Appendix 3

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Research Reports

A Biostatistical Perspective to Accelerate the Planning of Clinical Trials in Vaccine Development

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Study Abstract:

Efforts from various perspectives are required to accelerate the planning of clinical trials and development strategies for vaccine development. In this study, we assessed the current status of vaccine development in Japan and identified issues to be addressed through an investigation and summarization of review reports on approved vaccines. We also conducted a questionnaire survey regarding the Pharmaceuticals and Medical Devices Agency's system for providing clinical trial consultation and other services to companies that are developing vaccines. In addition, we identified highly probable infectious disease scenarios that require rapid vaccine development and representative candidate clinical trial designs for these scenarios. Further, we examined clinical trial designs and analysis methods that may contribute to efficient efficacy evaluation and rapid decision-making from a biostatistical perspective and reviewed points to be considered. Based on an analysis of clinical trial designs used for approved vaccines, we found that, although there are signs of change in the vaccine development landscape in Japan, domestic-origin vaccine development companies currently have no experience in conducting large-scale clinical trials that evaluate clinical outcomes such as the prevention of disease onset, nor experience in conducting multi-regional clinical trials and trials in other countries. In order to enable domestic companies to develop new vaccines under urgent conditions, it is essential to improve the clinical trial environment by establishing a clinical trial system and conducting clinical trials that evaluate clinical events as endpoints and multi-regional clinical trials, as well as trials that enable combined analyses under normal circumstances.

Further, in developing new vaccines under urgent situation, it is clearly important to design and

plan clinical trials rapidly and conduct trials using designs that efficiently generate evidence. Complex clinical trial designs, such as those using Bayesian approach, adaptive designs, and master protocols, are useful methods for rapid efficacy evaluation. For designing a clinical trial that incorporates these features, we recommend preparing not only the operating characteristics from a biostatistical viewpoint, but also a system to enable such a trial to be conducted. Furthermore, it is expected that the development and approval of vaccines in Japan will be accelerated by establishing a platform for generating scientific evidence that includes the construction of a database infrastructure for post-approval vaccine evaluation in Japan.

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A. Research objective

The coronavirus disease 2019 (COVID-19) pandemic has had a significant impact from various perspectives worldwide since the first patient was reported at the end of 2019. In Europe and the United States, developing new vaccines against novel coronaviruses has been moving at a breakneck pace. Several vaccines are currently in practical use within one year of development. The Japanese government has also called for rapid vaccine development, actively supporting the development of domestic new coronavirus vaccines by investing heavily[1)] in policy packages included in the "Strategy for Strengthening Vaccine Development and Production Systems"[2)], which the Cabinet approved on June 1, 2021[3)]. This effort was also reflected in the supplementary budget of 2020. However, despite the spending of these budgets, no domestic vaccines were made available for practical use in Japan as of the end of March 2022. This fact highlights the existence of various issues in the vaccine development system in Japan. Some of these challenges include the lack of a system for designing and planning clinical trials under unexpected, rapidly changing circumstances, and the necessity to consider planning and designing clinical trials when developing a new vaccine in the presence of an already established vaccine.

The sponsor company conducts the designing and planning of clinical trials for vaccine development, as with other pharmaceutical products. However, unlike therapeutic drugs, clinical trials for new vaccines are conducted rather infrequently. Although there have been cases of investigator-initiated clinical trials for the development of vaccines against novel influenza viruses, there is no framework for the accumulation of sufficient expertise in the design of clinical trials under academic initiatives. In addition, in situations requiring the rapid development of vaccines against emerging infectious diseases, the clinical trial design must be planned without sufficient basic, clinical, and epidemiological knowledge of infectious diseases. Even under such uncertainties, it is necessary to efficiently generate evidence based on data and appropriately evaluate the efficacy of vaccines with transparency. Clinical trial designs that incorporate biostatistical methods which have recently drawn attention, are considered to be useful in such situations.

While careful consideration is required in designing clinical trials, it is not feasible to do so rapidly during an emergent situation. Therefore, it is important to consider in advance, as much as possible, clinical trial designs and plans for possible scenarios, summarize the points to be considered and evaluate the operating characteristics of typical clinical trial designs. In addition, it would be valuable to review large-scale clinical trial designs conducted in other countries from a biostatistical perspective to aid in the rapid planning of clinical trials in the future.

Based on the above information, this research group, in collaboration with government and academia, aimed to examine the following: 1) review and summarize cases of newly approved vaccine development in Japan and contents of the application data packages; 2) a questionnaire

survey of companies with experience in vaccine approval review; 3) possible scenarios expected to require rapid vaccine development in the future; 4) possible clinical trial designs for highly expected scenarios that require rapid vaccine development; 5) features and considerations from a biostatistical perspective that should be taken into account in vaccine development; and 6) operating characteristics of the representative scenarios. Further, regarding biostatistical considerations in particular, we aimed to address the following points: 7) the possibility of utilizing Bayesian approach; 8) efficacy evaluation using pharmacoepidemiologic methods; and 9) clinical trials utilizing a master protocol format.

