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To: Commissioner of Prefectural Health Department (Bureau)

Director of Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Points to Consider, etc. for Reporting Clinical Trial Product Defects or Adverse Events, etc. relevant to Processed Cells, etc.

Handling of reports on Clinical Trial Product Defects or Adverse Events, etc. of processed cells, etc. was described in "Reporting of Defects or Adverse Events, etc. relevant to Processed Cells, etc. in Clinical Studies" (PFSB Notification No. 1002-23, by the Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (herein after referred to as MHLW), dated October 2, 2014) and "Points to Consider, etc. for Reporting Clinical Trial Product Defects or Adverse Events, etc. Relevant to Processed Cells, etc." (PFSB/ELD/OMDE Notification No. 1002-1 by the Counsellor of Minister's Secretariat, MHLW [Evaluation and Licensing of Medical Device/Regenerative Medical Products] dated October 2, 2014).

With enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 63 of 2019) as well as enforcement of the Ministerial Ordinance on Maintenance, etc. of Related Ministerial Ordinances in association with Enforcement of the Act for partially amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Ordinance No. 155 of 2020), the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals

and Medical Devices (Ministry of Health and Welfare Ordinance No.1 of 1961, hereinafter referred to as the "Enforcement Regulation of the Act") was revised following revision of the said Ministerial Ordinance; handling of reports on clinical trial product defects or adverse events, etc. of processed cells, etc. in accordance with Article 275-3 of the revised Enforcement Regulation of the Act has been described in "Reporting of Defects or Adverse Events, etc. Relevant to Processed Cells, etc. in Clinical Studies" (PSEHB Notification No. 0831-10 by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated August 31, 2020, hereinafter referred to as the "Director Notification"). Besides, it has been decided that reports on clinical trial product defects or adverse events, etc. of processed cells, etc. should be handled as shown in the Appendix in addition to Director Notification. Please inform related business operators, medical institutions, etc. in your jurisdiction of these matters.

With the enforcement of this notification, "Points to Consider, etc. for Reporting Clinical Trial Product Defects or Adverse Events, etc. Relevant to Processed Cells, etc." (PFSB/ELD/OMDE Notification No. 1002-1 by the Counsellor of Minister's Secretariat, MHLW [Evaluation and Licensing of Medical Device/Regenerative Medical Products] dated October 2, 2014) will be abolished on August 31, 2022.

Appendix

Points to Consider, etc. for Preparing Reports by Sponsors and Sponsor-investigators of Clinical Studies Relevant to Processed Cells, etc.

1 General considerations

(1) In principle, for reporting clinical trial product defects or adverse events, etc. under the provisions of Article 275-3, Paragraph 1, Paragraph 2, and Paragraph 4 of the Enforcement Regulation of the Act, submit CD-R or DVD-R (hereinafter referred to as "electronic media") in which the data are recorded electromagnetically and, along with a paper copy of the data, provided to the Review Planning Division, Office of Review Management, Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"). The size of the form to be used for the report shall be Japanese Industrial Standards A4, and the form shall be clearly printed in block letters using India ink or ink. The software and entry manual for creating electronic files are available on the PMDA website.
(https://www.pmda.go.jp/review-services/trials/0010.html, only in Japanese)

(2) If all of the required information cannot be entered in the specified column, enter "as per attachment" in the column and prepare the attachment.

(3) Enter the date using the Western calendar whenever entering the date in any column.

(4) If an appropriate Japanese name cannot be found in a medical dictionary, etc. for defects/adverse reactions reported from a foreign country, they shall not be translated unreasonably, and the original language shall be written as it is, or the Japanese translation shall be followed by the original language in parentheses.

(5) Be sure to enter the reporter's address (address of the main office), name, date of report, and name of the Chief Executive of the PMDA. If the reporter is a corporation, enter the name of the corporation and the name of the representative as the name.

2 How to fill out the Clinical Trial Product Defect or Adverse Event/Infection Case Report Form (Attached Form 1 of Director Notification)

If the suspected products are not single products used in the clinical study, information on these products should be presented in the same report to make one report per case.

(1) Management information

1) "Control No." column

a. For the first report, leave the "Identification No." column blank. For the second and subsequent reports, enter the identification number assigned by PMDA.
b. In the "Number of times of reporting to PMDA" column, enter the number of times of reporting to PMDA.
c. Be sure to select and circle one in the "Reporting category," "Reporting type," and "Location of occurrence of defects or adverse events, etc." columns. If the "Location of occurrence of defects or adverse events, etc." is a foreign country, enter the name of the country where the defect or adverse event occurred.

2) In the "date of receipt of initial report" column, be sure to enter the date when the reporter knew the defect or adverse event/infection or the health injury in the subject, etc. due to occurrence of the defect or adverse event (hereinafter referred to as "defects or adverse events, etc."). Note that the division of the reporter who obtained the information does not matter and that it is not the date when the reporter judged it necessary to report the clinical trial product defect or adverse event, etc.
3) In the "Date of receipt of latest information" column, enter the date of receipt of the latest information relevant to the report.
4) In the "Scheduled date of next reporting" column, enter the scheduled date of next reporting if sufficient information, etc. have not been obtained at the time of current reporting and an additional report needs to be made. In principle, the scheduled date of the next reporting shall be a day earlier than the date when the same number of the days, which is selected in the "Reporting category" of the "Control No." column, passes from the day following the date of submission of this report.
5) In the "Defect or adverse event status of clinical trial product" and "Health injury status of subject, etc.," be sure to select and enter or circle any one from the three choices. In the cases where more than one product is used in the clinical study, select "Yes" if a reportable defect or adverse event occurred with any of the products.
6) In the "Contact information of person in charge" field, be sure to fill in the "Name of person in charge," "Corporate name," "Department," "Address," "Tel," "Fax," and "E-mail" columns. If the sponsor-investigator reports a clinical trial product defect or adverse event, etc., enter the name of the institution in the "Corporation name" column.

