Essential Considerations for Requesting a Clinical Trial In-Country Representative <For Foreign Sponsor>

Japan CRO Association

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Chapter 1: Purpose and Scope

As globalization of drug development progresses, foreign companies are increasingly planning clinical trials in Japan. There is a regulatory system for these companies (hereinafter referred to as foreign sponsors) to promote drug development in Japan through outsourcing the operations of clinical trials to Contract Research Organizations (CROs). The following is described in the Ministerial Ordinance on Good Clinical Practice for Drugs (hereinafter referred to as J-GCP: Attachment 1-1).

(Clinical Trial In-Country Representative)

In order to take the necessary measures to prevent the occurrence or spread of health hazards due to drugs used in the clinical trial, a person who intends to sponsor a clinical trial and resides outside Japan shall appoint a person eligible for sponsoring the clinical trial on behalf of the person who intends to sponsor a clinical trial from among persons residing in Japan (including the head of a Japanese business office of a foreign company) to have him or her (hereinafter referred to as “Clinical Trial In-Country Representative*”) conduct the procedures for sponsoring the clinical trial (J-GCP Article 15).

*: Clinical Trial In-Country Representative is referred to as an In-country Clinical Caretaker (ICCC) in this document.

This document is designed to outline the key considerations for foreign sponsors when outsourcing the responsibilities of the ICCC to a CRO. It highlights points to be noted and differences between overseas and Japanese systems, as well as Japan-specific regulatory requirements. It is intended to serve as a useful reference when conducting clinical trials in Japan.

Additionally, this document focuses on clinical trials for drugs with new active ingredients. It is also applicable to clinical trials for medical devices or regenerative medicine products, but since some rules are different, it is advisable to consult with the company that entrusts the ICCC when dealing with such products.

Chapter 2: Clinical Trial Organizational Structure and Responsibility Allocation

When a foreign sponsor delegates responsibilities to the ICCC, it is essential to assess whether the trial can be conducted in compliance with Japanese regulatory requirements. If it is difficult for the foreign sponsor to make this judgment independently, it is possible to request confirmation from the ICCC. If the ICCC determines that the trial does not meet Japanese regulatory requirements, it is recommended that the foreign sponsor thoroughly consults with the ICCC regarding the issues and resolves them before commencing operations.

Section 1: Clinical Trial Organizational Structure Including the Foreign Sponsor

According to Article 4 of the Japanese GCP (J-GCP), when a sponsor intends to conduct a clinical trial in Japan, it is necessary to have a structure in place to conduct the clinical trial in Japan such as securing professionals with adequate expertise, preparing standard operating procedures (SOPs), and constructing processes for safety evaluations and regulatory reporting in compliance with Japanese regulations. In some cases, the ICCC can supplement the new functions or responsibilities that are required, so one option is to see if it is possible for the ICCC to respond. It is recommended that the foreign sponsor is provided with the necessary materials and information from the ICCC, confirms any unclear points, and cooperates with the ICCC to comply with the J-GCP and laws and regulations, establishes the necessary clinical trial implementation structure, agrees on the division of work, and documents this agreement.

Section 2: Responsibilities and Roles of the Foreign Sponsor and the ICCC

- **Responsibilities of the ICCC:**

  The ICCC, on behalf of the foreign sponsor, conducts the procedures for sponsoring the clinical trial in Japan. However, the foreign sponsor is required to understand the differences between J-GCP and ICH-GCP, as well as the laws and administrative notices pertaining to clinical trials in Japan. Therefore, it is necessary for the foreign sponsor to confirm methods for sharing information, ensuring that they can promptly obtain any information that may affect the trial, such as amendments to laws or guidelines in Japan during the trial period.

