Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 2)
Ethical Considerations for Subjects in Placebo-Controlled Studies

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## 1. INTRODUCTION

Since the temporary authorization of the first SARS-CoV-2 vaccine in the U.K. on December 2, 2020, multiple vaccines have been granted emergency use authorization or regulatory approval in various countries and regions, and vaccination is rapidly increasing around the world. In Japan, various efforts are also being undertaken to accelerate the vaccination rate ever since a SARS-CoV-2 vaccine was approved for the first time in Japan on February 14, 2021.

One of the essential requirements for vaccine development is the evaluation of its efficacy and safety in clinical trials. A placebo-controlled clinical trial is a particularly useful approach to establish robust evidence as it can control all potential influences on the course or incidence of the disease other than pharmacological effects of a trial drug/vaccine with blinding and randomization by setting a placebo group.[1)]

At the same time, ethical considerations are required to use of placebo. For example, the Declaration of Helsinki describes that the use of placebo in clinical studies is limited to the case that the patients will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.[2)] Based on the circumstances that the Official Vaccination Program against SARS-CoV-2 (hereinafter referred to as "Official Vaccination Program") has been initiated in Japan and an increasing number of citizens will be vaccinated in the future, ethical considerations is necessary not only for subjects assigned to a placebo group in a future clinical trial but also for those who have received placebo or investigational vaccine formulations with potentially less benefit in an ongoing clinical trial in order to ensure them receive some form of best medical care.

Thus, this document presents the examples of ethical considerations required when assigning subjects to a placebo and some of investigational vaccine groups in ongoing or future clinical studies in Japan for SARS-CoV-2 vaccine development. There may be some approaches for ethical considerations other than those described in this document such as applying a blinded crossover design after efficacy of the investigational vaccine is demonstrated. Sponsor can consult the Pharmaceuticals and Medical Devices Agency as required if any approach other than those described in this document is considered for providing ethical considerations.

When there is a content overlap between this document and "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" (September 2, 2020, Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency), this document shall be applied with priority.

Although the basic principles presented in this document are based on the social conditions in Japan as of May 2021 and have been developed after discussion with external experts, the principles may change depending on the prevalence of COVID-19, advances in SARS-CoV-2 vaccines development, and the progress of the Official Vaccination Program in Japan.

## 2. ACTIONS TO BE TAKEN IN ONGOING CLINICAL TRIALS

### 2.1. Ethical aspects to be considered and changes in a clinical trial protocol and other documents.

Ethical considerations for subjects in a clinical trial of a SARS-CoV-2 vaccine include providing those who may not receive any preventive effect against COVID-19 by the clinical trial vaccination (investigational vaccine or placebo) with information on available vaccines which have preventive effect against COVID-19 outside of the trial, advice to help them understand their situations in clinical trials, and means for protecting themselves against COVID-19.

When sponsors or investigators provide such information or advice to subjects, subjects' assigned groups in clinical trials should be informed to subjects in some situations. The allocation of individual subjects may be conveyed either to all subjects assigned to a certain group at once or to each subject when requested.

Unblinding may be required in some cases. Before unblinding, sponsors should determine an appropriate timing at which scientific values of the clinical trial can be maintained while they are balanced with ethical considerations. To consider the appropriate timing, the sponsor should refer the initial analysis plan defined in the protocol, the schedule for sampling and collecting of safety information, and the progress of the Official Vaccination Program in Japan.

If there is no description included in a protocol or an informed consent form defining how vaccination assignment is disclosed to subjects or how subjects can ask for disclosure of their assignment, these documents should be revised so that the subjects can be informed of procedure to know their assignment. If administering the investigational vaccine to subjects in the placebo group to protect them against COVID-19 as defined in Sections 2.3.1 and 2.4.1, the relevant plans should also be modified to accommodate such a vaccination.

### 2.2. Specific timing of unblinding

The strategy for the Official Vaccination Program prioritizes those at higher risk of severe COVID-19 (hereinafter referred to as "high-risk population"). Furthermore, various vaccination programs are being considered including vaccination at workplaces which may not have particular prioritization to accelerate vaccination in Japan. In order to collect as much safety information as possible after administration of an investigational vaccine or placebo in a clinical trial, it is recommended that an unblinding schedule is aligned with the progress in the Official Vaccination Program and that unblinding is applied first to those prioritized in the COVID-19 vaccination programs such as health care professionals, the elderly, and those with underlying medical conditions. Depending on the progress made in the Official Vaccination Program or the design of clinical trial cohorts in a clinical trial, in some cases, all subjects may need to be unblinded at once or in other cases, unblinding individual subjects may be more reasonable. Thus, the timing of unblinding and subjects to be unblinded should be determined in accordance with the circumstances of individual studies.

### 2.3. Considerations for subjects assigned to a placebo group

#### 2.3.1. Information and actions required to be provided to subjects

In the event that an investigational vaccine is granted regulatory approval or emergency use authorization either in Japan or other countries, the sponsor should preferably consider offering the subjects in the placebo group opportunities to receive the investigational vaccine as a means to protect them against COVID-19. A means to protect against COVID-19 can be provided also by recommending subjects to receive vaccination in the Official Vaccination Program if the investigational vaccine cannot be offered.

When a means to protect against COVID-19 is provided by administering an investigational vaccine, the investigator, sub-investigators, study collaborators, and other staff involved in the study (hereinafter referred to as "investigator and other staff") should provide updated information about the investigational vaccine (e.g., efficacy, safety, current developmental status in Japan, and usage conditions in other countries) in plain language to subjects. The sponsor needs to maintain the investigator and other staff updated on information useful for better understanding by subjects.