(2) Information on subjects, etc.

1) In the "Abbreviated name of subject, etc." column, enter the initials in Roman characters (one-byte characters). The subject identification code

of the study may be entered. If it is unreported or unavailable, leave the column blank.

2) In the "Age" column, enter the age at the time of occurrence of the defect or adverse event, etc. If an accurate age cannot be confirmed, "under 10 years," "in their 60s," "children," "elderly," etc. may be entered. If it is unreported or unavailable, leave the column blank.
3) In the "Gender" column, select and circle either one from the two choices. If it is unreported or unavailable, leave the column blank.
4) In the "Weight" column, enter the weight at the time of occurrence of the defect or adverse event, etc. If it is unreported or unavailable, leave the column blank.
5) In the "Height" column, enter the height at the time of occurrence of the defect or adverse event, etc. If it is unreported or unavailable, leave the column blank.
6) "Status of the subject, etc. at the time of occurrence of the defect or adverse event, etc." column
    a. In the "Defect or Adverse Event" column, describe all defects or adverse events that occurred. When multiple defects or adverse events are to be reported, enter "defect or adverse event name," "known/unknown," and "occurrence date" repeatedly for each defect or adverse event In the "Known/Unknown" column, be sure to select and circle either one. When defects or adverse events occurred with more than one product used in the clinical study, add supplement information in parentheses in the defect or adverse event name column so that each product can be identified.
    b. In the "Status of health injuries in subject" column, enter all adverse events and infections that occurred. When more than one adverse event and infection are to be reported, enter "name of adverse event/infection," "known/unknown," "date of onset," "date of resolution," "seriousness," "outcome," and "evaluation of causal relationship" repeatedly for each adverse event or infection.
        (a) In the "Known/Unknown" column, be sure to select and circle either one. If there is more than one suspected product, select Known if it is known for all suspected products.
        (b) In the "Seriousness" column, select and enter applicable one(s) from "Resulting in death," "Resulting in life-threatening disease or disorder," "Requiring hospitalization or prolongation of existing hospitalization," "Resulting in permanent impairment of the structure or functions of human body," "Causing congenital

anomaly, or fetal death or incapacity," or "Other medically important condition."

The meaning of each option is as follows.

- "Resulting in death" means "death" specified in Article 275-3, Paragraph 1, Item 1 (a) and Item 2 (b), Paragraph 2, Item 1 (a) and Item 2 (b) of the Enforcement Regulation of the Act.
- "Resulting in life-threatening disease or disability" refers to a "Case that may result in death" specified in Article 275-3, Paragraph 1, Item 1 (b), Item 2 (b), Paragraph 2, Item 1 (b) and Item 2 (b) of the Enforcement Regulation of the Act.
- "Requiring inpatient hospitalization or prolongation of existing hospitalization" refers to a "case requiring hospitalization in a hospital or clinic or extension of a hospitalization period for treatment" specified in Article 275-3, Paragraph 1, Item 2 (a) (1) and Paragraph 2, Item 2 (a) (1) of the Enforcement Regulation of the Act.
- "Resulting in permanent impairment of the structure or functions of the human body" refers to "Disability" specified in Article 275-3, Paragraph 1, Item 2 (a) (2) and Paragraph 2, Item 2 (a) (2) of the Enforcement Regulation of the Act.
- "Causing congenital anomaly, or fetal death or incapacity" refers to "Congenital disease or abnormality in later generations" specified in Article 275-3, Paragraph 1, Item 2 (a) (5) and Paragraph 2, Item 2 (a) (5) of the Enforcement Regulation of the Act.
- "Other medically important condition" refers to a "Case that may result in disability" specified in Article 275-3, Paragraph 1, Item 2 (a) (3) and Paragraph 2, Item 2 (a) (3) of the Enforcement Regulation of the Act and a "Case of a serious condition according to cases set forth in (1) through (3) and (a) and (b) of the preceding item" specified in Article 275-3, Paragraph 1, Item 2 (a) (4) and Paragraph 2, Item 2 (a) (4) of the Enforcement Regulation of the Act it is an important medical condition that does not cause immediate life-threatening or result in death or hospitalization but exposes subjects, etc. to danger, or requires medical or surgical intervention to prevent outcomes such as" Resulting in death," "Resulting in life-threatening disease or disorder," "Requiring inpatient hospitalization or prolongation of existing

hospitalization," "Resulting in permanent impairment of the structure or functions of human body," or "Causing congenital anomaly, or fetal death or incapacity."

(c) In the "Outcome" column, select and enter one from "Recovered," "Recovering," "Not recovered," "Recovered with sequelae," "Death," or "Unknown."

(d) In the column of "Causality assessment," select one from "Related," "Probably related," "Possibly related," "Unrelated," or "Unknown," and enter both assessment opinions from the attending physician, etc. and the reporter. If there is more than one suspected product, select the option of the strongest causality and provide a summary of the assessment for each suspected product in the free text field. Detail assessment in 2) Opinions from the attending physician, etc. and 3) Opinion from the reporter in 4. Investigation results and actions, etc.

