Safety Operations for ICCC in Clinical Trials Explanation to Sponsors

Introduction

In 2023, the Japan CRO Association established a new working group to examine Pharmacovigilance (PV) activities, including exploring issues and standardization related to safety operations for the In-Country Clinical Caretaker (ICCC).

As part of this effort, we have created a comprehensive document to explain Japan-specific safety operations to foreign clinical trial sponsors.

Please note that this document is based on information as of January 2025. Contents may be subject to change due to new notifications or other developments, so please keep this in mind when referencing.

Prepared in February 2025
Japan CRO Association (General Incorporated Association)
PV Working Group

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Chapter 1. Reflecting Japan-Specific Regulations in the Safety Management Plan (SMP)

1.1. Overview Explanation

The pharmaceutical regulations in Japan are prepared in accordance with the agreements of ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use). However, many interpretations and operations differ from other countries. In particular, when foreign clinical trial sponsors conduct clinical trials through ICCC (In-Country Clinical Caretaker) in Japan, differences in safety reporting requirements between Japan and other foreign countries often lead to reporting delays or omissions. To resolve these issues, it is recommended to clarify the roles and operational points of the sponsor, ICCC, and other related vendors in agreed documents such as the Safety Management Plan (SMP). This document aims to comprehensively cover the points of caution regarding the handling of safety information and serve as a guide to the safety reporting regulations in Japan for foreign vendors planning clinical trials in Japan.

1.2. Mandatory Preparations Before Clinical Trial Notification Submission

In Japan, the obligation to report safety information begins on the day the initial clinical trial notification (CTN) is submitted to the Pharmaceuticals and Medical Devices Agency (PMDA). Therefore, at the time of submitting the CTN, it is necessary to have a system in place to submit all safety reports, including those concerning the test drug, especially individual case reports, research reports, and a foreign regulatory measures reports.
In Japanese clinical trials, a concept similar to theEU "Auxiliary Medical Products" has been introduced in the form of "Drugs used in the clinical trial (DUCT)" (including medical devices and regenerative medical products), and different responses (preparations) may be required for each trial.
Depending on the nature of each trial and the type of work undertaken, the necessary preparations and preparation periods will vary. However, it is essential to finalize the SMP, which outlines the division of responsibilities and agreed procedures with foreign clinical trial sponsors, and to prepare for necessary tasks such as literature searches before submitting the CTN.

Chapter 2: Period of Safety Reporting Obligations

2.1. Reporting to Regulatory Authorities

2.1.1. General Matters

2.1.1.1. Beginning of Reporting Obligations

In Japan, the regulatory obligation for safety reporting begins on the date of the initial CTN submission, not at the time of First Patient In (FPI) at domestic clinical trial sites.
Therefore, since safety information from the submission date of the initial CTN (which serves as the date of receipt of information and the start of regulatory reporting: Day 0) is subject to reporting to the authorities, it is essential to establish an agreement between the foreign sponsor and ICCC regarding the handling of safety information before the submission of the initial CTN. Additionally, the agreement and signing of the SMP must be completed by the date of the initial CTN submission.

2.1.1.2. Regarding the Termination of Reporting Obligations

The safety reporting obligation continues until the day the notification of development discontinuation is submitted or the date of marketing authorization. It is important to note that this reporting obligation does not end upon the Last Patient Last Visit (LPLV) at domestic clinical trial sites or the submission of the clinical trial completion notification.
Even if ICCC receives safety information after the development discontinuation notification or marketing authorization date (Approval date), if the foreign sponsor obtained the information before the notification or Approval date, it must still be reported.
For DUCT other than Test Drug (DUCT OT), the termination period may differ, so refer to Section 2.1.2.2.

2.1.2. Period of Safety Reporting Obligations to Regulatory Authorities for Test Drug and DUCT OT

The period of safety reporting obligation to regulatory authorities for Test Drug and DUCT OT is as follows.

[Reference]
(Notification) PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3, "Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" Reference Material 1

2.1.2.1. Test Drug

The period for reporting safety information regarding the test drug begins from the date the initial CTN is

submitted for the test drug and continues until one of the following conditions is met:
1. Until the test drug obtains marketing authorization.
2. Until a development discontinuation notification is submitted for the test drug.

If the submission of a CTN is not required, the period begins from the start date specified in the clinical trial protocol for the test drug and continues until one of the following conditions is met:
1. Until the test drug obtains marketing authorization.
2. Until a written notification (in free format) regarding the discontinuation of the test drug's development is submitted to the Review Planning Division, Office of Review Management of PMDA.

2.1.2.2. DUCT OT
The period for reporting safety information regarding DUCT begins from the date the CTN for the clinical trial using the DUCT is submitted, and continues until one of the following conditions is met:
1. Until a clinical trial completion notification or clinical trial discontinuation notification for the relevant clinical trial is submitted.
2. Until the test drug used in the relevant clinical trial obtains marketing authorization.
3. Until a development discontinuation notification for the test drug is submitted.

If the submission of a CTN is not required, the period begins from the start date specified in the clinical trial protocol for the DUCT and continues until one of the following conditions is met:
1. Until the end date of the period specified in the clinical trial protocol for the DUCT.
2. Until the test drug used in the relevant clinical trial obtains marketing authorization.
3. Until a written notification (in free format) regarding the discontinuation of the test drug's development is submitted to the Review Planning Division, Office of Review Management of the PMDA.

