(Appendix)

General Investigation of COMIRNATY Intramuscular Injection

(Follow-up study for Subjects [Healthcare Professionals] Who are Vaccinated at an Early postApproval Stage)

Full Protocol

Pfizer Japan Inc.

STUDY INFORMATION

Title	General Investigation of COMIRNATY Intramuscular Injection (Follow-up study for Subjects [Healthcare Professionals] Who are Vaccinated at an Early postApproval Stage)
Protocol ID	C4591006
Protocol version identifier	Amended 5
Date	06 September 2022
Active substance	Tozinameran
Medicinal product	COMIRNATY Intramuscular Injection
Research question and objectives	The healthcare professionals who are vaccinated with this product early after the marketing approval of this product (participants in the Investigation of Health Status of Recipients Vaccinated First conducted by the Science Research Group of the Ministry of Health, Labour and Welfare) will be followed for 11 months from the day following 28 days after the final vaccination of the initial immunization with this product (end date of observation period in Investigation of Health Status of Recipients Vaccinated First) to 12 months after the final vaccination of the initial immunization with this product, information on serious adverse events and COVID-19 observed during the follow-up period will be collected. If booster vaccination isn't conducted, the long-term safety after the initial immunization of this product during the follow-up period will be assessed. If booster vaccination is conducted, the long-term safety after the initial immunization of this product up to the day before booster vaccination will be confirmed, and information on serious adverse events and COVID-19 will be continuously obtained after booster vaccination.
Author	PMS Affairs PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ECMO	Extracorporeal membrane oxygenation
ICU	Intensive care unit
IEC	Independent ethics committee
IRB	Institutional review board
N/A	Not applicable
SAP	Statistical analysis plan
SRSD	Single reference safety document
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
WHO	World Healthcare Organization

3. RESPONSIBLE PARTIES

The Japan Good Post-marketing Study Practice officer

4. AMENDMENTS AND UPDATES

Protocol version identifier	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Amended 5	06 September 2022	10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS	Description adjustments such as changes in Japanese translation	Changes associated with the amendment of in-house form
		12. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION	Deletion of the section (The numbers of the subsequent sections were moved up.)	Amendment associated with the notification "Planning and publication of Risk Management Plan" dated 18 March 2022
		12. NAME, AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED	Pfizer R&D Japan: Change in the scope of work contracted	Due to expansion of the scope of work contracted
		16. CONTACT INFORMATION 16.1. Contact information for inquiries about the study	Name: Change in the name of department	Change associated with the change of in-house organization
Amended 4	24 November 2021	STUDY INFORMATION Research question and objectives 7. RESEARCH QUESTION AND OBJECTIVES	With the approval of booster vaccination, a description was added that the long-term safety will be confirmed with the information up to the day before booster vaccination if booster vaccination is conducted.	Changes due to the approval of the booster vaccination

		6. RATIONAL AND BACKGROUND 8.2.6. Observation period 8.3.3. End-of-study/ discontinuation record 8.5.1 Planned sample size 8.6.3.2. Health status record form	The definition of the final vaccination with this product was clarified along with the approval of booster vaccination.	Changes due to the approval of the booster vaccination
		8.3. Variables	Table 1: "Other" was removed from the title "Information on inoculation of other vaccines".	To be consistent with other sections
		8.3. Variables 20. LIST OF FIGURES	(If booster vaccination isn't conducted) was added to the title of Figure 1. Figure 2: Schedule (If booster vaccination is conducted) was added.	Changes due to the approval of the booster vaccination
		8.3.4. Information on inoculation of vaccines	"Other" was removed from the title "Information on inoculation of other vaccines", "the information of the booster vaccination including this product will be collected" was added.	To collect the information of the booster vaccination including this product
Amended 3	14 October 2021	8.2.1. Registration criteria	Description of registration criteria was added.	To give more detailed and appropriate explanation
		8.2.5.1. Study method 8.5.1. Planned sample size 8.5.2. Rationale for sample size	In accordance with description of registration criteria, text was added in related sections.	To make target subjects clearer

Amended 2	27 May 2021	7.1 Safety specifications	Risk categories for safety specifications were added.	Due to an omission of the description
		8.3. Variables 8.3.1. Characteristics of subjects 8.6.1. Case report forms (CRFs)/Electronic data record 8.6.4. Subject registration (EDC)	"Consent for participation in the study" is to be checked in the EDC for this study and the description was changed according to actual specifications.	Due to change in the specifications for data linkage from the Investigation of Health Status of Recipients Vaccinated First
Amended 1	26 February 2021	8.3. Variables	Remove the item of "History of other vaccinations" Change from "Pregnancy" to "Suspected pregnancy/Lactation"	To be consistent with the Investigation of Health Status of Recipients Vaccinated First
Final	13 February 2021	N/A	N/A	N/A

5. MILESTONES

Milestone	Planned date
Start of data collection	March 2021
End of data collection	August 2022
Interim report 1	To be determined
Final study report	To be determined

6. RATIONALE AND BACKGROUND

In December 2019, pneumonia of unknown cause became epidemic in Wuhan China. In January 2020, it was revealed that a novel coronavirus (2019-nCoV) was the cause. On 12 February 2020, the virus was officially named SARS-CoV-2 and the WHO officially named the disease caused by

SARS-CoV-2 as COVID-19. SARS-CoV-2 and the resultant COVID-19 have spread globally with a steadily increasing number of individuals infected.