7) In the "Course of occurrence of defects or adverse events, etc." column, describe the course before and after the occurrence of the defects or adverse events, etc. in chronological order so that the occurrence status can be easily understood. If any adverse event occurred in the subject, etc., the status of the adverse event and whether or not any measure was taken by the medical institution for the subject, etc., and if taken, the details of the measures (including changes in laboratory test values, etc.) should be provided.

(3) Clinical Trial Product Information

1) In the "Study identification code" column, enter the study identification code of the main investigational product stated in the study protocol notification for the clinical trial product(s).

2) In the "Category" column, enter the category of the main investigational product stated in the study protocol notification for the clinical trial product(s).

3) In the "Nonproprietary name" column, enter the nonproprietary name of the main investigational product stated in the study protocol notification for the clinical trial product(s). If there is no applicable nonproprietary name, leave the column blank.

4) In the "Date of study protocol notification" column, enter the date of submission of the study protocol notification for the clinical trial product. If more than one notification is made, enter all dates of the notifications.

5) In the "Outline of clinical study" column, briefly enter information including the protocol identification code (protocol number) stated in the

study protocol notification for the clinical trial product, intended indication or performance, target disease, and presence or absence of cases in which the (investigational) product is used.

6) In the "Details of clinical trial product" column, enter the lot number, manufacturing number, etc. of the clinical trial product.
7) In the "Classification" column, select and circle either one depending on whether the product falls under the category of the designated regenerative medical products. If marketing approval has not been obtained for the clinical trial product, select and circle the one that is assumed to be applicable.
8) In the "Status of use of clinical trial product" column, enter the time elapsed after the start of use.
9) In the "Current status of clinical trial product" column, select and circle either one from the two choices. If the product has not been returned, select and circle the applicable one from "Disposal, remaining in the body, return scheduled, return impossible."
10) In the "Concomitant therapy" column, enter the nonproprietary name, brand name, name of marketing authorization holder, etc. of concomitant products used in the clinical study (excluding the investigational product) and concomitant drugs or medical devices used in the clinical study (regenerative medical products, drugs, or medical devices) as detailed as possible so that these concomitant drugs, etc. can be identified.
11) In the "Remarks" column, enter the number of times of occurrence of the same defects or adverse events, etc. in the past and their incidence as well as precautions and descriptions in the investigator's brochure and the protocol related to the report. If the sponsor-investigator reports a clinical trial product defect or adverse event, etc., enter the name of the clinical trial product provider (names of the corporation and the representative if the provider is a corporation). If the clinical trial product provider is a foreign manufacturer, enter the name of the foreign manufacturer (names of the corporation and the representative if the provider is a corporation) in Japanese and English. If the case was not reportable at the time of receipt of the initial report but became reportable at the time of receipt of additional information, describe that matter and enter the initial date of reckoning for reporting.

    If an investigational product other than the main investigational product is a suspected product, enter the category, nonproprietary name, intended indication or performance, target disease, presence or absence of cases in which the product is used, lot number,

manufacturing number, etc., classification, use status, and current status of the product, and mention that the product is a suspected product.

If any of the products used in the clinical study other than the investigational product falls under the category of suspected products, enter the category, nonproprietary name, brand name, date of approval, purpose of use (type such as control product or concomitant product), presence or absence of cases in which the product is used, lot number, manufacturing number, etc., classification, use status, and current status of the product if the product is approved in Japan, and enter the component cells or introduced genes, purpose of use (type such as control product or concomitant product), presence or absence of cases in which the product is used, lot number, manufacturing number, etc., classification, use status, and current status of the product, and mention that the product is a suspected product if the product is not approved in Japan. If any of the concomitant drugs or medical devices used in the clinical study fall under the category of suspected drugs or suspected devices, enter their information, according to the rules stated above regarding products used in the clinical study.

(4) Investigation results and actions, etc.

1) In the "Investigation results" column, be sure to enter the results of analysis, evaluation, and examination of the defect or adverse event, etc. Taking into account opinions on the clinical trial product (product used in the clinical study) from the attending physician, etc. and scientific grounds (raw data, etc.), briefly describe the cause of occurrence of the defect or adverse event, etc., use status by the user, possibility of occurrence of a similar defect or adverse event, etc. with the clinical trial product (product used in the clinical study), possibility that the defect or adverse event, etc. may cause health injuries, and views on opinions from the attending physician, etc.

2) In the "Opinion from attending physician, etc." column, describe opinions from the attending physician, etc. regarding the diagnosis or causal relationship assessment relevant to the defect or adverse event, etc., or other issues considered to be related to the defect or adverse event, etc. If no opinion is obtained from the attending physician, etc. because the information is received from a foreign country, etc., mention that matter.

3) In the "Reporter's opinion" column, describe the reporter's opinion on the causal relationship with a medical consideration. Also describe the effect of the defect or adverse event, etc. on subjects, etc. (effect of the defect or adverse event, etc. on subjects, etc. who have already used the

clinical trial product [product used in the clinical study] and subjects, etc. who will use the clinical trial product [product to be used in the clinical study] in the future.) If the assessment of seriousness is different between the attending physician, etc. and the reporter, provide the details. If information was obtained from a foreign country, enter the opinion from the reporter in Japan instead of the opinion from the foreign company.