2.2. Reporting to Clinical Trial Sites
2.2.1. Beginning of Reporting Obligations
As stipulated in Article 20 of GCP Reference Material 9, the sponsor must provide safety information, such as adverse drug reaction information, to the principal investigator and the head of the clinical trial site. Since there is no specific provision in GCP regarding the beginning of safety information provision, it will begin based on agreements with each clinical trial site.

2.2.2. Termination of Reporting Obligations
GCP does not specifically stipulate when the obligation to report safety information ends. However, the Japan Pharmaceutical Manufacturers Association (JPMA), a voluntary organization consisting of 70 R&D-oriented pharmaceutical companies in Japan (as of April 1, 2024), has provided the following response to Question (8) from Clinical Trial Hotline No. 119, regarding the timing for Termination of Safety Information Provision by Clinical Trial Sponsors (Part 1):
The purpose of Article 20 of GCP Reference Material 9 *is to ensure that the sponsor provides the principal investigator and the head of the clinical trial site with the latest safety information and ensures that maximum care is taken to protect the safety of subjects during the trial. This is intended to prevent the expansion of health hazards caused byDUCT. Therefore, it is considered that the sponsor should continue to provide safety information at least until the administration and observation periods defined in the clinical trial protocol are completed. After that point, the need for further safety information should be determined by each clinical trial site.*

[Reference]
JPMA website, Clinical Trial Q&A No. 119 (January 15, 2024, Edition), JPMA Committee on Drug Evaluation, Subcommittee on Clinical Evaluation Reference Material 2

Chapter 3. Reporting to Regulatory Authorities
3.1. Reporting Scope
3.1.1. DUCT
3.1.1.1. Definition
A test drug refers to a drug that is the subject of a clinical trial, and the objective of the trial is to apply for marketing authorization based on the trial results. The primary test drug refers to the single test drug in the case of trials with one product, or, in the case of multiple test drugs on the initial CTN, the one selected by the sponsor. Medical devices, for which the trial results will be used to apply for marketing authorization

(hereinafter referred to as "test device"), and regenerative medical products (hereinafter referred to as "test regenerative medical product"), are handled in the same manner as the test drug.
"DUCT" refers to a test drug, comparator, concomitant medication, rescue drug, or pre-administration drug that is designated in the clinical trial protocol to evaluate the efficacy and safety of the test drug. It should be noted that DUCT is not limited by whether or not its active ingredient is approved domestically or overseas. Additionally, medical devices (hereinafter referred to as "device used in the clinical trial") and regenerative medical products (hereinafter referred to as "regenerative medical product used in the clinical trial") designated in the clinical trial protocol to evaluate the efficacy and safety of the test drug will also be handled in the same manner as DUCT.

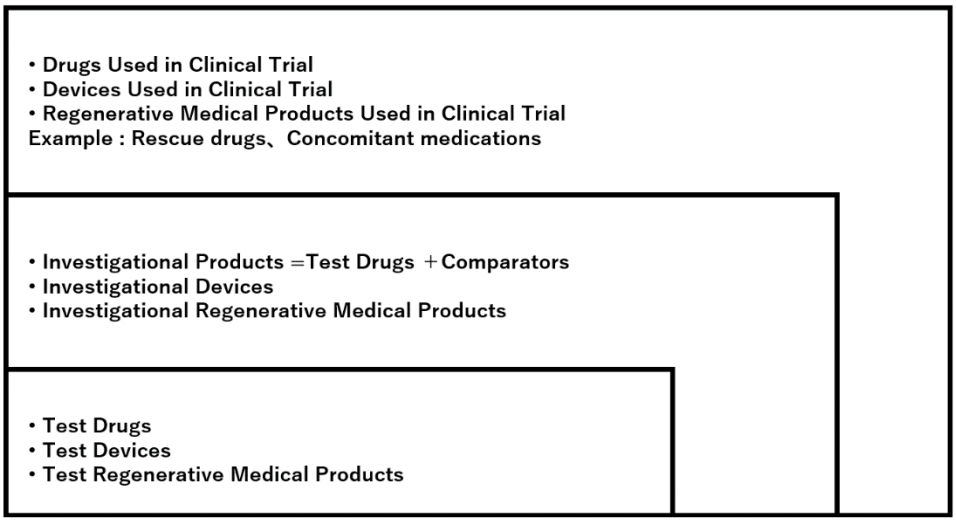

Image Diagram

[Reference]
(Notification) PSEHB/PED Notification No. 0831-10, "Handling of Notifications for Clinical Trial Plans Involving Drug Investigations by Sponsors" Reference Material 3

3.1.1.2. Points to Note
Be aware that the scope of safety information to be reported differs between the primary test drug and DUCT OT. Additionally, ensure that the details regarding the reporting scope and timeline are specified in the procedures to comply with regulations. When reporting to regulatory authorities, it is essential to set the timeline considering the working hours of ICCC. Details are explained in Section 3.1.2.

3.1.2. List of Safety Information to be Reported
The following reports are required in Japan:

- Individual case report (adverse drug reactions, malfunctions, and infections)
- Research report
- Foreign regulatory measures report
- Annual report

The scope and timelines for reporting must be specified in the procedures. The scope of each report and points to consider are explained below.