BioNTech has developed RNA vaccine candidates using a platform that enables rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. RNA vaccines encoding viral antigens have a significant advantage compared to conventional vaccines because they express proteins that induce a protective immune response in the vaccinated body and can be developed and manufactured rapidly.

COMIRNATY intramuscular injection (generic name: tozinameran) (hereinafter referred to as this product) is an RNA vaccine containing mRNA encoding the spike protein of SARS-CoV-2, and its marketing approval was obtained in February 2021 with the indication of prevention of infection with SARS-CoV-2.

Since this product is a highly novel vaccine, it has been decided to conduct focused investigation during an early period after the start of vaccination for the novel corona virus in the subjects (healthcare professionals) vaccinated at an early timing after approval of this product (hereinafter referred to as Investigation of Health Status of Recipients Vaccinated First) as Science Research of the Ministry of Health, Labour and Welfare (designated research) for the purpose of large-scale and prompt collection and publication of safety information immediately after the start of vaccination with this product.

Since the long-term safety information obtained by the time of marketing approval of this product is limited, "Drug Use Investigation of COMIRNATY Intramuscular Injection (follow-up investigation of subjects [healthcare professionals] vaccinated at an early timing after approval of this product)" will be conducted to collect and confirm the long-term safety information after vaccination of the initial immunization with this product, including the risks of enhancement of the disease and respiratory diseases. The subjects will be those participating in the Investigation of Health Status of Recipients Vaccinated First, and will be followed for 11 months from the day following 28 days after the final vaccination of the initial immunization with this product (end date of observation period in Investigation of Health Status of Recipients Vaccinated First) to 12 months after the final vaccination of the initial immunization with this product. Thus, information on serious adverse events and COVID-19 observed during the follow-up period will be collected.

This Study shall be conducted in strict compliance with the "MHLW Ordinance on the Standard for PostMarketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171, dated December 20, 2004), the "Enforcement of the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 1220008, dated December 20, 2004), "MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices and to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 26, dated March 11, 2013), the "Enforcement of the MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices, and to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 0311-7, dated March 11, 2013)., "MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 116, dated October 26, 2017), and "Announcement of the MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical

Trials of Medical Products (Regarding the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products)" (PSEHB Notification No. 1026-1, dated October 26, 2017).

7. RESEARCH QUESTION AND OBJECTIVES

In this investigation, the healthcare professionals who are vaccinated with this product early after the marketing approval of this product (participants in the Investigation of Health Status of Recipients Vaccinated First conducted by the Science Research Group of the Ministry of Health, Labour and Welfare) will be followed for 11 months from the day following 28 days after the final vaccination of the initial immunization with this product (end date of observation period in Investigation of Health Status of Recipients Vaccinated First) to 12 months after the final vaccination of the initial immunization with this product, information on serious adverse events and COVID19 observed during the follow-up period will be collected.
If booster vaccination isn't conducted, the long-term safety after the initial immunization of this product during the follow-up period will be assessed.
If booster vaccination is conducted, the long-term safety after the initial immunization of this product up to the day before booster vaccination will be confirmed, and information on serious adverse events and COVID-19 will be continuously obtained after booster vaccination.

7.1. Safety specifications

[Important Potential Risks]

- Vaccine-associated enhanced disease (VAED) and vaccine-associated enhanced respiratory disease (VAERD)

[Important Missing Information]

- Safety of administration to pregnant or lactating women

8. RESEARCH METHODS

8.1. Study design

This is a multicenter cohort study, and the investigator will enter the information required in this study in the case report forms based on the information obtained through medical interview, etc. and records such as medical records. A health status record form will be distributed to the subjects participating in this study and they will be requested to record information on serious adverse events and COVID-19 that occurred during the observation period. The investigator will collect information on the details from the subjects and enter them in the case report forms (CRFs) with reference to the information recorded in the health status record forms by the subjects after the end of the observation period.

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the subject population and healthcare provider specialty in the countries where this study (non-interventional study) is being conducted.

8.2. Setting

8.2.1. Registration criteria

Subjects must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Subjects who have participated in the Investigation of Health Status of Recipients Vaccinated First and have provided written consent to continue participation in this study*.

*: Subjects who have discontinued the Investigation of Health Status of Recipients Vaccinated First are not included. However, subjects who have discontinued the Investigation of Health Status of Recipients Vaccinated First at the discretion of the investigator and have provided written consent to participate in this study may be registered in this study.

8.2.2. Exclusion criteria

There are no exclusion criteria for this study.

8.2.3. Study sites

This study will be conducted at up to 100 institutions that have participated in the Investigation of Health Status of Recipients Vaccinated First and cooperate with this study by participation.