4) In the "Past actions" column, enter whether or not any measure was taken by the reporter after obtaining the information on the defect or adverse event, etc. by the time of reporting to prevent recurrence of similar cases or to ensure the safety of the subject, etc., and if taken, be sure to provide details of the measures and the reasons why the measures were taken.

5) In the "Future plans" column, enter the actions taken based on the reporter's assessment of the defect or adverse event, etc. and future actions with reference to the following.

a. Present whether actions, such as a notification to medical institutions, revision of the informed consent form, revision of the protocol, revision of the investigator's brochure, and revision of the summary document for approval application (draft precautions, etc.), have been taken or are scheduled to be taken in the future. If a notification to medical institutions is made, describe the means (sending of a notification, provision of the revised investigator's brochure, telephone communication, etc.) as well.

b. If information was obtained from a foreign country, describe the actions taken by the reporter in Japan instead of the actions taken by the foreign company.

6) If any of concomitant drugs or medical devices used in the clinical study is a suspected drug or suspected device, enter their information, according to the rules stated above regarding products used in the clinical study.

3 How to fill out the investigation report on clinical trial product research reports (hereinafter referred to as "research report") and investigation report on measures such as discontinuation of manufacturing, etc., recall, and disposal, etc. of clinical trial products in foreign countries (hereinafter referred to as "foreign measure report"). (Attached Form 2 of Director Notification)

(1) Management information

1) "Control No." column

a. For the first report, leave the "Identification No." column blank. For the second and subsequent reports, enter the identification number assigned by PMDA.
b. In the "Number of times of reporting to PMDA" column, enter the number of times of reporting to PMDA.
c. In the "Report Type" column, be sure to select and circle either one from the two choices.

2) In the "Date of receipt of initial report" column, be sure to enter the date when the reporter learned the information to be submitted as a research report or foreign measure report. Note that the division of the reporter who obtained the information does not matter and that it is not the date when the reporter judged it necessary to make a research report or a foreign measure report.
3) In the "Date of receipt of latest information" column, enter the date of receipt of the latest information relevant to the report.
4) In the "Scheduled date of next reporting" column, enter the scheduled date of next reporting if sufficient information, etc. have not been obtained at the time of current reporting and an additional report needs to be made. In principle, the scheduled date of the next reporting shall be a day within 15 days from the day following the date of submission of the report.
5) In the "Defect or adverse event status of clinical trial product" and "Health injury status of subject, etc.," column, be sure to select and circle any one from the three choices.
6) In the "Contact information of person in charge" field, be sure to fill in the "Name of person in charge," "Corporate name," "Department," "Address," "Tel," "Fax," and "E-mail" columns. If the sponsor-investigator makes a report, enter the name of the institution in the "Corporation name" column.

(2) Clinical Trial Product Information

1) In the "Study identification code" column, enter the study identification code of the main investigational product stated in the study protocol notification for the clinical trial product(s).
2) In the "Category" column, enter the category of the main investigational product stated in the study protocol notification for the clinical trial product(s).
3) In the "Nonproprietary name" column, enter the nonproprietary name of the main investigational product stated in the study protocol notification

for the clinical trial product(s). If there is no applicable nonproprietary name, leave the column blank.

4) In the "Date of study protocol notification" column, enter the date of submission of the study protocol notification for the clinical trial product. If more than one notification is made, enter all dates of the notifications.
5) In the "Outline of clinical study" column, briefly enter information including the protocol identification code (protocol number) stated in the study protocol notification for the clinical trial product, intended use, target disease, and presence or absence of cases in which the clinical trial product is used.
6) In the "Details of clinical trial product" column, enter the lot number, manufacturing number, etc. of the clinical trial product.
7) In the "Classification" column, select and circle either one depending on whether the product falls under the category of the designated regenerative medical products. If marketing approval has not been obtained for the clinical trial product, select and circle the one that is assumed to be applicable.
8) In the "Remarks" column, enter precautions and descriptions in the investigator's brochure and the protocol, related to the research report or foreign measure report.

   If the research report or foreign measure report concerns an investigational product other than the main investigational product, mention that matter and enter the category, nonproprietary name, intended use, target disease, presence or absence of cases in which the investigational product is used, lot number/manufacturing number, etc., and classification, etc. of the investigational product.

   If the foreign measure report concerns a product used in the clinical study other than the investigational product (limited to measures taken to prevent the occurrence or spread of public health hazards when used in combination with the investigational product), mention that matter and enter the category, nonproprietary name, brand name, date of approval, purpose of use (type such as control product or concomitant product), presence or absence of cases in which the investigational product is used, lot number/manufacturing number, and classification, etc. if the product is approved in Japan, and enter the component cells or introduced genes, purpose of use (type such as control product or concomitant product), presence or absence of cases in which the (investigational) product is used, lot number, manufacturing number, and classification, etc. of the product if the product is not approved in

Japan. If the foreign measure report concerns a concomitant drug or medical device used in the clinical study (limited to measures taken to prevent the occurrence or spread of public health hazards when used in combination with the investigational product), enter their information, according to the rules stated above regarding products used in the clinical study.

(3) Report contents and actions, etc.

1) "Research report or details of measures" column

a. Fill in the "Source of research report" column only for a research report so that scientific journals, etc. in which the information is published can be identified.

b. Fill in the "Country where measures were taken" column only for a foreign measure report, and enter the name of the country/region where the measures that triggered the report were taken.

c. Fill in the "Measure category" column only for a foreign measure report, and describe the measures concretely (examples: Recall, modification related to monitoring, warning, revision of the investigator's brochure, etc.).

d. In the column below the "Measure category," be sure to provide a brief description of the research report or foreign measure report."