3.1.2.1. Individual Case Reports
3.1.2.1.1. Scope
DUCT is subject to reporting. The reporting scope and timeline are outlined below. If the reporting deadline falls on a non-business day for the PMDA, the deadline will be extended to the next business day.

Test drug
Information to be reported: This includes information from domestic clinical trials, clinical trials outside Japan, and non-clinical trial use outside Japan (such as post-marketing cases, compassionate use programs, literature, etc.).

Expectedness	Seriousness	Reporting Timeline
Unexpected	Fatal or life-threatening	Within 7 days (additional report within 15 days*)
Unexpected	Other serious cases	Within 15 days
Expected	Fatal or life-threatening	Within 15 days
Expected	Other serious cases	Not required

DUCT OT
Information to be reported: This includes information from domestic clinical trials and clinical trials outside Japan**.

Expectedness	Seriousness	Reporting Timeline
Unexpected	Fatal or life-threatening	Within 7 days (additional report within 15 days*)
Unexpected	Other serious cases	Within 15 days
Expected	Fatal or life-threatening	Within 15 days
Expected	Other serious cases	Not required

* If additional reportable information is obtained for a case already reported within 7 days, a additional report must be submitted within 15 days. However, if new information requiring a 7-day report (such as a new adverse event, change in the adverse event term, or change in seriousness or criteria for seriousness) is obtained, a additional report must be submitted within 7 days.
** Reports from clinical trials outside Japan are limited to information from clinical trials that use the relevant test drug.

Additionally, the reporting scope for clinical trials used in applications for partial changes to approval concerning additions, modifications, or deletions related to dosage and administration, or indications and effects (Clinical trials for partial change of approval), is as follows.

Test drug
Information to be reported: This includes information from domestic clinical trials (for foreign cases, refer to Section 5.3).

Expectedness	Seriousness	Reporting Timeline
Unexpected	Fatal or life-threatening	Within 7 days (additional report within 15 days*)
Unexpected	Other serious cases	Within 15 days
Expected	Fatal or life-threatening	Within 15 days
Expected	Other serious cases	Not required

DUCT OT
Information to be reported: This includes information from domestic clinical trials.

Expectedness	Seriousness	Reporting Timeline
Unexpected	Fatal or life-threatening	Within 7 days (additional report within 15 days*)
Unexpected	Other serious cases	Within 15 days
Expected	Fatal or life-threatening	Within 15 days
Expected	Other serious cases	Not required

* If additional reportable information is obtained for a case already reported within 7 days, a additional report must be submitted within 15 days. However, if new information requiring a 7-day report (such as a new adverse event, change in the adverse event term, or change in seriousness or criteria for seriousness) is obtained, an additional report must be submitted within 7 days.

[Reference]
(Administrative Notice), "Revision of Q&A on Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" Reference Material 4

3.1.2.1.2. Determination of Expectedness
The Investigator's Brochure (IB) for the test drug will be used to assess the expectedness of the test drug. It should be noted that the same IB will be used for information received from foreign sources. For DUCT OT, a document detailing scientific knowledge must be specified in the clinical trial notification, and expectedness will be evaluated based on that document.

3.1.2.1.3. Definition of "malfunctions that may lead to serious outcomes" of Medical Devices or Regenerative medical product
In the clinical trials listed below, similar reporting obligations also apply to medical devices and regenerative medical products:

- When a test device or device used in the clinical trial is used
- When a test regenerative medical product or regenerative medical product used in the clinical trial is

used
For medical devices and regenerative medical products, note that, in addition to serious adverse reactions, "malfunctions that may lead to serious outcomes" (where a malfunction has occurred, no serious adverse event has occurred, but the malfunction could potentially lead to a serious adverse event) are also subject to reporting.

3.1.2.1.4. Reporting of Post-Marketing Cases from Foreign Countries
In Japan, depending on the domestic approval status of the test drug for which a CTN has been submitted, it is important to note that cases from all information sources other than clinical trials in foreign countries (such as post-marketing cases, compassionate use programs, literature, etc.) may also need to be reported.
If another domestic company conducts a separate clinical trial on the same test drug, ICCC and the domestic company must report the same foreign adverse drug reaction case from each company.

3.1.2.1.5. Reporting of Cases from Clinical Trials Conducted by Other Domestic Companies
There is no need to report domestic cases from clinical trials conducted by other domestic companies. However, it is important to ensure appropriate information exchange.

[Reference]
(Notification) PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3, "Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" Reference Material 1

3.1.2.1.6. Reporting from Non-Healthcare Professionals
For foreign cases where information comes from non-healthcare professionals, such as patients or their family members, cases that the sponsor determines to have no causal relationship may be excluded from reporting.

[Reference]
(Notification) PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3, "Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" Reference Material 1

3.1.2.2. Research Reports
3.1.2.2.1. Overview
If information specified in Section 3.1.2.2.2 is obtained regarding the test drug, it must be reported to the regulatory authorities within 15 days. Foreign sponsors and ICCC must establish procedures to obtain this information in a timely manner.

3.1.2.2.2. Subject to Reporting
The following research reports must be submitted to regulatory authorities. However, research reports that do not impact the evaluation of efficacy or safety for the target disease of the clinical trial of the test drug are excluded.