  - ✓ One of the responsibilities of the ICCC is to submit the clinical trial notification (CTN) (see Attachment 2) on behalf of the person who intends to sponsor a clinical trial.
  - ✓ The ICCC is appointed as “a person eligible for sponsoring the clinical trial on behalf of the person who intends to sponsor a clinical trial” and is required to take "the necessary measures to prevent the occurrence or spread of health hazards due to drugs used in the clinical trial." Therefore, the foreign sponsor should not consider the ICCC as merely an organization that handles procedural tasks; rather, they must establish a structure to promptly share information that may affect the continuation of the trial with the ICCC and consult on necessary actions.
  - ✓ If the foreign sponsor has affiliated companies in Japan, it is recommended that the roles and responsibilities of these affiliates, including the ICCC, be agreed upon and documented as necessary.
  - ✓ While the ICCC performs its contracted tasks in accordance with the standards required by J-GCP and fulfills quality assurance and quality control obligations, it is important to note that the foreign sponsor holds the ultimate responsibility for the quality and integrity of the clinical trial data.

#	Responsibilities for Conducting Clinical Trials	Foreign Sponsor	ICCC	Remarks
1	General responsibilities for conducting clinical trials (overseas, domestic)	✓		
2	All procedures for conducting domestic trials (on behalf of the foreign sponsor)		✓	Collaborate with foreign sponsor
3	Acting as the contact point with regulatory authorities		✓	Collaborate with foreign sponsor
4	Submission of CTNs		✓	Collaborate with foreign sponsor
5	Reporting safety information to authorities and clinical trial sites (See Attachment 3)		✓	Collaborate with foreign sponsor
6	Collection and provision of overseas safety information (to ICCC)	✓		
7	Labeling of investigational products	✓	△*	*Confirm labeling contents
8	Retention of trial-related documents (especially documents on the manufacturing and stability of investigational products)	✓	△*	*Storage of imported documents
9	Provision of domestic regulatory information to the foreign sponsor		✓	Regulatory revision information
10	Selection, contracting, and management of domestic vendors		✓	If necessary
11	Submission of clinical trial applications to the Institutional Review Board (IRB)		✓	Collaborate with foreign sponsor
12	Negotiations and contracting with clinical trial sites (including budget negotiations and payment of expenses)		✓	Collaborate with foreign sponsor
13	Delivery of investigational products to clinical trial sites	✓	△*	*Provision of judgment materials
14	Registration of clinical trials with the Japan Registry of Clinical Trials (jRCT)		✓	Collaborate with foreign sponsor
15	Resolution of issues arising in domestic clinical trials		✓	Collaborate with foreign sponsor
16	Compensation responsibility for health damage occurring during the clinical trial	✓	△*	*Provision of information
17	Liability for damages arising from the conduct of the clinical trial	✓		

- **Timeline until the start of the clinical trial**:

  The general flow from the conclusion of the contract with the ICCC to the First Patient First Treatment (FPFT) is as follows. A clinical trial consultation (F2F/Online) with the Pharmaceuticals and Medical Devices Agency (PMDA) is a program that allows consultation with the PMDA prior to submitting the CTN, but is not mandatory from a regulatory perspective. It is recommended that the foreign sponsor thoroughly discusses with the ICCC the necessity of conducting a clinical trial consultation. Please note that if a clinical trial consultation is conducted, it will take approximately two months from the time of application.

Item	Remarks
Contract with ICCC	
Clinical trial consultation with PMDA	Not mandatory, but recommended (see Chapter 3, Section 2)
Feasibility	
CTN	See Chapter 3, Section 2
Obligation to report safety information	See Chapter 3, Section 3
Agreement with the principal investigator	
Request to clinical trial sites for implementation (IRB submission)	
Importation of materials including investigational products	Customs clearance possible with a copy of the CTN
IRB approval	
Contract signing with clinical trial sites	
Delivery of investigational products to clinical trial sites	
Registration of information in jRCT	Required in Japanese and English
Administration of the investigational products	

Chapter 3: Japanese Regulatory Requirements and Practical Considerations

It is important for foreign sponsors to establish a good relationship with the ICCC and have a common understanding with the ICCC before starting work to ensure that the clinical trial is conducted without any delays or trouble. The necessary and major points are outlined below.

Section 1: Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act), J-GCP, Guidelines, and Notifications

The main law governing the sale and distribution of pharmaceuticals in Japan is the PMD Act. Based on this law, the J-GCP is stipulated by the Ministry of Health, Labour and Welfare (MHLW) as a ministerial ordinance, with further operational details provided by the GCP guidance. Additionally, more specific standards and procedures are issued through notifications from the Pharmaceutical Safety Bureau or Evaluation and Licensing Division of the MHLW. Clinical evaluation guidelines and the orphan drug designation system are set out in notification documents from the MHLW, and applicants should follow these when proceeding.