B. Methods

B-1. Summarization of development cases of approved vaccines (Shared Research 1: Yasuhiro Araki, Co-investigator)

We collected the review reports for vaccines that were newly approved (defined as new active ingredient-containing drugs in the "Application for Product Approval" [Notification No. 1121-2] of the Pharmaceutical and Food Safety Bureau, November 21, 2014) and published on the package insert information service web page, https://www.pmda.go.jp/PmdaSearch/iyakuSearch/. In total, there were 39 newly approved vaccines from April 1, 2004, when the Pharmaceuticals and Medical Devices Agency (PMDA) was established, to March 31, 2022 (including five vaccines sharing clinical trials with other drugs for reasons such as a single product with multiple names). In total, 63 studies were selected for review, and the following data were collected and summarized for each clinical trial: control drugs used, types of control drugs (placebo [adjuvant-only, saline, etc.]), primary and secondary endpoints, and the number of participants in the test group. In addition, the use of characterized designs and analyses (Bayesian approach, combined analysis, cluster randomized clinical trials) was summarized.

B-2. Questionnaire survey of companies with vaccine approval review (Shared Research 2: Taro Shibata, Co-investigator)

We identified companies with experience in the approval review of vaccines based on the above-mentioned review of application data packages and requested their cooperation in the survey as candidates. We then conducted a questionnaire survey on issues in the designing and planning of clinical trials related to their current systems and experience (number of in-house biostatisticians, number of past clinical trial plans, types of clinical trial designs that have been employed, etc.), and issues related to system development to be addressed in the future (requirements for more effective clinical trial consultation with the PMDA, company views regarding matters requiring preparation by industry, government, and academia, etc.).

B-3. Scenario construction

With consideration for clinical trial designs, scenarios assumed to have a high potential for

vaccine development were identified by interviews with infectious disease specialists. The interviews included discussion on the infectious diseases assumed to have high pandemic potential, the magnitude of public health impact in terms of infectiousness and virulence, and the endpoints that should be evaluated in vaccine efficacy.

B-4. Considerations for candidate clinical trial designs

Based on the clinical trial designs of existing vaccines identified in B-1 and the infectious disease scenarios with high development potential identified in B-3, we examined important considerations for the clinical trial design of confirmatory studies (pivotal studies), which are central in evaluating efficacy and safety in vaccine development. Since approaches regarding the definition of the control group, number of cases, and primary endpoints are expected to differ between the initial and subsequent vaccine development, we examined these issues for each stage of vaccine development.

B-5. Factors to be considered and possible trial designs in the development of vaccines for emerging infectious diseases (Shared Research 3: Yuki Ando, Co-investigator)

Based on public information for approved vaccines in Japan; international regulations; recommendations by various entities, including Japan and the World Health Organization (WHO); and the content of discussions at relevant international workshops regarding vaccine development since the outbreak of new coronavirus infectious diseases, we reviewed the factors to be considered, as well as possible clinical trial designs, in the development of vaccines against emerging infectious diseases.

B-6. Operating characteristics and performance evaluation under assumed scenarios (Shared Research 3: Yuki Ando, Co-investigator)

The operating characteristics and performance of trial designs identified in B-4 and B-5 were evaluated for scenarios assumed to have the highest priority. Assuming that the spread of infectious disease would require early decisions regarding the efficacy and vaccine approval, the operating characteristics (such as the target number of cases, alpha error, and power) were evaluated in a simulation study.

B-7. Consideration of the potential use of Bayesian approach (Shared Research 4: Kentaro Sakamaki, Co-investigator)

We reviewed and summarized the protocols of clinical trials using the Bayesian approach for a novel coronavirus vaccine already in practical use. In addition, we examined whether clinical trial designs using Bayesian approach could be utilized in vaccine development in Japan.

B-8. Efficacy evaluation using pharmacoepidemiologic methods (Shared Research 5: Chieko Ishiguro, Co-investigator)

We collected and summarized information on

surveys and studies on efficacy evaluation that were planned by each vaccine manufacturer for vaccines against COVID-19 used in Japan, the United States, and Europe that received special approval or were approved for emergency use. We also conducted a document review of various guidelines and previous studies on the efficacy evaluation of post-approval vaccines. In addition, possible patterns of post-marketing surveillance, etc. that could be selected according to the development scenario and clinical trial design to accelerate vaccine development were discussed.

B-9. Feasibility of master protocol clinical trials (Shared Research 6: Akihiro Hirakawa, Co-investigator)

A master protocol clinical trial is a clinical trial in which multiple drugs or diseases are evaluated using a single comprehensive protocol. We reviewed the draft guidance on master protocols for drug development for cancer treatment published by the United States Food and Drug Administration (FDA) in September 2018. We summarized design considerations for master protocol trials for vaccine development in Japan based on examples of master protocol trials.

(Ethical considerations)
No ethical considerations were required because this study was an investigation of previously published review reports.

C. Results

C-1. Summarization of development cases of approved vaccines (Abstract of Reports for Shared Research 1)

The active ingredient of 14 of 39 (35.9%) evaluated vaccines were developed by a domestic company (domestic-origin vaccines), and no domestic-origin vaccines have been approved since 2016.

In the 59 clinical trial designs evaluating the efficacy of the above vaccines, the mean and median number of participants were 7480.3 and 423, respectively (first quartile: 216; third quartile: 4277.5). However, no clinical trial for a domestic-origin vaccine had more than 1000 participants. Among 18 of the 20 trials with more than 1000 participants, a clinical endpoint (clinical event) was used as the primary endpoint. On the other hand, 37 of 39 trials with fewer than 1000 participants used an immunological surrogate marker as the primary endpoint. No clinical trials using a clinical endpoint as the primary efficacy endpoint have been conducted in the development of domestic-origin vaccines.