- Research reports indicating that adverse reactions to the test drug or infections caused by its use could lead to cancer, other serious diseases, disabilities, or death.
- Research reports showing significant changes in the number of occurrences, frequency, or conditions of occurrence of diseases suspected to be caused by adverse reactions to the test drug or infections suspected to be caused by its use.
- Research reports indicating that the test drug has no efficacy or effect on the target disease of the clinical trial.

"Possibility of causing cancer, other serious diseases, disabilities, or death" refers to cases where the results of epidemiological studies, animal studies, physical tests, or chemical tests indicate the occurrence or potential occurrence of serious diseases (such as cancer, hearing loss, blindness, etc.) due to adverse reactions to the test drug or infections caused by its use.
"Significant changes in the number of occurrences, frequency, or conditions of occurrence of diseases suspected to be caused by adverse reactions to the test drug or infections suspected to be caused by its use" refers to clear changes in the number of occurrences, frequency, conditions (for example, while overall changes in the number or frequency may not be large, stratified analysis may reveal significant increases in certain age groups, comorbidities, methods of use, dosage, etc.), symptoms, or severity of diseases suspected to be caused by adverse reactions or infections caused by the test drug.

"Lack of efficacy or effect on the target disease of the clinical trial" refers to cases where detailed and objective clinical trials or animal studies indicate that the test drug or its active ingredient does not have efficacy or effects on the target disease of the clinical trial.

"Research reports that do not impact the evaluation of efficacy or safety for the target disease of the clinical trial of the test drug " refers to cases where, for example, expected adverse reactions in the clinical trial have already been addressed with safety measures for subjects (such as exclusion of certain subjects or planning appropriate testing during the clinical trial) or where there is no observed increase in the number or frequency of diseases suspected to be caused by adverse reactions to the test drug or infections suspected to be caused by its use.

[Reference]

(Ministerial Ordinance on theEnforcement Regulations of the PMD Act "Article 273, Paragraph 2, Item 2 (iv)" Reference Material 5

(Notification) PSEHB Notification No. 0831-8, "Reporting of Clinical Trial Adverse Drug Reaction, etc., to the Pharmaceuticals and Medical Devices Agency" Reference Material 6

3.1.2.3. Foreign regulatory measures reports

3.1.2.3.1. Overview

If information specified in Section 3.1.2.3.2 is obtained regarding the DUCT, it must be reported to the regulatory authorities within 15 days. Foreign sponsors and ICCC must establish procedures to obtain this information in a timely manner.

3.1.2.3.2. Subject to Reporting

The following actions must be reported to the regulatory authorities. However, for DUCT OT, reporting is limited to measures taken to prevent the occurrence or spread of health hazards when used in combination with the test drug.

- Actions such as the cessation of manufacture, import, or sale, recall, disposal, or other measures to prevent the occurrence or spread of health hazards for products used abroad that are recognized as having the same ingredients as DUCT.

"Cessation of manufacture, import, or sale, recall, disposal, or other measures to prevent the occurrence or spread of health hazards for products used abroad that are recognized as having the same ingredients as DUCT" includes not only cessation due to concerns about efficacy or safety abroad but also changes in indications, usage and dosage, manufacturing methods, and revisions to important precautions such as the distribution of doctor letters. However, if the report is for a product with a different route of administration and it is clear that the safety information depends on that route of administration, the report may be omitted.

"Measures to prevent the occurrence or spread of health hazards for DUCT OT when used in combination with the test drug" refers to measures taken to address the high likelihood of the occurrence or spread of health hazards when the DUCT OT is used in combination with the test drug in the clinical trial among the measures to prevent the occurrence or spread of health hazards related to DUCT OT.

If a measure involving a DUCT that is either in an ongoing clinical trial for application for approval of the test drug or has completed all clinical trials of the test drug and is in the application preparation or submission stage is taken for a domestically marketed drug with the same ingredients, and this measure is expected to affect the content of the clinical trial or the application, a foreign regulatory measures report regarding the DUCT must be submitted immediately within the reporting deadline.

[Reference]

(Ministerial Ordinance on the Enforcement Regulations of the PMD Act) "Article 273, Paragraph 2, Item 2 (iii)" Reference Material 5

(Notification) PSEHB Notification No. 0831-8, "Reporting of Clinical Trial Adverse Drug Reaction, etc., to the Pharmaceuticals and Medical Devices Agency," Reference Material 6

(Notification) PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3, "Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" Reference Material 1

3.1.2.4. Annual Reports

3.1.2.4.1. Overview

For annual reports, as specified in Section 3.1.2.4.2, in addition to the DSUR (Development Safety Update Report), Japan-specific forms must be submitted to the regulatory authorities. These forms must be prepared in Japanese, and certain items are based on the contents of the DSUR. Therefore, it should be noted that

preparation will require time for the ICCC. Foreign sponsors and ICCC must set a timeline for providing the DSUR to ICCC, taking into account the time required to prepare the Japan-specific forms.

3.1.2.4.2. Content and Forms for Submission

The following documents must be submitted to the regulatory authorities. For DUCT OT, the annual report must be submitted in combination with the test drug. DSUR is not required for DUCT OT.