In addition, various notifications from PMDA, an independent administrative agency under the jurisdiction of the MHLW, stipulate procedures for applying for clinical trial consultations, submitting CTNs, safety reports, and marketing approval.

Section 2: Clinical Trial Notifications (CTNs)

- **Pre-Submission Checklist for CTNs:**

Validity of Conducting the Clinical Trial: Before proceeding with the requested clinical trial, it is essential to confirm that all necessary studies, including "studies on the quality, toxicity, and pharmacological effects of the test drugs," have been completed. Regarding the timing of non-clinical safety studies required for conducting clinical trials of pharmaceuticals, refer to ICH M3 (R2) (Attachment 1-8).

Additionally, the following guidance should be referenced to evaluate, based on the available data, whether safety for Japanese subjects can be explained and whether the associated risks are acceptable. These evaluations must be included as supporting documents in the CTN.

- ✓ "Basic principles for conducting phase I studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan" (Attachment 1-2)
- ✓ "Q&A for basic principles for conducting phase I studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan" (Attachment 1-3)
- ✓ "Basic Principles on Global Clinical Trials" (Attachment 1-4)
- ✓ "Partial Revision of Basic Principles on Global Clinical Trials (Reference Cases)" (Attachment 1-5)
- ✓ "Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials" (Attachment 1-6)
- ✓ "Guidance for Establishing Safety in First-in-Human Studies during Drug Development" (Attachment 1-7)

Moreover, it is recommended to conduct a clinical trial consultation with the PMDA in advance to assess the validity of the Japanese subject sample size planned for the trial and to ensure that a Complete Clinical Data Package, which is necessary for obtaining approval, can be constructed.

- ➢ **Notification of clinical trials:**
  - ✓ In Japan, CTN is a notification system. Since it is not an approval system, an "Approval Letter" is not issued. When inquiries are issued by authorities regarding the notified documents and it becomes necessary to make revisions based on the response to the inquiries, a revised version of the relevant documents is submitted, and once the review period (initial CTN: 30 days, second and subsequent (N notifications): 14 days) has passed, it will be possible to conclude a clinical trial contract with the clinical trial sites.
  - ✓ Refer to Attachment 2 for the scope of drugs that need to be notified for clinical trials and the documents that should be attached to the notification.
  - ✓ In the case of a notification of a clinical trial that falls under the category of a drug with a new active ingredient, a drug with a new route of administration, or a drug with a new medical combination among the test drugs to be administered to people for the first time in Japan, it is subject to a 30-day review by the PMDA in accordance with laws and regulations, and it is

necessary to respond to inquiries from the PMDA within a limited review period. The implementation procedure should be agreed upon in advance between the foreign sponsor and the ICCC, including the division of roles and translation work, in order to respond to these inquiries. Please note that if the foreign sponsor is not able to agree on a response within the PMDA review period, or if the foreign sponsor is not able to submit the revised documents, the foreign sponsor will be instructed to withdraw the CTN.

- ✓ Even for a CTN (N notifications) for which the initial CTN has already been submitted, it is necessary to respond to inquiries from the PMDA within a limited period of time, so the same implementation procedure as above should be agreed upon.
- ✓ If there is a change in the matters to be notified, it is necessary to notify the change in advance or after the fact. If there is a change in information regarding the foreign sponsor, manufacturing location, etc., provide the information to the ICCC in advance (see Attachment 2).
- ✓ When the initial CTN is submitted, it is necessary to register the information related to the clinical trial in Japanese and English in the jRCT in Japan, in principle, before obtaining consent from the first subject. In addition, the results of the study must be registered within 1 year after the end of the study. (See Attachment 1-8). Since there may be a gap between the end of the clinical trial in Japan and the time of publication of the CSR, it is desirable to discuss with the ICCC in advance the procedure and timing necessary for registering a summary of the clinical trial results.