8.2.4. Planned study period

The planned period covered by this study is as follows.

- Investigation period: From the day following the day of completion of the observation period for the first subject who has completed the observation period in the Investigation of Health Status of Recipients Vaccinated First to the end of the observation period for the last subject investigated in this study (scheduled from March 2021 to August 2022)

8.2.5. Study procedures

8.2.5.1. Study method

This study will be conducted in all subjects who meet the registration criteria, have been vaccinated with this product and have consented to participate in this study during participation in the Investigation of Health Status of Recipients Vaccinated First at contract sites.

8.2.6. Observation period

The observation period will be 11 months from the day following 28 days after the final vaccination of the initial immunization with this product (end date of observation period in Investigation of Health Status of Recipients Vaccinated First).

In this study, information will be collected using booklet type CRF. Information for the following periods will be entered in each booklet.

- Booklet 01: From the day following 28 days after the final vaccination of the initial immunization with this product to 6 months (24 weeks) after the final vaccination of this product

- Booklet 02: From the day following 6 months after the final vaccination of the initial immunization with this product to 12 months (52 weeks) after the final vaccination of this product

However, in cases where treatment has been discontinued, observation is continued until discontinuation of treatment.

8.3. Variables

This study will be conducted according to the following schedule.

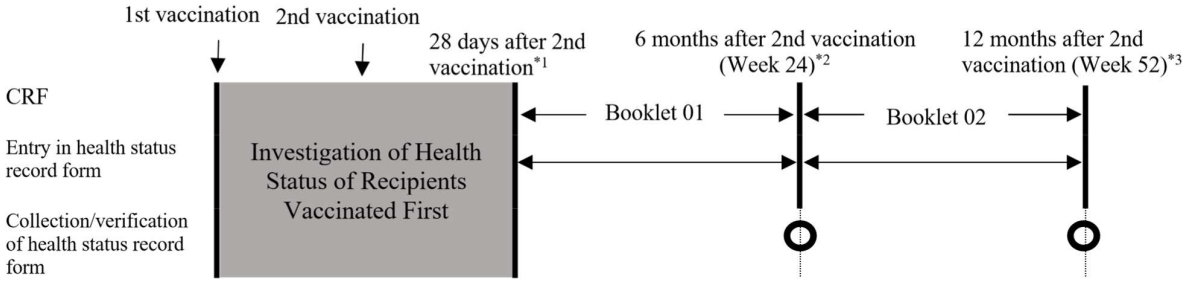
Table 1. Variables

Variable		CRF Booklet 01	CRF Booklet 02
Written consent to participate in this study		●*	
Characteristics of subjects	Subject ID	○	
	Gender	○	
	Date of birth	○	
	Record of vaccination with this product	○	
	Clinical history (concurent illness/past history)	○	
	Allegy information	○	
	Suspected pregnancy/Lactation (women only)	○	
	Current medications	○	
Pregnancy and lactation (woman only)		←	→
Information on inoculation of vaccines		←	→
Information on COVID-19 pathogen test		←	→
Information on COVID-19		←	→
Serious adverse events		←	→
End-of-study discontinuation record (reason)		●	●

* : Identify subjects consented to participate in this study.

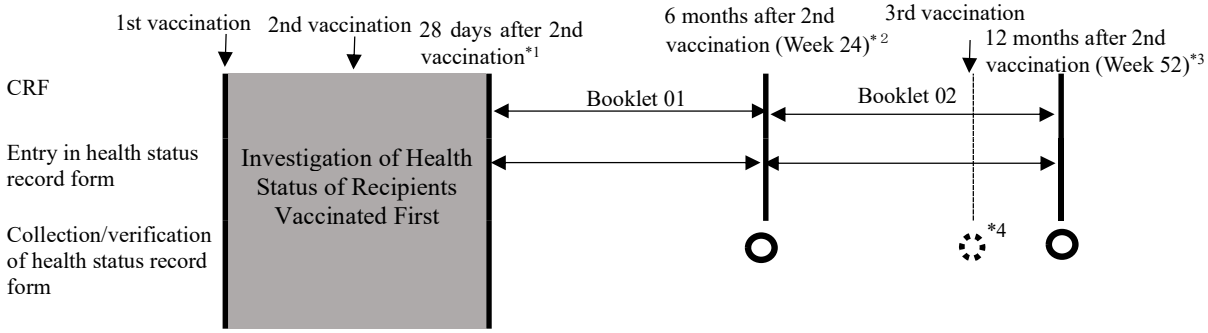
○: For patients consented to participate in this study, the data collected in the Investigation of Health Status of Recipients Vaccinated First will be replicated and stored in the database for this study.

Figure 1. Schedule (If booster vaccination isn't conducted)



*1: 28 days after 1st vaccination if the subject is vaccinated only once
*2: 6 months after 1st vaccination if the subject is vaccinated only once
*3: 12 months after 1st vaccination if the subject is vaccinated only once

Figure 2. **Schedule** (If booster vaccination is conducted)



*1: 28 days after 1st vaccination if the subject is vaccinated only once
*2: 6 months after 1st vaccination if the subject is vaccinated only once
*3: 12 months after 1st vaccination if the subject is vaccinated only once
*4: Health status record may be collected as needed, the form for remaining period may be distributed again.