In addition, the efficacy of three vaccines was evaluated in multi-regional clinical trials, with participants enrolled from Japan; all of these trials were for foreign-origin vaccines. No clinical trials for a domestic-origin vaccine have been conducted in foreign countries or as multi-regional clinical trials for efficacy evaluation.

One example of a distinctive trial design was the C4591001 Study of the Comirnaty intramuscular injection, BNT162b2, in which a Bayesian approach was used in the statistical methods. Adaptive design trials were conducted to evaluate the efficacy of the following agents,

which allowed for pre-planned modifications based on factors such as the number of participants enrolled or dose selection: Comirnaty intramuscular injection (Study C4591001), Silgard 9 aqueous suspension for Intramuscular Injection Syringes (Study 001), and RotaTeq oral solution (Study 006). In addition, some trials employed a cluster-randomized, double-blind design and trials utilizing a combined analysis.

C-2. Questionnaire survey of companies with vaccine approval review (Abstract of Reports for Shared Research 2)

The questionnaire (including questions on eligibility for the survey and other detailed questions) was sent via e-mail to 22 companies in March 2022. We received replies from 17 (77%) companies. Of these, 12 met the survey criteria of "having experience in obtaining regulatory approval for vaccines in the past and having a clinical development department." The results were summarized for 10 companies, after excluding two companies that could not answer the detailed questions.

The questions were categorized as follows: A) matters related to the organization; B) matters related to the content of clinical trial consultation; and C) matters related to measures to be taken in an emergency. One of the 10 companies responded only to item C.

The survey results indicated that most companies have more than one biostatistician within the company. No major problems were identified with the current PMDA system. In addition, respondents were asked to provide their suggestions for changes to the current industry-government-academia structure and system to design clinical trials and formulate development strategies more rapidly “in response to an emergency situation” (here, vaccines requiring urgent development were assumed, although it is difficult to assume this in advance). In particular, in the case of an urgent situation, it was assumed that environmental factors might also influence the speed of the clinical trial design and development strategy planning. Some respondents pointed out the need for closer collaboration between the PMDA, Ministry of Health, Labour, and Welfare (MHLW), and related departments within the MHLW.

C-3. Scenario construction

We interviewed the following four infectious disease specialists regarding the types of infectious diseases that are assumed to have a high potential for vaccine development.

- Dr. Mugen Ujiie, Director of Vaccination Support Center, Disease Control and Prevention Center, National Center for Global Health and Medicine (2021/8/30)
- Dr. Tomoya Saito, Director of the Center for Emergency Preparedness and Response, National Institute of Infectious Diseases (2021/9/03)
- Dr. Takao Omagari, Director of the Center for Global Infectious Diseases, National Center for Global Health and Medicine (2021/9/03)
- Professor Hitoshi Oshitani, Professor, Graduate School of Medicine Medical Sciences Pathology Virology, Tohoku University

(2021/9/07)

The most likely outbreak of an emerging infectious disease critical to public health risk management would be a viral respiratory infection of a type that spreads easily from human to human, and thus has a high probability and priority for vaccine development. Specifically, new infectious diseases caused by coronaviruses and influenza viruses were considered likely. The emergence of new coronavirus infections began with Severe Acute Respiratory Syndrome (SARS) in 2002, followed by (Middle East Respiratory Syndrome (MERS) and COVID-19, and the emergence of new viruses with human-to-human transmission cannot be ruled out due to mutations of naturally occurring coronaviruses in the future. In addition, H1N1 pandemic occurred in 2009 under the assumption that influenza A viruses can produce new influenza viruses that may transmit efficiently from human to human through antigenic discontinuous mutations (antigenic shift). Fortunately, the virulence was low in the 2009 pandemic, although, it is not unlikely that the next outbreak of a new influenza virus could be efficiently transmitted from human to human with higher virulence. It is also possible that some viruses, including the H5 subtype, may acquire the ability to be transmitted from human to human. Although these outbreaks can be categorized as infectious diseases caused by pathogens closely related to past outbreaks, the possibility that known coronaviruses such as SARS and MERS may cause an outbreak above a certain level in Japan cannot be ruled out.

Known infectious diseases such as yellow fever, dengue fever, and viral hemorrhagic fever, mainly transmitted by contact or mosquito vectors, may also cause a certain level of epidemic in Japan and abroad. Although these diseases are unlikely to become pandemics and are more likely to be localized epidemics, the possibility that highly lethal infectious diseases currently without efficient human-to-human transmission may become more infectious in the future through mutation cannot be denied. Although the probability of development is assumed to be higher for the above-mentioned viral respiratory infections, these diseases should be included in the scenarios for consideration in clinical trial design. Enterovirus infections should also be considered because of their potential to cause serious infections.

As mentioned above, although viral respiratory infections are considered a high priority scenario for clinical trial design, it is extremely difficult to predict which infections will be prevalent in the future. There is low predictability regarding the intensity of infectiousness and lethality of infections with mutated pathogens.

C-4. Considerations as candidates for clinical trial designs

Candidate trial designs were examined with consideration of the results reported in C-1 and C-3. Trial designs were highly influenced by whether a vaccine was developed in the absence of other vaccines approved in Japan (initial vaccine development) or in the presence of an already approved vaccine (subsequent

vaccine development).