- Summary of the Development Safety Update Report (Attachment Form 1)
- List of the Occurrence Status of Serious Adverse Drug Reactions etc. in Japan (Attachment Form 2)
- DSUR

Attachment Form 1 includes information about the test drug, such as "approval status in major advanced countries," as well as information on DUCT OT. The section "Conclusions and safety measures based on the assessment of serious adverse reactions and other safety information (non-clinical trial data, foreign clinical trial data, post-marketing data, etc.)" is primarily based on the DSUR contents (particularly the executive summary).

Attachment Form 2 lists all serious adverse reaction cases reported from domestic clinical trials. This form is prepared for each DUCT.

Regarding the DSUR, if it is written in English, a Japanese translation is not required. However, attaching a Japanese translation is also acceptable.

3.1.2.4.3. Subject to Reporting

The following is subject to reporting for the test drug and DUCT OT.

Expectedness	Seriousness	Test drug		DUCT OT	
		Domestic	Foreign	Domestic	Foreign
Unexpected	Fatal or life-threatening	○	○	○	-
	Other serious	○	○	○	-
Expected	Fatal or life-threatening	○	○	○	-
	Other serious	○	○	○	-

3.1.2.4.4. Reporting Timeline

The report must be submitted every year, starting from the date the initial clinical trial plan for the test drug was notified, within two months after the end of that period. If two months is less than 60 days, the report must be submitted within 60 days. For DUCT OT, the report should be submitted according to the test drug’s reporting period.

3.1.2.4.5. Submission of Final Report

The reporting obligation period for the test drug is from the date the initial CTN is submitted until the Approval date or a development discontinuation notification is submitted.

For DUCT OT, the reporting obligation period is from the date the notification for the clinical trial using the DUCT is submitted and continues until either the clinical trial completion notification or clinical trial discontinuation notification is submitted, marketing authorization for the test drug is obtained, or a development discontinuation notification for the test drug is submitted.

The final periodic report after marketing authorization is obtained or the development discontinuation notification is submitted must be reported within two months from the date of authorization or submission of the development discontinuation notification. This report should be submitted using the "Clinical Trial Safety Report Summary (Attachment Form 1)" and the "List of the Occurrence Status of Serious Adverse Drug Reactions etc. in Japan (Attachment Form 2)."

3.1.2.4.6. Communication in Joint Submissions by Multiple CROs

When multiple parties are jointly developing a pharmaceutical product, it is recommended that a single annual report be prepared and submitted under the joint names of the parties involved, with one acting as the representative. If multiple CROs are involved in the development of the test drug, the foreign sponsor and ICCC must establish procedures for communication between the CROs. If it is not possible to prepare a single annual report, it is permissible for each co-developer to submit their own report. The foreign sponsor must ensure that each ICCC's annual report includes all relevant information about the clinical trials being conducted domestically.

[Reference]
(Ministerial Ordinance on the Enforcement Regulations of the PMD Act) "Article 273, Paragraph 4," Reference Material 5

(Notification) PSEHB/PED Notification No. 0831-14, "Points to Consider for Periodic Reporting of Clinical Trial Adverse Drug Reaction Cases" Reference Material 7

3.2. Reporting Timelines and Points to Note

3.2.1. Reporting Timelines

As indicated in Section 3.1.2.1.

3.2.2. Timelines for Additional Reporting of 7-Day Reported Cases

As indicated in Section 3.1.2.1.1.

For cases already reported within 7 days, if additional reportable information is obtained, an additional report must be submitted within 15 days. However, if new information that must be reported within 7 days (such as a new adverse event, a change in the name of the adverse event, or a change in the seriousness or seriousness criteria) is obtained, an additional report must be submitted within 7 days

3.2.3. Timelines for Corrective Reporting

Although no specific timeline is indicated in the notification, the response should be prompt.

3.2.4. Timelines for Non-Targeted Additional Reporting

Although no specific timeline is indicated in the notification, the response should be prompt.

3.2.5. Timelines for Withdrawal Reporting

Although no specific timeline is indicated in the notification, the response should be prompt.

3.3. Literature Search

3.3.1. Overview

Literature searches in clinical trials are conducted to comprehensively collect information from literature and conference presentations that may include the contents of individual case reports of adverse reactions and infections and research reports subject to safety reporting as stipulated in Article 273 of the Enforcement Regulations of the PMD Act.

It is necessary to search for literature information on the test drug and DUCT OT used in domestic clinical trials and clinical trials outside Japan. If the sponsor conducts the literature search and collection for foreign literature, the sponsor should follow procedures that ensure the use of appropriate search strategies capable of identifying literature that may be relevant to individual case reports and research reports in Japan. This includes procedures for sharing information about individual case reports (whether sharing the literature only or through individual case reports such as CIOMS).

On the other hand, when ICCC conducts a literature search and collection for Japanese local literature, the procedure for providing information to the sponsor should also follow predetermined agreements.

Additionally, Article 273 of the Enforcement Regulations of the PMD Act requires the foreign regulatory measures reports on test drugs used in clinical trials, and it is necessary to search for and collect information on measures taken by regulatory authorities in various countries regarding test drugs used in trials.

[Reference]
(Notification) PSEHB Notification No. 0831-8, "Reporting of Clinical Trial Adverse Drug Reaction, etc., to the Pharmaceuticals and Medical Devices Agency" Reference Material 6

3.3.2. Literature Search from Literature Databases by Literature Search Companies

The comprehensive collection of literature that may be subject to individual case reports and research reports is essential. Appropriate search conditions must be used to search literature databases, and any relevant literature identified through the search must be promptly collected.