8.3.1. Characteristics of subjects

Enter the presence or absence of written consent for participation in this study.

Identify subjects from whom written consent was obtained through entry, and the following data of relevant subjects collected in the Investigation of Health Status of Recipients Vaccinated First will be replicated and stored in the database for this study.

Such information will be used as subject characteristics for this study.

- Subject ID
- Gender
- Date of birth
- Record of vaccination with this product (date of vaccination/name of vaccine/lot number/side of vaccination)
- Clinical history (concurrent illness and past history)
- Allergy information (information on presence/absence of allergy and allergen)
- History of other vaccinations (within 1 month after the first or second vaccination with this product)
- Suspected pregnancy/Lactation (women only)
- Current medications (names of drugs concomitantly used at the time of 1st or 2nd vaccination)

8.3.2. Pregnancy and lactation (women only)

If the subject participating in this survey is female, the presence or absence of pregnancy and lactation during the observation period will be entered.

8.3.3. End-of-study/discontinuation record

The investigator shall enter the date when the information of subject is confirmed at the end of the observation period for each booklet, that is, at 6 months after the final vaccination of the initial immunization with this product (Booklet 01) and at 12 months after the final vaccination of the initial immunization with this product (Booklet 02) (or later), as the date of completion of observation for each booklet (date of final observation).

For confirmation of information of subjects, inquiries by telephone etc. are acceptable.

If information on the subject cannot be confirmed and the date of final confirmation of the information on the subject does not meet the observation period, the date on which information on the subject can be confirmed for the last time will be entered as the date of discontinuation of observation (date of final observation) and the reason for discontinuation will be entered.

1. Date of the end of observation (discontinuation) (date of final observation)

2. End of study or reason for discontinuation

   - End of study
   - Adverse events
   - Death
   - Lost to follow-up
   - Consent withdrawal
   - Other

8.3.4. Information on inoculation of vaccines

The investigator will confirm the presence or absence of vaccine including vaccination for the novel corona virus* inoculated during the observation period and enter the information. If a vaccine including vaccination for the novel corona virus is inoculated during the observation period, the type of vaccine and the date of vaccination will be entered. (*: Booster vaccination of this product is included.)

8.3.5. Information on COVID-19 pathogen (SARS-CoV-2 infection) test

The investigator will confirm the presence or absence of the test for COVID-19 pathogen (SARS-CoV-2) received during the observation period and enter the information. If a pathogen test is performed, enter the date of test (date of specimen collection), type of test and test results in the CRF for each test.

8.3.6. Information on COVID-19

The investigator will confirm the presence or absence of the onset of COVID-19 during the observation period and enter the information.

- Presence or absence of occurrence of COVID-19

If The occurrence of COVID-19 is "present," the following information will also be entered.

- Date of diagnosis of COVID-19
- Presence or absence of actions/procedures taken (hospitalisation, oxygen administration, ICU admission, use of mechanical ventilation, and use of ECMO)
- Outcome (resolved/recovered, resolved with sequelae, death, not resolved, and unknown) and date of outcome

  The outcome should be followed up as much as possible after the end of the observation period.

8.3.7. Serious adverse events

The investigator will provide the health status record form to the subjects participating in the study, perform medical interview, etc. with reference to the information in the record form entered by the subjects to confirm the presence or absence and details of serious adverse events, and enter the following information in the CRF.

Also, further investigation should be separately conducted, if deemed necessary by Sponsor for subjects who experienced a serious adverse reaction.

- Presence/absence of adverse event
- Name of adverse event
- Severity
- Date of occurrence
- Presence or absence of treatment
- Seriousness
- Criteria for seriousness
- Outcome (including the date of outcome)
- Causal relationship to this drug

8.3.7.1. Severity assessment

The investigator will assess the maximum severity of serious adverse events reported during the observation period from onset to confirmation of outcome and classify them into one of the following categories. Severity is defined as follows.

Table 2. Definition of Severity

Severity	Definition
Mild	Not interfering with usual activities of subjects
Moderate	Interfering with usual activities of subjects to some extent
Severe	Markedly interfering with usual activities of subjects
Life-threatening	Life-threatening, or necessitating urgent intervention

8.3.7.2. Criteria for seriousness

The investigator will select and enter the applicable criteria for serious adverse events reported during the observation period.

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.
- Other medically important events

8.4. Data sources

In this study, the investigator will extract necessary information based on the full protocol from the information obtained by medical interview, etc. based on the health status record form filled in by the subject as needed, and the records including medical records.

8.5. Study size

8.5.1. Planned sample size

All subjects who meet the registration criteria and have consented to participate in the 11-month follow-up investigation from 28 days after the final vaccination of the initial immunization with this product to 12 months after the final vaccination of the initial immunization with this product among those who participated in the Investigation of Health Status of Recipients Vaccinated First (up to 20,000 subjects).