1) *Trial designs for initial vaccine development*

A placebo-controlled randomized trial with clinical events as the primary endpoint was considered scientifically appropriate as a confirmative study of the efficacy and safety of vaccines for the prevention of infectious diseases. In particular, regarding viral respiratory infections (an infectious disease type with a high probability of development), it was considered appropriate to evaluate the prevention of disease onset as the primary endpoint, with safety, immunogenicity, severe disease, and death as secondary endpoints. However, if it was clear at the development stage that mortality was high and no therapeutic agents existed, severe disease or death may be defined as the primary endpoint[5].

As noted above, in principle, the clinical trial design for a pivotal trial for developing an initial vaccine would be appropriate to set clinical events such as incidence as the primary endpoint, and the number of required participants is likely to be large. For instance, we may assume a randomized controlled trial of a novel coronavirus infection scenario, with an allocation ratio of 1:1 between the vaccine and placebo groups, incidence rate of 1% at 6 months for the placebo group and expected VE of 60%. Based on the above assumption, the required sample size would be 19,350 to confirm the lower limit of the 95% confidence interval for VE, based on the hazard ratio, exceeds 30%.

In urgent vaccine development situations, where information on the actual infectiousness and incidence of an infectious disease is limited, a relatively large-scale clinical trial may be planned as described above. Therefore, it would be useful to use an adaptive design, allowing for decision-making such as efficacy/non-efficacy discontinuation based on efficacy evaluation during the trial. Furthermore, as various factors can affect the clinical trial plan, such as changes in the infection rate due to infectious disease countermeasures and mutant strains, or the impact of temporal changes in the infection environment due to an increase in vaccines in development, the possibility of early discontinuation of the trial not pre-planned may be required according to the infection situation based on public health needs. In this report, we summarized the points that should be assumed and considered in advance when planning a clinical trial for vaccine development, including such factors that may occur during the study, as well as possible design techniques and points to consider when utilizing those in the clinical trial plan. In addition, regarding a placebo-controlled randomized clinical trial with prevention of disease onset as the primary endpoint, which is a representative trial design, we conducted simulation experiments to evaluate the performance of the trial, including the timing and uncertainty of the results if the trial was discontinued early.

A Bayesian approach is one of the techniques that can be particularly valuable in such scenarios. During the initial stages of vaccine development, it is likely that clinical trials will need to be designed with limited basic, clinical,

and epidemiological knowledge and in the face of uncertainties regarding infectivity, lethality, and the vaccine's mechanism of action. Additionally, as previously mentioned, various factors may affect the trial design, and the trial may be terminated prematurely without prior specification. Bayesian approach is effective in quantifying such uncertainties and is also useful in efficiently evaluating efficacy. In fact, the Bayesian approach was used in the Comirnaty intramuscular injection trial (Study C4591001); the use and potential benefits of Bayesian approach in vaccine development have been summarized in Shared Report 4 (by Dr. Sakamaki). As noted above, in principle, for initial vaccine development, we consider the evaluation of efficacy and safety by a placebo-controlled randomized controlled trial with a clinical outcome as the primary endpoint to be scientifically valid; however, a cluster randomized double-blind trial design may also be an option.

A rare example of a surrogate marker based on immunogenicity as a primary endpoint is the confirmative study of Chikungunya (mosquito-borne infection) conducted in the United States in July 2020. The main reasons for setting the prevalence of antibody as the primary endpoint were that outbreaks had already occurred in neighboring countries, although the number of cases in United States was very limited, and immunogenicity had been confirmed as a surrogate for the pathogenesis in the phase 1 study and other studies. In general, studies with immunogenicity-based surrogate markers as primary endpoints are likely to be small in size; however, this study included 4131 patients, which is more than the minimum of 3000 patients as the target population for safety evaluation recommended in the WHO guidelines on the clinical evaluation of vaccines[5].

2) *Clinical trial designs for subsequent vaccine development*

In situations where initial vaccination with a validated efficacy in preventing the onset of disease is in place, it would be impractical to conduct a placebo-controlled randomized trial. Instead, conducting a randomized controlled trial using a previously approved primary vaccine with confirmed efficacy as a control may be recommended. Although clinical events such as the prevention of disease onset are desirable as primary endpoints from the viewpoint of scientific evaluation, it has been reported that conducting a controlled clinical trial to verify non-inferiority in efficacy for the prevention of disease onset would require 2 to 3 times more patient-years than that required for a placebo-controlled trial in initial vaccine development[6], thus raising issues in terms of feasibility.

On the other hand, when scientific knowledge of the mechanism of action is available and an immunogenicity-based surrogate marker that correlates with efficacy against a clinical event exists, a randomized active vaccine-controlled trial with appropriate immunogenicity as the primary endpoint may be an option. In fact, the International Collaboration of Medicinal Regulatory

Agencies (ICMRA)[6] and the PMDA Vaccine and Other Products Review Division[7] have proposed the use of immunogenicity-based primary endpoints for efficacy evaluation of newly developed vaccines when clinical endpoints are no longer feasible in vaccine development against COVID-19.