Therefore, it is common to request such searches from literature search companies.

In clinical trials for biosimilars, safety information for the reference biopharmaceutical product is also required by regulatory authorities, so literature searches should include the reference product as well.

Information on measures by regulatory authorities in various countries related to the foreign regulatory measures reports is collected through searches of regulatory authority websites, and this is also often outsourced to literature search companies.

3.3.3. Implementation Period

According to regulatory notifications, the reporting obligation period for the test drug is from the date the initial CTN is submitted until the Approval date or a development discontinuation notification is submitted.
For DUCT OT, the reporting obligation period is from the date the CTN is submitted until either the clinical trial completion notification or clinical trial discontinuation notification is submitted, the Approval date for the test drug is obtained, or a development discontinuation notification for the test drug is submitted. Thus, literature searches for individual case reports and research reports concerning DUCT OT used in the clinical trial must be conducted during the corresponding reporting period.

[Reference]
(Notification) PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3, "Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" Reference Material 1

3.3.4. Retrospective Search

The literature search period described in Section 3.3.3 begins from the submission date of the initial CTN and continues with ongoing literature searches. The contents of any literature subject to regulatory reporting must be reported. It is necessary to ensure that the literature required for adverse reaction reports is comprehensively searched from the beginning.
If the search strategy is modified to appropriate search criteria during the trial period, it is necessary to perform a retrospective search using the appropriate search conditions for the period before the change, and any literature subject to regulatory reporting must be retrospectively reported.

3.4. Reporting Format and Method

When reporting to the PMDA, it is necessary to prepare a report in a unique format based on Japan's regulatory requirements, including the addition of Japan-specific items in addition to the ICH ICSR data items specified in ICH E2B (R3). Submission of only English documents (e.g., CIOMS I) or translations will not be accepted. Therefore, sufficient time is required for ICCC between the provision of safety information from the foreign sponsor to ICCC and the PMDA reporting.

3.5. Points to Note Regarding Causality Assessment

If both the reporter and the sponsor judge that "causality can be denied," the case does not need to be reported as a "case with denied causality." In other cases, the case must be treated as one where "causality cannot be denied." If the investigator assesses the causality as unknown, even if the sponsor judges that causality can be denied, the case must be reported as an adverse drug reaction.
Additionally, as clarified in a Q&A issued by the regulatory authorities, "suspected to be caused by adverse reactions" refers to cases other than those where "causality can be denied," and cases where "causality is unknown" must also be reported ("Administrative Notice on Revision of Q&A on Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" issued on August 10, 2023, A1). It is required that cases be reported unless causality is denied.

3.6. Points to Note Regarding Delayed Reporting

3.6.1. Response in Case of Delayed Reporting

If delayed reporting occurs, the PMDA must be notified of the delay along with the report to PMDA, and a report on the reason for the delay (CAPA) and summarizing preventive measures must be promptly submitted. The report on the reason for the delay should explain the circumstances, causes, preventive measures, and whether similar delays have occurred in the past. The report should be prepared in cooperation between the sponsor and ICCC. Once ICCC prepares a draft report, it should be submitted to the PMDA as a draft report on the reason for the delay. If the PMDA approves the content after review, the report will be formally submitted. The procedures for response are not publicly specified by the PMDA, and instructions are given on a case-by-case basis.

3.6.2. Requests for the Sponsor in the CAPA

Since the report on the reason for the delay must include details of the circumstances, reasons for the delay, and corrective and preventive measures, the sponsor should be requested to provide detailed actions, dates, and other relevant information.

3.6.3. Impact of Delayed Reporting

Although not clearly stated in notifications or Q&A, in serious cases, the PMDA may consider suspending clinical trials or suspending approval reviews until appropriate systems are in place.
ICCC may face additional work due to preparation of the report on the reason for the delay and communication with the sponsor and the PMDA.
If the CAPA is not completed by the end of the project, ICCC may be required to continue addressing the issue until the PMDA's approval is obtained, possibly resulting in a contract extension with the sponsor.

3.6.4. Format of the Report on the Reason for the Delay

There is no official format for the report on the reason for the delay, and companies are instructed to include necessary items based on the PMDA's guidance. Typically, the following items are requested to be included:

- Overview of the report for the relevant case
    - Information on the ongoing clinical trial
    - Primary test drug code
    - Case identification number (not required for the report on the reason for the delay in the annual report)
    - Reporting start date
    - Reporting due date
    - Date of report submission to the authorities
    - Number of days delayed
    - Number of reports to the agency
    - Name of the adverse reaction (for individual case reports)
    - Overview of the report (for research reports or reports on measures taken overseas)
    - Type of report (7-day report, 15-day report), etc.
- Circumstances from the receipt of information to the report submission
- Reason for the delay in meeting the reporting deadline stipulated in Article 273 of the Enforcement Regulations of the Pharmaceuticals and Medical Devices Act
- Corrective actions
- Preventive actions
- Whether there have been other delays for similar reasons

3.6.5. Due date for Submission of the Report on the Reason for the Delay and PMDA Review Timeframe

There is no specific due date for submission, but prompt action is required. If there is a delay in response, the PMDA may contact ICCC by phone to inquire about the situation and follow up. There is also no specific timeframe for the PMDA's review period.