The sponsor should also take an appropriate action to prevent any disadvantage that subjects may incur when they receive an extra dose, which means the dose in addition to the originally assigned ineffective dose, in a clinical trial instead of being vaccinated in the Official Vaccination Program. Such actions may include consulting the regulatory authorities or asking the investigator or other staff to prepare a document that indicates the name of the administered investigational vaccine and date of vaccination, in preparation for possible issuance of official vaccination certificates which are currently proposed globally, once they are introduced in Japan.

2.3.2. Collection of data from subjects receiving an extra active vaccine for ethical considerations

When extra doses of an investigational vaccine are administered based on ethical considerations as defined in Section 2.3.1, the sponsor needs to ask the investigator and other staff to answer any inquiries from subjects about the safety of the investigational vaccine as well as to establish an appropriate procedure required to ensure subjects' safety such as collecting safety information.

It is also preferable that the sponsor collect data on specific local reactions (e.g., swelling, redness, induration, and pain) and systemic reactions (e.g., pyrexia, headache, malaise, and myalgia) occurring within seven days after extra doses of investigational vaccine at the dosage and administration deemed safe and effective, adverse events occurring in about 28 days after the extra doses of investigational vaccine, and other adverse events. If the investigational vaccine has already been granted regulatory approval or emergency use authorization either in Japan or other countries, safety information including data on adverse events can be collected through routine pharmacovigilance activities of the study instead of collecting the information described above. No new immunogenicity data are required from those subjects receiving the extra doses of the investigational vaccine.

2.4. Considerations for subjects assigned to investigational vaccine groups

2.4.1. Information and actions required to be provided to subjects

The Subjects are unlikely to need another vaccination in the Official Vaccination Program if they have received an investigational vaccine that has already been granted regulatory approval or emergency use authorization in Japan or other countries at the dosage and administration defined in the approval or the authorization.

On the contrary, those in a regimen different from the potential dosage and administration in regulatory approval or emergency use authorization may need to receive a vaccine in the Official Vaccination Program or an investigational vaccine dose as do subjects in the placebo group. If the lack of efficacy of an investigational vaccine is confirmed or suspected at any dosage and administration, all subjects who have received investigational vaccine doses should be encouraged to be vaccinated immediately in the Official Vaccination Program.

Ethical considerations for the latter subjects are generally the same as for subjects in a placebo group, and actions should be taken as described in Section 2.3. Any impact of the investigational vaccine administered to those subjects should be taken into consideration when providing information or administering investigational vaccine doses to them.

2.4.2. Collection of information from subjects assigned to investigational vaccine groups

Investigators should continue to collect safety information and samples from subjects who received investigational vaccines (excluding those provided vaccination opportunities by ethical considerations based on the definition in Sections 2.3.1 and 2.4.1) and to maintain the planned analysis, as per the predetermined protocol. However it excludes cases in which the efficacy of the vaccine was insufficient or not observed at a certain dosage and administration. To that end, the sponsor is encouraged to support the investigator and other staff so that they can provide subjects with information on an amended protocol as described in Section 2.1 while they explain to subjects how significant it is that they continue to take part in the clinical trial and cooperate with collection of safety information and samples of the clinical trial.

## 3. ACTIONS TO BE TAKEN WHEN USING PLACEBO IN A FUTURE CLINICAL TRIAL

In some cases, setting placebo groups in future clinical studies for developing SARS-CoV-2 vaccines can be ethically acceptable depending on situations. These circumstances may include following cases, to answer clinical questions that can be solved only by conducting a placebo-controlled clinical trial, and the timing of a clinical trial at which no health problem is caused by a delay in SARS-CoV-2 official vaccination.[3)] Specific examples of situation in clinical studies are; enrolling subjects who are not eligible to the Official Vaccination Program at that enrolling timing; enrolling subjects for whom efficacy or safety of an existing SARS-CoV-2 vaccine is not established; and confirming booster immunization to subjects who have already received doses of a SARS-CoV-2 vaccine. The protocol of such clinical studies need to describe ethical considerations for subjects as defined in Section 2, and their informed consent forms and other documents should also reflect ethical considerations in an appropriate manner.

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OUCHI Kazunobu, Professor, Department of Medical Welfare for Children, Faculty of Health and Welfare, Kawasaki University of Medical Welfare

OBA Koji, Associate Professor, Interfaculty Initiative in Information Studies and Department of Biostatistics, Graduate School of Medicine, The University of Tokyo

OKADA Kenji, Professor, Division of Basic Medical Science and Fundamental Nursing, Fukuoka Nursing College

OKABE Nobuhiko, Director General, Kawasaki City Institute for Public Health

HAMADA Atsuo, Specially Appointed Professor, Travellers' Medical Center, Tokyo Medical University Hospital

HAYASHI Kunihiko, Professor, Gunma University Graduate School of Health Sciences

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1) "Choice of Control Group and Related Issues in Clinical Trials" (PMSB/ELD Notification No. 136 dated February 27, 2001 issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) https://www.pmda.go.jp/files/000156803.pdf

2) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (adopted in June 1964; amended in October 2013)

3) Emergency Use Designation of COVID-19 candidate vaccines: Ethical considerations for current and future COVID-19 placebo-controlled vaccine trials and trial unblinding, WHO, December 2020