2) In the "Past actions" column, enter whether or not any measure was taken by the reporter in Japan after obtaining the information by the time of reporting, and if taken, be sure to describe the measures and the reasons why the measures were taken.

3) In the "Future actions" column, enter the actions taken based on the reporter's assessment of the defect or adverse event, etc. and future actions with reference to the following.

a. Present whether actions, such as a notification to medical institutions, revision of the informed consent form, revision of the protocol, revision of the investigator's brochure, and revision of the summary document for approval application (draft precautions, etc.), have been taken or are scheduled to be taken in the future. If a notification to medical institutions is made, describe the means (sending of a notification, provision of the revised investigator's brochure, telephone communication, etc.) as well.

b. If information was obtained from a foreign country, describe the actions taken by the reporter in Japan instead of the actions taken by the foreign company.

4 How to fill out the Clinical Trial Product Periodic Safety Report (Attached Form 3-1 of Director Notification)

(1) In the "Study identification code" column, enter the study identification code of the main investigational product stated in the study protocol notification for the clinical trial product(s).

(2) In the "Category" column, enter the category of the main investigational product stated in the study protocol notification for the clinical trial product(s).

(3) In the "Nonproprietary name" column, enter the nonproprietary name of the main investigational product stated in the study protocol notification for the clinical trial product(s). If there is no applicable nonproprietary name, leave the column blank.

(4) In the "Date of initial notification" column, enter the date of first submission of the study protocol notification for the clinical trial product.

(5) In the "Initial date of reckoning for reporting" column, enter the initial date of reckoning for reporting determined for the annual periodic report on the clinical trial product specified in Article 275-3, Paragraph 4 of the Enforcement Regulation of the Act (hereinafter referred to as the "annual report"). The initial date of reckoning for reporting shall be, in principle, the date of first submission of the study protocol notification for the clinical trial product. (If a study protocol notification was submitted before November 24, 2014 for the clinical trial product as a drug, machinery/equipment, etc. but newly submitted on or after November 25, 2014, it is the date when the study protocol notification was submitted as a drug, machinery/equipment, etc.) If the initial date of reckoning for reporting is to be changed, consult with the Review Planning Division, Office of Review Management, PMDA in advance, and submit a request for change of the initial date of reckoning for reporting. In the "Request for change of the initial date of reckoning for reporting" (free format), enter the "clinical study identification code," "original initial date of reckoning," "new initial date of reckoning," "reason for changing the initial date of reckoning," and "planned survey interval for future reporting."

(6) In the "Outline of clinical study" column, briefly enter information including the protocol identification code (protocol number) stated in the study protocol notification for the clinical trial product, intended indication or performance, target disease, and presence or absence of cases in which the (investigational) product is used.

(7) In the "Details of clinical trial product" column, enter the lot number, manufacturing number, etc. of the investigational product.

(8) In the "Classification of Clinical Trial Product" column, select and circle either one depending on whether the product falls under the category of the

designated regenerative medical products. If marketing approval has not been obtained for the clinical trial product, select and circle the one that is assumed to be applicable.

(9) In the "Reporting period" column, enter the period when defects or adverse events, etc. were accumulated for the report.

(10) In the "Number of times of reporting to PMDA" column, enter the total number of times of submission of the report.

(11) In the "Information on changes in the clinical trial product" column, provide the details of the changes and the reason for the changes if a change was made to the clinical trial product during the reporting period. If a change was made to the clinical trial product for safety reasons, describe the occurrence status of defects or adverse events, etc. after the changes.

(12) In the "Approval status in foreign countries" column, enter the name of countries where the product is approved, date of approval, quantity shipped, etc. as far as possible when the clinical trial product has been approved in foreign countries.

(13) In the "Occurrence status of defects or adverse events, etc." column, briefly describe the occurrence status of defects or adverse events, etc. of the products used in the clinical study that were collected during the reporting period. Attach the "List of Occurrence Status of Clinical trial Product Defects or Adverse Events/Infection Cases" specified in Attached Form 3-2 of Director Notification. If clinical trial product defects or adverse events, etc. have been reported from a double-blind study without unblinding, describe the method of aggregation of blinded cases.

(14) In the "Opinions and safety measures based on the accumulation" column, enter the reporter's opinions based on the cumulative evaluation of defects or adverse events, etc. accumulated during the reporting period and the cumulative evaluation up to the previous reporting. The reporter's opinions shall include the following contents.

1) Describe new safety assurance actions taken by the reporter and future safety actions.
2) Describe whether actions such as revision of the informed consent form to be given to subjects, and revision of the protocol have been taken or are scheduled to be taken in the future, and the reason.
3) If information was obtained from a foreign country, describe the actions taken by the reporter in Japan instead of the actions taken by the foreign company.

(15) "Remarks" column

1) Enter the contact information including the name of the person in charge, name of the corporation or institution, department, address, telephone number, and fax number etc.
2) If the initial date of reckoning for reporting has been changed, mention the fact that the initial date of reckoning for reporting has been changed, and enter the date of submission of the request for change of the initial date of reckoning for reporting.
3) If the report becomes the final report because of approval or discontinuation of development, enter the date of approval or date of discontinuation of development.
4) If any investigation product is used other than the main investigational product, enter the category, nonproprietary name, intended use, target disease, presence or absence of cases in which the (investigational) product is used, lot number/manufacturing number, classification, information on changes, and approval status in foreign countries, etc. of the product.