When conducting a randomized, active drug-controlled trial with an immunogenicity-based surrogate marker as the primary endpoint, deciding whether to conduct a superiority or non-inferiority trial should consider the magnitude of the effect obtained by the control drug and the degree of correlation between the surrogate marker and the clinical event. In addition, if a non-inferiority trial is conducted, an appropriate margin of non-inferiority should be established. Furthermore, even when immunogenicity is set as the primary endpoint, we consider it necessary to appropriately evaluate important clinical events, such as the prevention of disease onset, severe disease, and death. In other words, a possible scheme would be to submit a regulatory application based on data from pivotal studies with immunogenicity as the primary endpoint and then evaluate clinical events through post-marketing surveillance and other means. Results regarding the possible utilization of post-marketing surveillance in Japan are summarized in Shared Report 5 (by Dr. Ishiguro).

Furthermore, when multiple candidate vaccines are expected, conducting individual clinical trials for each vaccine is an inefficient strategy, from the viewpoint of the utilization of resources such as clinical trial participants and sites. Recently, platform clinical trials using a master protocol to enable more efficient and rapid development have been conducted, mainly in the field of therapeutic drug development for COVID-19[8]. Furthermore, in May 2021, guidance on master protocols for drug development to treat or prevent COVID-19 was published[9]. Potential utilization of a master protocol format for clinical trials in vaccine development is summarized in Shared Report 6 (by Dr. Hirakawa).

C-5. Factors to be considered and possible trial designs in the development of vaccines for emerging infectious diseases (Abstract of Reports for Shared Research 3-1)

The following four points should be considered in the design of clinical trials and possible study designs for urgent vaccine development against emerging infectious disease outbreaks: (1) the amount of information on the infectious disease; (2) changes in the infectious disease due to infectious disease control measures and mutant strains; (3) increases in immunization rates of already approved vaccines; and (4) increases in the number of vaccines developed concurrently.

1. *The amount of information on the infectious disease.*

In the period between the outbreak of an emerging infectious disease and the beginning of an epidemic, when information on the actual infectiousness and incidence of infectious diseases is scarce, a relatively large-scale study may be planned. Therefore, adaptive designs,

including a sequential group design (interim analysis), could be utilized for decision-making, such as effective/ineffective discontinuation based on efficacy evaluation during study implementation. Furthermore, in situations where the amount of information on both infectious diseases and vaccines is limited, multiple doses may be studied in multiple small trials, multiple administration targets (cohorts) may be studied, or studies may be conducted in specific regions. In such cases, an evaluation of the effect on the prevention of disease onset, which typically requires a large number of participants, could be conducted in a pre-planned integrated analysis using a design in which individual trials have specific objectives and a certain degree of similarity.

2. *Changes in the infection rate due to infectious disease control measures and mutant strains*

The incidence of clinical events, which is typically considered the primary endpoint in vaccine development trials, especially in the early stages of an infectious disease epidemic, may change due to the decreases in infection and incidence rates resulting from the promotion of infectious disease control measures or the prevalence of mutant strains with different infectious potential. To accommodate such changes, the number of participants may be modified based on the accumulation of information on the incidence rate in a blinded manner. Accordingly, it is useful to plan in advance for possible design modification, including determining whether or not the modification is necessary, especially in pivotal trials. In addition, the possibility that the trial be terminated early for public health reasons not specified in advance cannot be ruled out. Therefore, it would be useful to confirm the performance evaluation regarding the timing and uncertainty of the results by simulation tests in such cases.

3. *Increases in the immunization rates of previously approved vaccines*

If development is initiated early in an infectious disease outbreak and vaccination proceeds with an approved vaccine with verified efficacy in preventing the disease onset (initial vaccine development), it becomes difficult to conduct placebo-controlled clinical trials to confirm the efficacy and safety of subsequent vaccines from the viewpoint of feasibility and other factors. In such cases, a non-inferiority study may be planned using the approved vaccine in the control group, with a clinically appropriate non-inferiority margin. As the primary endpoint, an immunogenicity index could be set as a surrogate measure of efficacy in the prevention of disease onset based on the contents of C-4[2)].

4. *Increases in the number of vaccines developed*

In situations in which multiple vaccines have been developed simultaneously in a relatively short period, multiple test vaccines may be evaluated under one common clinical trial protocol (master protocol) using a common platform in order to evaluate their efficacy more efficiently (platform study)[10)]. This may be particularly useful in cases where evaluation is conducted using an approved vaccine as a

common control vaccine. However, vaccines developed by multiple companies evaluated in platform studies require large-scale, long-term platform management. Developing a study implementation system is important to ensure that the clinical trials are simultaneously appropriately managed through the platform.

Further, efficacy evaluation through large-scale global clinical trials also has an important place in applications for approval. In addition, in vaccine development under many uncertainties, Bayesian statistical approaches may be used as the main analysis in pivotal trials, in place of the statistical hypothesis testing that has been commonly used in the past. Therefore, prior consultation with regulatory authorities is recommended.

C-6. Operating characteristics and performance evaluation under assumed scenarios (Abstract of Reports for Shared Research 3-2)

In a randomized controlled trial of a novel coronavirus infection scenario with an allocation ratio of 1:1 between vaccine and placebo groups, assuming an incidence rate of 1% at 6 months for the placebo group and an expected vaccine efficacy (VE) of 60%, we confirmed that the lower limit of the 95% confidence interval for VE based on the hazard ratio exceeded 30%[11]. Assuming an enrollment period of 3 months and a maximum observation period of 6 months for each participant, 19350 participants would be required to evaluate efficacy at 9 months from the start of the study. The requirement exceeded 10000 for most combinations[12].