8.5.2. Rationale for sample size

Follow-up investigation will be conducted in all of the subjects who meet the registration criteria and have given informed consent after participating in the Investigation of Health Status of Recipients Vaccinated First conducted in healthcare professionals who are the candidates for prioritized vaccination with this product, for whom early investigation results are expected to be obtained, and whose health condition can be easily monitored continuously.

8.6. Data management

8.6.1. Case report forms (CRFs)/Electronic data record

As used in this full protocol, the term CRF should be understood to refer to an electronic data record, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in the encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed (or stamped "correction seal"), and explained (if necessary) and should not obscure the original entry. In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

The ownership of the data replicated from the Investigation of Health Status of Recipients Vaccinated First and stored in the database for this study is specified in the contract with the Science Research Group of the Ministry of Health, Labour and Welfare.

8.6.2. Record retention

The records related to this study should be retained at the study site until the End of Study Letter by Pfizer is received or during the period defined by the study site, whichever is longer.

8.6.3. Data collection method

8.6.3.1. Case report form (EDC)

The data for this study will be collected and confirmed by using the electronic system on the internet designed for collecting post-marketing survey data (Electronic Data Capture, EDC).

8.6.3.2. Health status record form

The investigator will distribute a health status record form to the subjects participating in this study, and request them to record the information on the occurrence of events and COVID-19 in order to obtain as accurate information as possible about severe symptoms, etc. accompanying hospitalisation in the subjects during the observation period.

The investigator will collect the health status record form recorded by the subject during the observation period (6 months after the final vaccination of the initial immunization with this product and 12 months after the final vaccination of the initial immunization with this product)

(collection by mail is also acceptable), check the detailed contents at the time of medical interview if necessary with reference to the entered information, collect information on serious adverse events and COVID-19, and enter the information in the CRF. For confirmation of information of subjects, inquiries by telephone etc. are acceptable.

8.6.4. Subject registration (EDC)

The investigator will enter the presence or absence of written consent in the EDC if he/she has obtained written consent for participation in this study. Background data of consented subjects collected in the Investigation of Health Status of Recipients Vaccinated First will be replicated and stored in the database as that of registered subjects in this study, and therefore a registration form will not be prepared.

8.6.5. Points to consider for completion, revision, and submission of case report form (EDC)

8.6.5.1. Data entry

The investigator will check the survey items and enter the data in the EDC based on the source documents such as medical records and the information in the health status record form entered by the subject.

8.6.5.2. Data revision

Upon receiving query from Sponsor on the contents of the CRF (follow-up survey), the investigator will again confirm the contents of medical records, and as required, correct relevant sections and save the data.

8.6.5.3. Submission

After data entry and revision are completed, CRFs should be signed electrically by the investigator following confirmation of entry and follow-up survey.

8.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol, and any major modifications will be reflected in a protocol amendment.

8.7.1. Definition of analysis set

The safety analysis set will be the full analysis set as close as possible to all subjects who have given consent to participate in this study.

8.7.2. Safety analyses

Serious adverse events entered in the CRF submitted by the investigator for which the causal relationship with this product cannot be ruled out will be handled as serious adverse reactions, and the number and proportion of subjects with serious adverse reactions ([%]: number of patients with adverse reactions/number of subjects included in safety analysis) will be tabulated. Exploratory analyses will be performed as needed.

8.7.3. Analyses of information on COVID-19

By using the information on COVID-19 entered in the CRF submitted by the investigator, subjects who are considered to be in a severe condition will be identified and the number and proportion of

the subjects will be tabulated with reference to the severity classification in the "Guidance for Treatment of Novel Coronavirus Infection (COVID-19)." Exploratory analyses will be performed as needed.

8.8. Quality control

Prior to conducting the study, the site staff will explain to the investigator about the contents of the protocol, etc. and ask the investigator to create CRFs based on medical interview based on health status record forms and records such as medical records.

8.9. Limitations of the research methods

There may be potential limitations in this study:

1. Since no control group is included in the study, there is a limitation in determining whether or not a risk of developing adverse events and adverse reactions increases with inoculation of this product.

2. Due consideration may not be given to confounding factors due to insufficient background information collected.

3. Since this study collects the information from medical interview based on health status record forms and records such as medical records, specified data may not be collected or may be missing.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Information of subjects

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of personal data of subjects. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the clinical study agreement and applicable privacy laws.

9.2. Consent of subjects

The informed consent documents must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The investigator must ensure that each subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian if a minor, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a subject's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the subject (e.g., parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/IEC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s), or legal guardian if a minor, before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

9.3. Subject withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.4. Institutional review board (IRB)/Independent ethics committee (IEC)

The informed consent documents used during the informed consent process must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use.

9.5. Ethical conduct of the study

This study will be conducted in compliance with the "MHLW Ordinance on the Standard for PostMarketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171, dated December 20, 2004). Also, the study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Record and report requirements

The following table summarizes the requirements for recording safety events on CRFs and for reporting safety events to Pfizer Safety on a Non-Interventional Study Adverse Event Report Form (NIS AE Report Form). These requirements are described for three types of events: (1) serious adverse events, (2) nonserious adverse events (if applicable), and (3) drug exposure-related scenarios including exposure during pregnancy, exposure during breast feeding, medication error, drug overdose, drug misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section of “Safety event definition.”