   If any product other than the investigational product is used, enter the category, nonproprietary name, brand name, date of approval, purpose of use (type such as control product or concomitant product), presence or absence of cases in which the (investigational) product is used, lot number/manufacturing number, classification, information on changes, and approval status in foreign countries, etc. of the product if the product is approved in Japan, and enter the component cells or introduced genes, purpose of use (type such as control product or concomitant product), presence or absence of cases in which the (investigational) product is used, lot number/manufacturing number, classification, information on changes, and approval status in foreign countries, etc. if the product is not approved in Japan. If any concomitant drug or medical device is used in the clinical study, enter their information, according to the rules stated above regarding products used in the clinical study.

5 How to fill out the List of Occurrence Status of Clinical Trial Product Defect/Adverse Event Cases (Attached Form 3-2 of Director Notification)

(1) Classify cases into clinical studies in Japan, foreign clinical studies, and foreign post-marketing spontaneous reports to prepare a report. If the case concerns a product that is used in a foreign country and found to contain the same component cells or introduced genes as the product used in the clinical study, include the case in counting in the column for foreign clinical studies in cases where the product is not approved in the country, and include the

case in counting in the column for foreign post-marketing spontaneous reports if the product is approved in the country.

(2) In the "Approximate Number of Subjects, etc." column, enter the approximate number of subjects in the clinical studies that were already conducted and registered subjects in the ongoing clinical studies, and the approximate number of users in foreign countries as far as possible, regarding the clinical trial product, or product used in a foreign country and found to contain the same component cells or introduced genes as the clinical trial product.

(3) In the "Type of defect or adverse event" and "Number of times of defects or adverse events by type" columns, enter the aggregate number of times of cases by type of products used in the clinical study and type of defects or adverse events, etc., regarding cases of known and unknown serious adverse events (excluding those attributable to the effect of infection) and cases of defects or adverse events that may cause a serious condition (excluding those due to the effect of infection), based on Article 275-3, Paragraph 4 of the Enforcement Regulation of the Act. Each adverse event to be reported shall be counted as one event when more than one adverse event occurs in the same case.

(4) In the "Type of infection" and "Number of cases by type of infection" columns, enter the aggregate number of cases by type of products used in the clinical study and type of infection, regarding cases of known and unknown serious infection that were caused by or suspected to be caused by the use of a product in the clinical study, under Article 275-3, Paragraph 4 of the Enforcement Regulation of the Act.

(5) In the "Cumulative" column, enter the total calculated number from the first reporting period to this reporting period.

(6) In the "Remarks" column, describe any reference matters such as prerequisites for counting the number of cases.

(7) If an adverse reaction or defect or adverse event, etc. that occurred with a concomitant drug or medical device used in the clinical study is to be reported, include the case in counting, according to the rules stated above regarding products used in the clinical study.

6 Other considerations

When making a report on clinical trial product defects or adverse events, etc., pay attention to the following points.

(1) Criteria, etc. for judgment of predictability

For reporting on a clinical trial product defect or adverse event, etc., determine the predictability based on the following.

1) In principle, determine the predictability based on a defect or adverse event, etc. noted in the Investigator's Brochure or documents describing scientific knowledge related to the product used in the clinical study (excluding the investigational product) (package insert, published literature, etc.) (hereinafter referred to as "Investigator's Brochure, etc.").
2) The time point when considered to be "predictable" shall be the date of preparation or revision of the investigator's brochure, etc. or the date of preparation of a communication document. Therefore, an adverse event notified to medical institutions via a communication document is regarded as "predictable" even if the investigator's brochure has not been revised.
3) Even if events are noted in the investigator's brochure, etc. but the tendency of occurrence such as the number of times of occurrences, frequency, conditions for occurrence, etc. is not consistent with the descriptions in the documents, they shall be regarded as "unexpected."
4) If the clinical study has been completed and an application for approval is being filed for the product, the document used for judgment of the predictability shall be the summary document for application for the product, regardless of 1).
5) If the clinical study is ongoing after the application for approval and completed before the approval of the product, the document used for judgment of the predictability shall be the summary document for application, replacing the investigator's brochure as of the date of submission of the clinical study completion notification for the clinical study.
6) If the clinical study is ongoing after the application for approval and completed before the approval of the product but a clinical study for a product with the same component cells or introduced gene as the product is ongoing, the document used for judgment of the predictability shall be switched to the investigator's brochure regardless of 5).

(2) Causal relationship

The causal relationship shall be determined as follows in reports on clinical trial product defects or adverse events, etc.

1) Any case is to be reported unless both the investigator, etc. and the sponsor deny the causal relationship. Also, if the report is made by the sponsor-investigator, any case is to be reported unless both the attending physician, etc. and the sponsor-investigator deny the causal relationship.

2) If the report is about a foreign case based on information from persons other than healthcare professionals such as subjects or patients, or their family members, and the sponsor or sponsor-investigator judged that the causal relationship can be ruled out, the case is not to be reported.

3) An "additional report to notify that the case is no longer to be reported" should be made when all the causality of the reported events is ruled out based on additional information obtained. When all reported events are withdrawn for other reasons, an "additional withdrawal report" should be made.

