the ORR more efficiently than they can evaluate each cancer type separately.

(2) Platform trials for developing treatments for emerging and re-emerging infectious diseases during the pandemic

In the context of pandemics, the clinical development of treatments for emerging and re-emerging infectious diseases often needs to begin extremely rapidly, owing to high societal demands, despite insufficient knowledge about the target infection. After initiating the trials, it may be necessary to make unplanned changes to the trial design (e.g., primary endpoints, statistical hypotheses, target sample size, and allocation ratios) based on accumulated data and new knowledge about the infection. In addition, other new treatment trials may need to be initiated swiftly. Platform trials can be an effective approach in such scenarios. Examples include:

ACTT trials for patients with SARS-CoV-2 infection (ACTT-1: Report on Special Approval for Emergency – Remdesivir, May 5, 2020, Pharmaceuticals and Medical Devices Agency; ACTT-2: Review Report – Baricitinib, April 12, 2021, Pharmaceuticals and Medical Devices Agency (Japanese only)).

RECOVERY trial for patients with SARS-CoV-2 pneumonia (Review Report–Tocilizumab (genetic recombination), January 7, 2022, Pharmaceuticals and Medical Devices Agency). Formulation of a plan that considers the specific characteristics and development strategies of a drug is crucial. This example should be used solely as a reference, and is not intended as a recommendation for trial planning.

In Japan, investigator-initiated platform trials evaluating multiple drugs during the pandemic are expected to be planned and conducted by academic institutions. To promote efficient coordination with participating medical institutions, ethics committee procedures, regulatory filings, distribution and management of investigational drugs, and standardization of informed consent documents, well-experienced physicians and medical institutions should lead these trials. A centralized data center should manage the data collected from platform trials. It is also important to define the selection criteria for drugs to be included in trials.

To ensure rapid trial commencement during a pandemic, it is advisable to prepare related documents (e.g., master protocols and informed consent documents) during normal times and share trial plans with relevant ethics committees. Preliminary investigations of trial sites and related procedures are recommended. After trial initiation, it is crucial to prepare documents summarizing the key trial characteristics (e.g., treatment groups, eligibility criteria, primary endpoints, and statistical analysis plans) to ensure that all stakeholders understand the trial's overall structure and progress.

Participating in master protocol trials led by overseas government agencies or academia requires building relationships with foreign regulatory agencies, actively engaging in international collaborative clinical trials, establishing support systems for medical institutions with limited trial experience, and organizing the distribution and management of investigational drugs and related materials. It is important to ensure budgets/funding to conduct legal proceedings.

If movement restrictions are imposed during the state of emergency, conventional trial implementation may become infeasible. The digitalization of trial operations, including electronic consent acquisition, remote monitoring, and remote source data verification (SDV), can be beneficial. Gaining experience in decentralized clinical trials (DCTs) may also be helpful. For more information on obtaining electronic consent, refer to “Points to Consider for Informed Consent Using Electromagnetic Means in Clinical Trials and Post-marketing Clinical Trials” (March 30, 2023, PSEHB/PED Notification No. 0330-6, PSEHB/MDED Notification No. 0330-1).

10. Conclusion

This document was prepared and published with the support of research funds from the Japan Agency for Medical Research and Development (AMED). The considerations and points

of attention described in this document are based on the scientific knowledge available at the time of its creation. However, given the progress in science and academic advancement, it is not necessary to adhere strictly to the ideas and considerations presented here as long as appropriate and scientifically grounded justifications are provided.