Safety event	Record in CRF.	Report to Pfizer Safety within 24 hours of awareness of the event using the NIS AE Report Form.
Serious adverse events	All	All
Non-serious adverse events	None	None
Scenarios related to exposure to this product including exposure during pregnancy, exposure during breast feeding, medication error, drug overdose, drug misuse, extravasation, lack of efficacy, occupational exposure	None	All (with or without adverse events) Note: All adverse events related to drug administration will be reported with exposure scenarios.

For each adverse event, the investigator must obtain information adequate for confirming the outcome, and determining whether the event meets the criteria for a serious adverse event (see the section of "Serious adverse events" below).

The safety events for which reporting to the Safety division is required in the above table must be reported to Pfizer within 24 hours of the investigator's knowledge of the event, **regardless of whether the event is determined by the investigator to be related to this product.** In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare event that the investigator does not become aware of the occurrence of a safety event immediately, the investigator is to report the event within 24 hours after learning of it and record the time of his/her first awareness of the event.

For those safety events that are considered serious or that are specified in the far right column of the table above as requiring reporting to Pfizer within 24 hours of awareness, the investigator must conduct the follow-up investigation, and must provide any additional information to Pfizer in accordance with the 24hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific additional information in an expedited fashion. This information needs to be more detailed than that recorded on the CRF. In general, this information should include sufficient detail to allow for a complete medical assessment of the event and independent determination of causality. Information regarding this event, such as concomitant medications and illnesses, must also be provided. In the event of a subject's death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

10.2. Reporting period

The reporting period for safety events (see the table above) in each subject to Safety division begins on the day of commencement of this study and ends at the completion of the observation period. If a safety event of the type described in the table above has occurred during the reporting period, the investigator will submit a report to Pfizer Safety (or its designated representative). If a subject is vaccinated with this product on the last day of the observation period, the reporting period should be extended by 28 calendar days after the end of the observation period. In most cases, the date of informed consent is the same as the date of enrollment. In some circumstances, there may be a difference between the date of informed consent and the date of enrollment. The reporting period will end on the day the decision is made not to include the subject if a subject has given consent but is not enrolled in the study (e.g., the subject has changed his/her intention to participate in the study).

If the investigator becomes aware of the occurrence of a serious adverse event at any time after completion of the study and the serious adverse event is determined to be related to this product, the serious adverse event will also be reported to Pfizer Safety.

10.3. Evaluation of causal relationship

The investigator will be asked to evaluate and record the causal relationship. In addition, the investigator should obtain sufficient information to assess the causal relationship of each adverse event. For adverse events related to this product, follow-up investigation by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

The evaluation of the causal relationship by the investigator will be determined by whether there exists a reasonable possibility that the drug has caused or contributed to the adverse event. If the investigator’s final judgement regarding the causal relationship is "unknown," and it cannot be

decided whether this product has caused the event, the safety event must be reported within 24 hours.

If the investigator cannot identify the cause of the event, but judges that this product has not caused the event, it should be clearly stated in the CRF and the NIS AE Report Form.

10.4. Safety event definition

10.4.1. Adverse events

An adverse event is any untoward medical occurrence in a subject. The event does not necessarily have a causal relationship with inoculation or use of the product. Examples of adverse events include, but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event)
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Progression/worsening of underlying disease
- Lack of efficacy
- Drug abuse
- Drug dependence

In addition, they may include signs and symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug misuse
- Off label use
- Drug interaction
- Extravasation
- Exposure during pregnancy
- Exposure during breast feeding
- Medication error

- Occupational exposure

Abnormal test findings

The criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- The test result is accompanied by associated symptoms.
- Additional diagnostic testing or medical/surgical intervention is required.
- The test result leads to a change in administration of this product, discontinuation of the study, or addition of concomitant drug treatment or other therapy.
- The investigator or Pfizer regards the test result as an adverse event.

A case in which none of the above situations is present but simply an abnormal value continues will not be regarded as an adverse event. Any abnormal test result that is determined to be due to a laboratory error does not require reporting as an adverse event.

10.4.2. Serious adverse events

A serious adverse event is any untoward medical occurrence in a subject who has received a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation (see below for circumstances in which an abnormal test finding does not constitute an adverse event).
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether an event is an important medical event. Significant medical events may not be immediately life-threatening or result in death or hospitalisation. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, the event should be reported as serious.

Examples of such events are intensive care in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse.

In addition, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The onset of the event may be suspected from clinical signs or laboratory findings suggestive of infection in a subject exposed to a Pfizer product. The term "suspected transmission" is considered the synonym of "transmission." These cases are considered

unexpected and will be handled as serious expedited cases by Safety division. Such cases should also be considered for reporting as product defects, if appropriate.