(3) Handling of cases of a product for which an application for partial changes is being prepared or filed

Regarding regenerative medical products already approved in Japan, in cases where a clinical study is being conducted for an application for partial changes in approved items, or all clinical studies relevant to the processed cells, etc. have been completed and an application for partial changes in approved items is being prepared or being filed, and if measures, etc. that may influence the clinical study or application have been taken for a regenerative medical product with the same component cells or introduced genes with the product marketed in Japan, a foreign measure report shall be submitted to the Review Planning Division, Office of Review Management, PMDA within the reporting time frame.

(4) Handling of cases related to the control product in comparative studies

Regarding defects or adverse events, etc. of the control product that is not in a blinded state, the sponsor or sponsor-investigator shall report them to the company providing the control product, and the company providing the control product shall also report the cases of the defect or adverse event, etc. as a "Post-marketing Report on Defects or Adverse Reactions, etc." In this case, defects or adverse events, etc. of the control product shall be handled according to the "Reporting of Adverse Reactions, etc. of Drugs, etc." (PFSB Notification No. 1002-20, by the Director of Pharmaceutical and Food Safety Bureau, MHLW, dated October 2, 2014). In addition, if the report was received from a double-blind study, and the used product was found to be the investigational product after unblinding, an additional report should be submitted for the investigational product, while if the used product was found to be the control product, a report should be submitted to state that matter.

(5) Reporting time frame

1) In the report under Article 275-3, Paragraph 1 or Paragraph 2 of the Enforcement Regulation of the Act, the due date for reporting shall be a

day calculated from the day following the date of receipt of information. If the due date for reporting falls on a non-business day of PMDA, the next business day will be the date.

2) The report under Article 275-2, Paragraph 4 of the Enforcement Regulation of the Act shall be submitted within 2 months from the date of expiration of each reporting period. If the due date for reporting falls on a non-business day of PMDA, the next business day will be the date. The last annual report after approval or submission of a development discontinuation notification shall be submitted within 2 months from the date of approval or submission of a development discontinuation notification.

(6) Setting of the mandatory reporting period

In principle, the mandatory reporting period for reports under Article 275-2, Paragraph 1 of the Enforcement Regulation of the Act shall be the period from the submission of the first study protocol notification to the approval for the clinical trial product or the submission of a development discontinuation; while that for reports under Article 275-2, Paragraph 3 of the Enforcement Regulation of the Act shall be the period from the initial date of reckoning for reporting to the approval or submission of a development discontinuation. However, after completion of all clinical studies conducted by the sponsor-investigator and submission of a notification of completion or discontinuation, if the clinical trial product provider (including the approval applicant. The same shall apply hereinafter in this section.) continues to develop the product, the clinical trial product provider should make reports on clinical trial product defects or adverse events, etc. regarding the product or other products used in the clinical study until the provider obtains approval or submits a development discontinuation notification. If any defects or adverse events, etc. occurred with an implantable clinical trial product after the approval, the defects or adverse events, etc. shall be reported as a "Report on Post-marketing defects or adverse events, etc." If an improved implantable product is approved based on the results of the clinical study of the product, defects or adverse events, etc. of the implanted clinical trial product after approval shall be reported as a "Report on Post-marketing Defect or Adverse Events, etc." in the same manner. If clinical studies are conducted by the sponsor-investigator, and the duration of each study is less than 1 year, annual reporting is not required.

(7) Handling of information on overlapping defects or adverse events, etc. when there is more than one notifier

1) If more than one clinical study is being conducted in Japan for the investigational product by different sponsors or sponsor-investigators, duplicate reports may be omitted by submitting a case report on defects or adverse events, etc. in Japan for each clinical study to the regulatory authorities. However, even in such cases, information shall be appropriately shared between both parties.
2) Regarding a report on clinical trial product defects or adverse events, etc., foreign measure report, and research report, the sponsor-investigator may omit duplicate reports if the clinical trial product provider, etc. had already submitted the reports to the regulatory authorities, or they confirmed that submission of the reports to the regulatory authorities was scheduled within the period specified by laws and regulations by means such as receiving a notice of the scheduled date of reporting, at the time point when they became aware of the information relevant to the report. In that case, information shall be appropriately shared between both parties, and also, "Submission of reports will be omitted based on Appendix 6 (7) 2) of ‘Points to Consider, etc. for Reporting of Study Product Defects or Adverse Events, etc. relevant to Processed Cells, etc.‘ (PSEHB/MDED Notification No. 0831-11 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated August 31, 2020) where applicable" must be stated in the remark column of the study protocol notification in advance. However, it should be noted that the defects or adverse events, etc. occurring in a clinical study conducted by a sponsor-investigator need to be reported to the regulatory authorities. It should be noted that this note does not affect the provisions of Article 39, Paragraph 2 of the Ministerial Ordinance on Good Clinical Practice for Regenerative medical Products (Ordinance of the MHLW No. 89 of 2014) which requires the sponsor-investigator to notify the head of the medical institution performing the study of information on defects or adverse events, etc. relevant to products used in the clinical study.
3) Regarding a regenerative medical product already approved in Japan, if a person other than the approval holder of the regenerative medical product conducts a clinical study for application for partial changes in indications, etc. as a sponsor, and the information is appropriately shared between the two parties, it is acceptable for the approval holder to submit a foreign case report on defects or adverse events, etc. However, matters relevant to foreign case reporting and information sharing should be agreed between the sponsor and the approval holder

in advance. In this case, the sponsor should enter the approval number of the regenerative medical product in the remarks column of the study protocol notification. The approval holder shall enter "TIKEN" in one-byte characters in the "Remarks" column when reporting post-marketing defects or adverse events, etc. for the regenerative medical product.