Chapter 4. Site Reporting

4.1. Reporting Scope

Individual Case Reports: Among the serious adverse reactions related to the DUCT listed in Article 273 of the Enforcement Regulations of the Pharmaceuticals and Medical Devices Act, those that cannot be expected based on the Investigator's Brochure (IB) for the test drug or the scientific knowledge related to the DUCT OT (J-GCP Article 20, Paragraph 3 Reference Material 9).
However, for the test drug, if the source of information is other than a clinical trial outside Japan, reporting is not required if it is recognized that there is no risk of influencing safety judgments regarding the protection of subjects in the relevant clinical trial.
Note that even if the test drug used in a clinical trial for partial change does not require a PMDA report, it may still be subject to site reporting(Points to Note on Regulatory Amendments Regarding the Handling of Safety Information for Investigational Drugs in Clinical Trials Reference Material 13).
Annual Trial Report: Among the serious adverse reactions related to the DUCT listed in Article 273 of the Enforcement Regulations of the Pharmaceuticals and Medical Devices Act, information after the date of the initial CTN for the test drug (J-GCP Article 20, Paragraph 2 Reference Material 9).

4.2. Reporting Timeline

Individual Case Reports: Immediately (J-GCP Article 20, Paragraph 3 Reference Material 9).
Although a specific reporting timeline is not defined, a 30-calendar-day timeframe is commonly used. In some cases, this may be stipulated in advance in the procedures. It is also possible to set a different reporting timeline from the test drug for DUCT OT.

4.3. Reporting Format and Method

4.3.1. Reporting Format

4.3.1.1. JPMA Line List

In a proposal from the Japan Pharmaceutical Manufacturers Association (JPMA) in 2009, the use of a common line listing format written in Japanese for individual case reports, compliant with the provisions of GCP Ordinance Article 20 Reference Material 9, was recommended.
Also, it is important to note that many clinical trial sites do not accept reports submitted in English only, such as CIOMS forms.

4.3.1.2. Other

To ensure that safety information reports to clinical trial sites include key points relevant to the drug profile, the use of a common summary table for individual case reports, in addition to the JPMA line list, has been proposed by JPMA. There may also be requests from clinical trial sites or IRBs for the provision of additional documentation that supplements the information not covered by the line list. While it is not prohibited to submit materials in formats other than the recommended format, using the JPMA-recommended format is generally the standard practice.
The reporting formats for research reports, reports on measures taken overseas, and annual reports should be defined in the procedures in advance.

4.3.2. Reporting Method

4.3.2.1. Reporting Frequency

There are no specific regulations regarding reporting frequency. Assuming reports are submitted within 30 calendar days of receiving the information, it is common practice to compile and report multiple cases approximately once every two weeks.

4.3.2.2. Reporting Method

Safety information is typically reported to the principal investigator and the head of the clinical trial site through the clinical development department (e.g., CRAs) rather than directly by ICCC's Pharmacovigilance (PV) department. However, the reporting method is essentially based on agreements with the clinical trial site. Afterward, the head of the clinical trial site reports the safety information to the IRB (J-GCP Article 40, Paragraph 1 Reference Material 12).

4.4. Others

4.4.1. Gap Pack

For the initial IRB submission, it may be necessary to provide safety information as part of the materials related to the safety of trial subjects, up until the date of the CTN submission in Japan (e.g., unexpected serious adverse events related to the test drug from the day after the IB cutoff date to the day before the CTN submission). If the trial has already commenced overseas, it may be necessary to include information on foreign cases related to the trial, as well as cases from other trials using the same test drug or post-marketing cases, depending on the development status of the test drug. When preparing materials for the IRB submission in Japan, the sponsor should consult with ICCC in advance regarding the scope of the report and ensure that the necessary information is provided to ICCC.

4.4.2. Termination of the Reporting Period

There are no specific regulations on how long safety information must continue to be notified and provided to the principal investigator and the head of the clinical trial site. However, considering the intent of Article 20 of the J-GCP Reference Material 9, it is generally expected that the sponsor (ICCC) should continue providing safety information at least until the administration and observation specified in the clinical trial protocol are completed. After that, the necessity of continuing to provide safety information is left to the decision of each clinical trial site, and once agreement is obtained from all participating clinical trial sites, safety reporting can be terminated.

[Reference]
Japan Pharmaceutical Manufacturers Association Website: "(8) Timing for Termination of Safety Information Provision by Clinical Trial Sponsors (Part 1)" Reference Material 8

5. Others

5.1. Collaboration in Cases Where Multiple ICCCs Are Involved

Annual reports are, in principle, submitted for each active ingredient. In the case of joint development, a single annual report should be prepared whenever possible, and the representative should submit it in the joint names of the co-developers.

[Reference]
(Notification) PSEHB/PED Notification No. 0831-14, "Points to Consider for Periodic Reporting of Clinical Trial Adverse Drug Reaction Cases" Reference Material 7

5.2. Communication with PMDA
Except in emergencies, inquiries should be submitted via email by completing the required fields on the inquiry form. If email communication is difficult, fax may also be used; however, it is recommended to confirm receipt by phone after sending. Responses from the PMDA will be provided via telephone. For further details on the inquiry procedure, please refer to the reference material below.