Hospitalisation

Hospitalisation is defined as any initial admission (even less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation of existing hospitalisation. Hospitalisation also includes transfer within the hospital to another department or an acute/intensive care unit (eg, from the psychiatric floor to the medical floor, from the medical floor to the coronary care unit, from the neurological floor to the tuberculosis unit, etc.). A visit to the emergency room is not necessarily regarded as hospitalisation; however, the event leading to the emergency room visit should be assessed for medical significance.

Hospitalisation without a medical adverse event is not in itself an adverse event and are not reportable. For example, hospitalisation without any of the following medical adverse events need not be reported.

- Hospitalisation for social reasons (e.g., no place of accommodation for subjects)
- Administrative hospitalisation (eg, for yearly physical examination)
- Optional hospitalisation not associated with a precipitating clinical illness (eg, for elective cosmetic surgery)
- Hospitalisation for observation without a medical adverse event
- Hospitalisation for treatment of a preexisting condition not associated with the occurrence of a new adverse event or with worsening of the preexisting condition (eg, for precise examination of abnormal laboratory test values observed before the start of the treatment)

10.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios related to exposure during pregnancy, exposure during breast feeding, medication error, drug overdose, drug misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

Exposure during pregnancy (EDP) occurs when:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed to (e.g., environmental) this product. A female becomes, or is found to be, pregnant after discontinuing or having been directly exposed to this product (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure, to a Pfizer product prior to or around the time of conception. A male has been exposed during pregnancy of his partner (paternal exposure).

For exposure during pregnancy in studies of pregnant women, data on the exposure to this product during pregnancy are not reportable unless associated with serious or non-serious adverse events.

As a general rule, prospective and retrospective reports of exposure during pregnancy from any source are reportable irrespective of the presence of an associated adverse event and the procedures for reporting serious adverse events should be followed, with the exception of those studies conducted in pregnant women (as described in above), for which data on the exposure are not reportable unless associated with serious or non-serious adverse events.

If a subject or a subject's partner becomes or is found to be pregnant during the period of treatment with this product, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred, using the NIS AE Report Form and the EDP Supplemental Form.

In addition, information regarding environmental exposure to this product in pregnant women (e.g., a subject report that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AE Report Form and the EDP Supplemental Form. This must be done irrespective of whether an adverse event has occurred.

The information submitted should include the anticipated date of delivery (see below for information on termination of pregnancy).

Follow-up investigation should be conducted to obtain general information on the pregnancy. In addition, follow-up investigation of EDP outcome information is required for all EDP reports with an unknown pregnancy outcome. The pregnancy will be followed until completion or until pregnancy termination (eg, abortion induced) and the outcome should be reported to Pfizer. This information should be submitted as the follow-up investigation of the initial EDP report. In the case of a live birth, the absence of external malformations should be evaluated at birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for a serious adverse event (ie, ectopic pregnancy, abortion spontaneous, foetal death in utero, death neonatal, or congenital anomaly [in a live born, a terminated fetus, an foetal death in utero, or a death neonatal]), the procedures for reporting serious adverse events should be followed.

Additional information on pregnancy outcomes that are reported as serious adverse events is as follows:

- Abortion spontaneous includes abortion and abortion missed.
- Death neonatal that occur within 1 month of birth should be reported as serious adverse events, without regard to causality. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information on exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on premature baby to identify developmental delays).

In the case of paternal exposure, subjects will be provided with a document on "Disclosure of Information on Pregnant Partners," which is to be given to their partners. It must be documented that this document to be given to his partner has been provided to the subject.

Exposure during breast feeding

Scenarios involving exposure during breastfeeding must be reported, irrespective of the presence of an associated adverse event. A report of exposure during breast feeding will not be prepared when a Pfizer product specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if an infant experience an adverse event associated with the use of these agents, the adverse event should be reported along with the exposure during breastfeeding.

Medication error

A medication error is any event which may cause or lead to inappropriate use of a medicinal product under the control of the healthcare professional, subject, or consumer, and which is preventable. Such events may be related to the medical practice, product, procedure, or system, including prescription, delivery of prescribing information, product labeling, packaging and name, compounding, dispensing, distribution, administration, education, monitoring, and use.

Examples of medication errors include:

- Medication errors prevented in advance, irrespective of whether or not having direct effects on recipients (e.g., inadvertent/incorrect administration by a healthcare professional or recipient/consumer using the product incorrectly at an administration method or dose level not indicated on the product label or prescription).

- Confusion of names (e.g., trade name)

The investigator must submit the following medication errors irrespective of the presence or absence of associated adverse events/serious adverse events:

- Medication errors involving subject exposure to the product, whether or not the medication error is accompanied by an adverse event

- Medication errors that do not involve a subject directly (e.g., possible medication errors or near misses, including potential ones or those prevented in advance). If the medication error does not involve subject exposure to the product, a medication error report will be created based on the following minimum criteria:

- Identifiable reporter

- Suspected product

- Medication error events

Drug overdose, drug misuse, and extravasation

The investigator must report drug overdose, misuse, and extravasation associated with the use of a Pfizer product to Pfizer, irrespective of the presence or absence of adverse events/serious adverse events.