(8) Handling of cases such as where development is suspended for a long period

If the development is suspended for a long period of time, this matter shall be notified in writing to the Review Planning Division, Office of Review Management, PMDA, and reporting may be suspended until the development is resumed. However, efforts should be made to collect safety information even during the suspension period, and the information should be reflected in the investigator's brochure, etc. and protocol at the time of resumption of development. In addition, when reporting is resumed in association with resumption of development, necessary documents should be submitted to the Review Planning Division, Office of Review Management, PMDA.

1) Documents for application for suspension

Prepare a document describing the following contents and submit it to the Review Planning Division, Office of Management, PMDA.

a. The title shall be "Application for suspension of reporting of clinical trial product defects or adverse events, etc."
b. Enter the study identification code, and state the planned nonproprietary name in parentheses.
c. Enter the number of times of submission of the study protocol notification and the date of the first submission of the study protocol notification.
d. Describe the intended use and indications.
e. State the development phase of the clinical study to be suspended.
f. Specify the "reasons for suspension of reporting."
g. Notes such as "efforts will be continuously made to collect information relevant to defects or adverse events, etc.," "if the development is resumed, adverse reactions, etc. collected during the period of suspension of the development will be reported," and "if the development is to be resumed, the Review Planning Division, Office of Review Management, PMDA will be notified in advance." shall be included.

2) Documents to be submitted at the time of resumption of development

If the development is resumed, the suspension shall be canceled to

resume reporting on defects or adverse events, etc. In this regard, a document describing the following contents shall be prepared and submitted to the Review Planning Division, Office of Review Management, PMDA.

a. The title should be "Application for Cancellation of Suspension of Reporting of Clinical trial product Defect or Adverse Events" and the reason for suspension, suspension period and reason for cancellation of suspension should be described.
b. The information collected during the suspension period shall be submitted using Attached Forms 3 and 4 of Director Notification.
c. Investigator's brochure, etc. or the protocol and revised or corresponding parts of the summary document for application, prepared based on information collected during the suspension period shall be submitted.

(9) Reports on adverse reactions, etc. or defects or adverse events, etc. relevant to drugs, machinery/equipment, etc., respectively used in clinical studies of processed cells, etc.

Regarding reports on adverse reactions, etc. or defects or adverse events, etc. relevant to drugs (concomitant drugs) or machinery/equipment, etc. (concomitant devices) used in clinical studies of processed cells, etc., the scope and time frame, etc. of reporting shall conform with the prescription in "Reporting of Adverse Reactions, etc. in Clinical Studies to Pharmaceuticals and Medical Devices Agency" (PSEHB Notification No. 0831-8 issued by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated August 31, 2020), "Reporting of Post-marketing Adverse Reactions, etc. and Adverse Reactions in Clinical Trials, etc. in Response to E2B (R3) Implementation Guide" (PSEHB/PED Notification No. 0831-12 and PSEHB/SD Notification No. 0831-3 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated August 31, 2020), "Reporting of Adverse Reactions, etc. in Clinical Trials by Sponsor-investigators" (PSEHB/PED Notification No. 0831-13 issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated August 31, 2020), "Reporting of Clinical trial product Defects or Adverse Events, etc. Relevant to Machinery/equipment to Pharmaceuticals and Medical Devices Agency" (PSEHB Notification No. 0831-9 issued by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated August 31, 2020), and "Points to Consider, etc. for Reporting of Clinical Trial Product Defects

or Adverse Events, etc. relevant to machinery/equipment, etc. to Pharmaceuticals and Medical Devices Agency" (PSEHB/MDED Notification No. 0831-10 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated August 31, 2020). The reporting method (including reporting forms) shall be in accordance with the method of reporting defects or adverse events, etc. relevant to products used in clinical studies shown in Director Notification and this notification.

(10) Others

1) In an emergency situation that requires discontinuation of the clinical study, the initial report should be sent by fax or e-mail after contacting the Review Planning Division, Office of Review Management, PMDA by phone in advance. In this case, the date of receiving the report shall be regarded as the date of reporting, but a formal report shall be submitted at a later date. In addition, the initial report should not be included in the number of times of reporting to PMDA. If sending the report by fax, the currently available information shall be entered in the applicable fields of Attached Form 1 of Director Notification, with a clear statement of "Report by FAX (e-mail)/To the Review Planning Division, Office of Review Management, PMDA" to send the report by FAX (e-mail).
2) Even if sufficient descriptions necessary for case reporting or information for evaluation cannot be obtained within the deadline specified in Article 275-3, Paragraph 1, Items 1 to 3 and Paragraph 2, Items 1 to 3 of the Enforcement Regulation of the Act, the initial report should be submitted within the deadline as long as information on defects or adverse events, etc. that can be judged to be serious and unexpected (such as the status of health injury in subjects, etc. or the status of investigational product defects or adverse events) has been obtained at least, in light of the purpose of the emergency reporting.
3) Reporting shall be done for each study identification code.
4) In the case of joint development, a report on defects or adverse events, etc. should be made in joint names in principle.
5) If there are any attachments, submit one copy. In principle, MedWatch report forms and other safety information, etc. reported to medical institutions do not need to be attached. However, the presentation or submission may be requested as necessary.