When interim analyses for early discontinuation due to efficacy were conducted at 50% and 75% of the total number of events, the time period from study start to analysis was reduced to 5 and 6 months, respectively. However, the power at each time point was 20% and 60%. The O'Brien-Fleming type α-spending function, based on the Lan-DeMets method, was used for multiplicity adjustment in the interim analysis. When early termination for public health reasons was conducted at 40%, 60%, and 80% of the total number of events without multiplicity adjustment, the time required for analysis was reduced to 4, 5, and 6 months from the study start, respectively. The power at each time point was 46%, 65%, and 76%, respectively.

In addition, for clinical trial designs that can obtain a conclusion within a short period from the start of the study (3 months in accordance with the100 Days mission proposed at the Carbis Bay G7 Summit[13], we used MERS as an example scenario with a relatively high mortality rate.

C-7. Considerations in the potential use of Bayesian methods (Abstract of Reports for Shared Research 4)

VE is one of the indicators used to evaluate the efficacy of a vaccine, which is defined as 100 × (1 - IRR), where IRR represents the infection rate ratio or incidence rate ratio. In the C4591001 Study of Comirnaty intramuscular injection, BNT162b2, VE was set as the primary endpoint, and the vaccine was

considered effective when the VE was 30% or greater.

Using Bayesian approach, it is possible to express uncertainty of the VE (posterior distribution of parameters) by using a type of confidence level assumed in advance for the VE (prior distribution of parameters), along with actually observed data. From the prior distribution and observed data, inferences such as the following can be made: "the likelihood (probability) that the VE is greater than 30% is 99%." Assuming little prior confidence in the VE in the C4591001 Study (pre-distribution), the likelihood of an observed VE exceeding 30% was calculated to be greater than 99.99%, indicating that BNT162b2 is effective.

These criteria could also be used in interim analyses. At each analysis time point, the VE is evaluated based on the confidence level of the VE. For example, the C4591001 study pre-specified that the vaccine would be considered effective if the probability of the VE exceeding 30% was greater than 99.50% at the four interim analyses and greater than 98.60% at the final analysis, and the study would be stopped (terminated) due to efficacy. The design of the C4591001 Study assumed a beta-binomial distribution (thus, the probability of a Type 1 error was explicitly calculable); using the above criteria, the probability of a Type 1 error was less than 2.5%.

C-8. Efficacy evaluation using pharmacoepidemiologic methods (Abstract of Reports for Shared Research 5)

Based on the information at the time of special approval or emergency use approval for COVID-19 vaccines in Japan, the United States, and Europe, we found that only two bureaus outside Japan (the FDA and European Medicines Agency) imposed observational studies (both primary data collection and secondary data utilization) with comparisons for the purpose of efficacy evaluation.

Additionally, we summarized potential patterns in post-marketing surveillance, etc. in Japan according to two scenarios: (1) an initial vaccine is approved based on data from a randomized placebo-controlled trial with the prevention of disease onset as the primary endpoint; and (2) a subsequent vaccine is approved based on a randomized active drug-controlled trial with surrogate markers as the primary endpoint. As a result, the following five patterns were identified in terms of either starting a new trial or continuing a clinical trial/study design: (1) continuation of clinical trials/continuation of enrollment in randomized controlled trials, or continuation of clinical trials/follow-up of randomized controlled trials only (completion of enrollment); (2) continuation of clinical trials/single group (+ external control) studies; (3) newly started/randomized controlled trials; (4) newly started/comparative observational studies using primary data collection (test, negative case-control); and (5) newly started/comparative observational studies using a database (cohort design, test, negative case-control). We summarized the design, GSPS framework, possible efficacy endpoints, and

correspondence with the development scenario for each pattern.

C-9. Feasibility of master protocol clinical trials (Abstract of Reports for Shared Research 6)

In cases where there are many drugs to be developed in Japan, conducting multiple simultaneous individual clinical trials would consume resources, such as clinical trial participants and sites. Therefore, the implementation of a master protocol clinical trial to screen multiple drugs and identify promising drugs, while simultaneously evaluating the evidence for efficacy and safety of such drugs, can increase the overall speed and efficiency of vaccine development.

Clinical trials using master protocols have several features and considerations for the design and statistical analysis. The main features in terms of the study design are the randomization method and sharing of control groups. As an example of the former feature, a master protocol trial may involve a two-stage randomization procedure since it evaluates multiple drugs (e.g. the first stage involves the assignment of the drug, and the second stage involves the assignment of the concerned drug and a placebo). Regarding the latter feature, to efficiently evaluate the drugs, the number of participants in the control group can be minimized by sharing the participants who receive the control drug; this simultaneously reduces the overall sample size for vaccine development. However, there are considerations in terms of safety, bias, etc. for both features. For example, with regard to the latter feature, if there is a change in the infection rate due to infection control measures or mutant strains, etc., there is a possibility of bias in the evaluation of vaccine effectiveness when using a single control group at different time points. Therefore, it is necessary to determine whether it is possible to use data from the control group over time, and if so, to what extent data over time can be used in the primary analysis of efficacy.