Lack of efficacy

The investigator must report lack of efficacy of Pfizer products to Pfizer, irrespective of the presence or absence of adverse events/serious adverse events, and the indication of the Pfizer product.

Occupational exposure

The investigator must report occupational exposure to Pfizer products to Pfizer, irrespective of the presence or absence of adverse events/serious adverse events.

10.5. Single Reference Safety Document

In this study, the package insert of this product in Japan will serve as the Single Reference Safety Document. This document will be used by Pfizer Safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

Single reference safety document should be used by the investigator for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Information collected in this study will be used for reporting purposes to Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals and Medical Devices Agency (PMDA), Pfizer Inc. which is the corporate parent of the sponsor of this study, and the group companies, or regulatory agency in other countries. Also, it will be used for submitting application of re-examination (including Japan Periodic Safety Update Report), re-evaluation, preparation of material for proper use information of this drug, publications and activities for information provision. In addition, Pfizer may disclose the study results to provide information for proper use, as needed, on www.clinicaltrials.gov (ClinicalTrials.gov), publish as presentations at academic conferences or, as manuscripts, etc.

Data obtained from the subjects registered in this Study will be reported to the MHLW pursuant to the Pharmaceutical and Medical Device Act. In this case, the data may be publicly posted in MHLW's "Pharmaceutical and Medical Device Safety Information" and "Pharmaceuticals and Medical Devices Information Website (http://www.info.pmda.go.jp)" as a listing of subjects, which will include the names of drugs, adverse reactions, gender, age (increment of 10 years), and other relevant information. Furthermore, data collected may also be disclosed if the MHLW is required to disclose such information in accordance with the "Act on Access to Information Held by Administrative Organs" (Law No. 42 dated May 14, 1999); provided that in no event will the names of physicians, medical institutions, and other personal information be subject to such disclosure, nor will it be posted or disclosed.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the subjects against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

12. NAME, AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED

- Company name: Pfizer R&D Japan
  Address: Shinjuku Bunka Quint Bldg., 3-22-7, Yoyogi, Shibuya-ku, Tokyo
  Scope of work of contracted: Works related to planning of study, drafting of plan, implementation of study and monitoring, etc.

- Company name: CMIC Co., Ltd.
  Address: Hamamatsucho Building, 1-1-1 Shibaura, Minato-ku, Tokyo
  Scope of work contracted: Establishment, operation and maintenance of the EDC system, etc.

- Company name: EPS Corporation
  Address: 2-23 Shimomiyabicho, Shinjuku-ku, Tokyo
  Scope of work contracted: Monitoring operations, data management, statistical analysis etc.

13. ADDITIONAL MEASURES THAT MAY BE TAKEN BASED ON THE STUDY RESULTS AND CRITERIA FOR DETERMINATION OF THE INITIATION

Review the risk management plan including the following contents at the scheduled timing of milestones.

1. Review the necessity for changing the contents of risk minimization activities for the current safety specifications.

2. Review the necessity for changing the contents of this study plan including the presence or absence of new safety specifications (continuation of the study, implementation of additional study, etc.).

3. Review the necessity for formulating risk minimization measures for new safety specifications.

14. SCHEDULED TIMING OF MILESTONES AND THEIR RATIONALES FOR EVALUATION OF STUDY IMPLEMENTATION STATUS AND RESULTS AND REPORTING TO THE PMDA

Safety review and reporting at the time of preparing the Periodic Safety Update Reports and completion of the study.

15. OTHER ASPECTS

1. Revision of full protocol

Based on the new knowledge to be obtained according to the progress of this study, the need for amendment of the full protocol will be examined and the full protocol will be amended if necessary. Also, the need for amendment of the full protocol will be examined and the full protocol will be amended when the partial change in the dosage and administration or indication is approved during the reexamination period (except when the reexamination period is newly designated), etc.

2. Actions to be taken for any problem or issue

Revision of the package insert and conduct of a new Post-marketing surveillance or new Post-marketing Clinical Trial should be considered for the following cases: any serious and unknown adverse reaction is suggested; a significant increase in the frequency of adverse reactions; any effectiveness or safety concern compared to pre-approval; rare adverse reaction is suggested.

16. CONTACT INFORMATION

16.1. Contact information for inquiries about the study

Name	PMS Affairs, Pfizer R&D Japan
Address	Shinjuku Bunka Quint Building, 3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589
FAX	03-5309-9186
E-mail address	BNT_COM_EX_DRPMS@pfizer.com

16.2. Contact information for inquiries about the EDC system

Name	CMIC HealthCare Institute Co., Ltd.

For other information on contact information (telephone number/e-mail address/reception time, etc.), refer to the materials provided separately.

17. REFERENCES

1. Guidance for Treatment of Novel Coronavirus Infection (COVID-19)

18. LIST OF TABLES

19. LIST OF FIGURES

APPENDIX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable.

APPENDIX 2. ADDITIONAL INFORMATION

1. Drug Use Investigation case report form

2. Health status record form