[Reference]
PMDA Website: "Inquiries Regarding Submission of CTNs and Reports of Clinical Trial Adverse Drug Reaction/Malfunctions, etc. (for Sponsors)" Reference Material 10
https://www.pmda.go.jp/review-services/trials/0020.html

5.3. Exception Handling
For clinical trials conducted for partial change applications (e.g., changes in indications, dosage, and administration) for pharmaceuticals already approved domestically, if information is appropriately shared between the marketing authorization holder and ICCC, the marketing authorization holder's report on foreign cases can replace ICCC's report. However, the conditions for appropriate information sharing differ between adverse reaction reporting and malfunction reporting, as described below.

For Pharmaceuticals:
A document detailing the reporting and information-sharing procedures for foreign adverse reaction case reports should be prepared in advance between the clinical trial sponsor and the marketing authorization holder and if the document is not submitted to the Office of Review Management, Review Planning Division, PMDA, ICCC must submit report on foreign adverse reaction cases.
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[Reference]
(Notification) PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3, "Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" Reference Material 1

For Medical Devices/ Regenerative Medical Products:
The clinical trial sponsor and marketing authorization holder should establish agreements in advance regarding the reporting and information-sharing procedures for foreign case reports.
[Reference]
(Notification) PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3, "Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" Reference Material 1
(Notification) PSEHB/PED Notification No. 0831-11, "Points to Consider in Reporting Clinical Trial Malfunctions Related to Processed Cells, etc." Reference Material 11

6. Reference Materials
1. "Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" (PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3, August 31, 2020)
   https://www.pmda.go.jp/files/000236397.pdf
   "Partial Amendment to Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" (PSEHB/PED Notification No. 0115-1, PSB/PSD Notification No. 0115-1, January 15, 2024)
   https://www.pmda.go.jp/files/000266330.pdf
2. "Reception of Clinical Trial or GCP-related Inquiries via Clinical Trial Hotline No. 119"
   https://www.jpma.or.jp/information/evaluation/tiken119/index.html#/
3. "Handling of Notifications for Clinical Trial Plans Involving Drug Investigations by Sponsors" (PSEHB/PED Notification No. 0831-10, August 31, 2020)
   https://www.pmda.go.jp/files/000236408.pdf
   "Partial Amendment to Handling of Notifications for Clinical Trial Plans Involving Drug Investigations by

Sponsors" (PSB/PED Notification No. 0820-1, August 20, 2024)
https://www.pmda.go.jp/files/000270151.pdf
4. "Revision of Q&A on Post-marketing Adverse Drug Reaction Reporting and Clinical Trial Adverse Drug Reaction Reporting in accordance with the E2B(R3) Implementation Guide" (Administrative Notice, August 10, 2023)
https://www.pmda.go.jp/files/000263677.pdf
5. Ministerial Ordinance on the Enforcement Regulations of the PMD Act: Articles 273–275, concerning adverse event and malfunction reporting
https://www.mhlw.go.jp/web/t_doc?dataId=81006000&dataType=0
6. "Reporting of Clinical Trial Adverse Drug Reaction, etc., to the Pharmaceuticals and Medical Devices Agency" (PSEHB Notification No. 0831-8, August 31, 2020)
https://www.pmda.go.jp/files/000236487.pdf
7. "Points to Consider for Periodic Reporting of Clinical Trial Adverse Drug Reaction Cases" (PSEHB/PED Notification No. 0831-14, August 31, 2020)
https://www.pmda.go.jp/files/000236400.pdf
"Partial Amendment to Points to Consider for Periodic Reporting of Clinical Trial Adverse Drug Reaction Cases" (PSB/PED Notification No. 1226-3, December 26, 2023)
https://www.pmda.go.jp/files/000266154.pdf
8. "(8) Timing for Termination of Safety Information Provision by Clinical Trial Sponsors (Part 1)" (Japan Pharmaceutical Manufacturers Association Website, Revised March 2021)
https://www.jpma.or.jp/information/evaluation/tiken119/08.html
9. J-GCP (Ministerial Ordinance on Good Clinical Practice for Pharmaceuticals): Article 20, covering adverse event information
https://www.mhlw.go.jp/web/t_doc?dataId=00tc4391&dataType=1&pageNo=1
10. "Inquiries Regarding Submission of CTNs and Reports of Clinical Trial Adverse Drug Reaction/Malfunctions, etc. (for Sponsors)"
https://www.pmda.go.jp/review-services/trials/0020.html
11. "Points to Consider in Reporting Clinical Trial Malfunctions Related to Processed Cells, etc." (PSEHB/PED Notification No. 0831-11, August 31, 2020)
https://www.mhlw.go.jp/content/11120000/000665749.pdf
12. J-GCP (Ministerial Ordinance on Good Clinical Practice for Pharmaceuticals): Article 40, covering clinical trial suspension, etc.
https://www.mhlw.go.jp/web/t_doc?dataId=00tc4391&dataType=1&pageNo=4
13. "Points to Note on Regulatory Amendments Regarding the Handling of Safety Information for Investigational Drugs in Clinical Trials"
（JPMA Pharmaceutical Evaluation Committee Clinical Evaluation Subcommittee Continuing Issues Response Team 4）
https://www.jpma.or.jp/information/evaluation/results/allotment/bbh7c90000000bso-att/CL_202308_safetyPTC.pdf