In platform studies using master protocol trials, complex adaptations are possible, such as those assessing the futility of VE during the trial and optimizing resources to other promising agents, sample size re-estimation under blinded review, or incorporating a Bayesian approach. However, such designs require careful consideration because of the increased complexity of the statistical analysis and interpretation of the results. In addition, if an adaptive design such as the one described above is used, its statistical performance should be evaluated through large-scale simulation experiments. Therefore, a prototype of the simulation program should be constructed in advance.

Although the time and resources required for preplanning master protocol clinical trials substantially exceed those required for conventional protocols, as described above, master protocols are still a useful approach in situations where rapid vaccine development is required because of a pandemic.

D. Discussion

Efforts from various perspectives are needed to expedite clinical trial planning and development strategy formulation for vaccine development. In this study, the actual status of vaccine development was ascertained and issues to be addressed in the future were summarized through a survey on the PMDA's system for providing clinical trial consultations and other services to companies that develop vaccines and a review of reports on existing vaccines approved in Japan. In addition, we reviewed candidate representative clinical trial designs for infectious disease scenarios with a high probability of requiring urgent vaccine development. Further, we discussed clinical trial designs and analytic methods that may contribute to efficient efficacy evaluation and rapid decision-making from a biostatistical perspective and summarized the points to be considered.

(1) Current status of the clinical development of vaccines in Japan

An analysis of 59 clinical trial designs for efficacy evaluation of 39 vaccines approved since the establishment of the PMDA revealed that there have been no large-scale clinical trials, multi-regional clinical trials, or foreign clinical trials using efficacy endpoints based on clinical outcomes as primary endpoints conducted by domestic-origin vaccine companies. Several policy proposals related to vaccine development have been published, including the "Vaccine Industry Vision" in 2007, and the "Strategy for Strengthening Vaccine Development and Production Systems" approved by the Cabinet on June 1, 2021, which have also raised new concerns. However, it has become clear that difficulties in conducting Phase III trials and the lack of results in international development remain even after 14 years of effort. Currently, clinical trials are gradually beginning to evaluate efficacy based on clinical events. However, for domestic companies to efficiently develop vaccines against new diseases, it is necessary to conduct pivotal clinical trials and establish a system with clinical endpoints as the primary endpoints.

A characteristic difference between vaccine and drug development is the number of products under international co-development. While the number of multi-regional clinical trials for pharmaceutical development with participation by Japan has been increasing in recent years (440 of 780 clinical trial plan notifications submitted to the PMDA in FY2021), Japan has participated in only 3 of 59 cases of multi-regional clinical trials for vaccine development. In emergencies, it is crucial to develop vaccines through international joint development. When conducting large-scale clinical trials with clinical events as the primary endpoint in Japan alone is challenging, Japanese developers may propose multi-regional clinical trials or trials that can be analyzed by combined analysis. Moreover, it is necessary to conduct such trials under normal circumstances to gain experience and establish a robust clinical trial environment, including development system for clinical trials.

In addition, we conducted a questionnaire

survey of 10 companies that develop vaccines to determine whether there are any issues with the company's system or the PMDA's system for providing clinical trial consultations and other services to speed the planning of clinical trials and development of strategies for vaccine development. No major problems with the current PMDA system were identified. On the other hand, some respondents pointed out the need for closer collaboration among PMDA, MHLW, and related departments within MHLW regarding issues concerning the current industry-government-academia structure and system for the rapid design of clinical trials and development strategies, especially in situations where an emergency response is needed. This may an issue to be considered in the future.

(2) Biostatistical Considerations in Clinical Trial Designs for Vaccine Development

The most likely outbreak of an emerging infectious disease critical to public health risk management was considered a viral respiratory infection of a type that spreads easily, and thus has a high probability and priority for vaccine development. Potential trial designs for efficient efficacy evaluation and rapid decision-making in both initial and subsequent vaccine development were examined from a biostatistical point of view.

During an outbreak and the early epidemic period of emerging infectious diseases for which initial vaccines are being developed, there is insufficient information on the infectivity, pathogenesis, degree of severity, and mortality of the infectious disease. Efficacy and safety evaluation through placebo-controlled randomized trials with efficacy endpoints based on clinical outcomes as the primary endpoints is required. In such cases, the number of participants required to ensure a statistical number of events is expected to be large, compelling the implementation of a relatively large-scale clinical trial. Therefore, we considered the use of an adaptive design, which involves design changes based on preplanned decisions, such as effective/ineffective discontinuation based on efficacy evaluation during the study and re-estimation of the sample size. In addition, as conducting a large-scale clinical trial in Japan alone may be difficult, conducting a multi-regional clinical trial or a clinical trial that enables combined analysis may be necessary, as described in (1) above.

Furthermore, unlike other common diseases, the development of vaccines for emerging infectious diseases may be affected by changes in the infection rate due to infectious disease countermeasures, mutant strains, and increases in the number of vaccines developed, all of which may affect the clinical trial plan assumed at the time of planning. In this study, simulation study was performed, with interim analyses based on a specified protocol and early termination of the trial that were not pre-specified for public health reasons. It is important to consider potential changes in the clinical trial plan as far in advance as possible and to evaluate the impact of such changes through the simulation studies.

Vaccine development for emerging infectious disease outbreaks involves various

uncertainties, and we examined the possibility of using Bayesian approach under such circumstances. We examined the points to be considered and the usefulness of these approach through examples of their application in foreign studies. Bayesian approach can probabilistically express the confidence (uncertainty) of the results and clarify the criteria for decision-making in vaccine development for emerging infectious diseases. However, when using Bayesian approach, it is important to evaluate the appropriateness of the prior information used and the operating characteristics of the analysis. Accordingly, we recommend consultation with regulatory authorities concerning its use. Moreover, since applied clinical trial designs useful for emerging infectious diseases (as mentioned above) are more likely to include an increased probability of Type 1 errors and bias due to multiplicity compared to that for general designs, it is important to specify details of the analysis methods, changes, and descriptions in advance, in the clinical trial protocol, after appropriate simulations are conducted.

In subsequent vaccine development, it is recommended to conduct a randomized, active vaccine-controlled trial with a defined immunogenicity-based surrogate marker. In such cases, a scheme could be considered where data from pivotal studies with immunogenicity as the primary endpoint are used for regulatory approval, and clinical events are evaluated through post-marketing surveillance. We have examined the possibility of selecting each of the five possible patterns of clinical trial design and post-marketing surveillance in Japan. In terms of post-marketing surveillance, research using a database infrastructure was considered useful. Specifically, a database infrastructure that comprehensively includes both pre- and post-marketing data could lead to the rapid development of new vaccines, as it would be possible to construct a framework to integrate and evaluate both pre- and post-marketing data from the development stage. In addition to biostatistics specialists, it would be important to include pharmacoepidemiology specialists to (1) establish a framework and system to examine post-marketing data collection systems; (2) examine the composition of application data packages and packages that include post-application data; and (3) establish evidence-building methods using information from clinical trials and observational studies, which are the elements of such data packages.

However, no such database infrastructure is currently available for vaccine evaluation in Japan. Numerous studies evaluating the efficacy of COVID-19 vaccines have been conducted abroad using cohort and test-negative designs utilizing large-scale databases as real-world evidence. Through these studies, it has become clear that large-scale databases play a very valuable role in the generation of post-marketing evidence. Since database infrastructure for vaccine evaluation is lacking in Japan, post-marketing evidence generation cannot be conducted rapidly. Therefore, it is urgently necessary to establish a system for generating scientific evidence that includes the

construction of database infrastructure for post-approval vaccine evaluation in Japan.

Furthermore, in situations in which multiple vaccines are developed simultaneously, a master protocol platform-based clinical trial would be useful. While scientific rigor may be sacrificed in favor of speed during a pandemic, master protocol trials are a powerful means of achieving balance between speed, efficiency, and rigor, quickly producing clinically meaningful and definitive results. On the other hand, platform clinical trials are, in some cases, large-scale and long-term, and it is essential to establish a system for conducting such trials in which experts in several important fields collaborate organically, and manage the platform appropriately. In the event of a pandemic, partnerships for domestic vaccine development led primarily by government agencies are desirable. Such partnerships may include not only regulatory authorities, pharmaceutical companies, and academia, but also clinical trial sites, contract research organizations (CROs), and other stakeholders responsible for patient registration, logistics, and clinical trial data management (including CDISC). Establishing a clinical trial network, unifying all facilities capable of conducting trials in the absence of an active pandemic, is a recommended measure for the government and the infectious disease community. This approach ensures proactive "clinical trial preparation" during normal conditions, thus enabling rapid and efficient clinical trial implementation in the event of a pandemic.

E. Conclusion

Efforts from various perspectives are needed to accelerate clinical trial planning and development strategy formulation for vaccine development. In this study, the actual status of vaccine development was identified, and future issues were summarized through a survey and summarization of review reports on existing vaccines approved in Japan and through a written questionnaire survey on the PMDA's system for providing clinical trial consultation and other services to companies that develop vaccines. In addition, we reviewed representative candidate clinical trial designs for infectious disease scenarios that have a high probability of requiring urgent vaccine development. We examined clinical trial designs and analysis methods that may contribute to efficient efficacy evaluation and rapid decision-making from a biostatistical perspective, and summarized points to be considered. Although there are signs of change in the status of vaccine development in Japan, companies developing domestic-origin vaccines lack experience in conducting large-scale, multi-regional, and foreign clinical trials with clinical events, such as the prevention of disease onset, as the primary endpoint. In order to rapidly develop new vaccines, clinical trials that evaluate clinical events, as well as multi-regional clinical trials and clinical trials that enable combined analysis, are necessary. Further, the establishment of a clinical trial environment, including the development of a clinical trial system, is needed.

Moreover, to develop new vaccines in

emergency situations, the ability to rapidly design and plan clinical trials using designs that efficiently generate evidence are important. Applied clinical trial designs such as Bayesian approach, adaptive designs, and master protocols are valuable methods for rapid efficacy evaluation. Accordingly, we recommend preparing for such clinical trials under normal conditions. This would include the development of a system to enable such trials, as well as determining the operating characteristics from a biostatistical perspective for incorporating such methods. Furthermore, the development and approval of vaccines in Japan are expected to be accelerated by establishing a system that can generate scientific evidence, including the development of database infrastructure for post-approval vaccine evaluation.

This study provides the knowledge that may be widely shared in advance when designing and planning clinical trials for vaccines in general, including the development of vaccines for emerging infectious diseases that may occur in the future, during consultations with companies, academia, and PMDA for planning the trial. We also hope that this study contributes to the planning the clinical trial.

F. Research presentation

Not applicable

G. Status of the acquisition of intellectual property rights

Not applicable

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