Section 3: Safety Reporting

- **Handling of Safety Information:**

From the date the initial CTN is submitted until approval is obtained or a development discontinuation notification is submitted by the ICCC, there is an obligation to report safety information. Therefore, before submitting the CTN, it is crucial for the foreign sponsor and the ICCC to establish and agree upon procedures, including the provision of information to the ICCC, to ensure that safety information is reported appropriately within the legal deadlines. This is also important for the ICCC's responsibility to "take the necessary measures to prevent the occurrence or spread of health hazards due to drugs used in the clinical trial." The following points should be noted: (For details, see Attachment 3)

- ✓ The day on which the foreign sponsor or the ICCC first receives the information, whichever is earlier, should be considered the date of receipt (Day 0), and the information must be reported to the regulatory authorities within 7 or 15 days from that date.
- ✓ All safety reports to Japanese authorities must use the prescribed format. Simply translating CIOMS forms obtained from overseas is not sufficient for submission. Reports must be customized for the authorities, and it is essential to agree with the ICCC on procedures that allow for timely reporting, considering the time required for customization.
- ✓ In addition to individual case reports, "foreign regulatory measures reports" and "research reports"

are required to be submitted to the authorities in Japan. Procedures regarding the scope and handling of these reports should be agreed upon.

- ✓ In cases where the clinical trial involves a drug already approved overseas, adverse drug reactions from the same active ingredient in marketed drugs overseas are also targets for reporting. When reporting, the predictability of adverse events should be determined based on IB of the Investigational Product or existing scientific knowledge of the same active ingredient in marketed drugs overseas (e.g., package inserts, interview forms, academic papers). Confirm which events are subject to reporting and the deadlines to avoid omissions when reporting to the Japanese regulatory authorities. (Refer to Article 273 of the Enforcement Regulations of the PMD Act/Report of Adverse Drug Reactions in Clinical Trials Concerning Drugs)
- ✓ Safety information reporting is required not only for the test drugs but also for drugs used in the clinical trial other than the test drug, so procedures regarding information sources and reporting must be agreed upon.

Additionally, in Japan, it is necessary to prepare an annual report in the prescribed format and submit it to the regulatory authorities, attaching the latest Development Safety Update Report (DSUR) (see Attachment 1-9).

- ➢ **Regarding Drugs Used in the Clinical Trial:**

In recent years, there has been an increase in cases where multiple drugs are used simultaneously for disease treatment, leading to clinical trials where various drugs other than the test drugs are also used. Additionally, in global studies, there are cases where drugs that have not yet been approved in Japan are used.

In light of these circumstances, with the revision of the PMD Act in September 2020, the concept of "Drugs used in the Clinical Trial" was introduced. When comparators, concomitant drugs, etc. other than the investigational drug used in clinical trials fall under this category, the trial sponsor or the ICCC is required also to report adverse drug reactions related to these drugs to the Minister of Health, Labour and Welfare.

- ✓ **"Drugs Used in the Clinical Trial"** refers to drugs specified in the clinical trial protocol, containing approved or unapproved active ingredients (including the test drugs), that are used for the evaluation of the test drugs' efficacy and safety in the clinical trials. Specifically, this includes test drugs, comparators, concomitant drugs, rescue drugs, and pre-treatment drugs, among others, that meet this definition. Furthermore, under J-GCP, the requirements for "Drugs used in the Clinical Trial" are similarly applied to medical devices or processed cells used for the evaluation of the test drugs' efficacy and safety in clinical trials concerning drugs.
- ✓ If it is unclear whether the drugs etc. used in the clinical trial qualify as the "Drugs used in the Clinical Trial," it is necessary to consult with the ICCC. If they qualify, the following measures must also be taken for Drugs used in the Clinical Trial other than the test drug, and it is recommended

that matters related to the management of Drugs used in the Clinical Trial be included in the contract with the ICCC:

- Confirm whether an overview of the Drugs used in the Clinical Trial is included in the clinical trial protocol.
- Prepare documents containing scientific information (to be submitted to PMDA and clinical trial sites).
- Prepare a procedural manual for management.

➢ **Compensation and Legal Liability:**

The trial sponsor is responsible for providing compensation for any health damage suffered by participants in the clinical trial. Additionally, if health damage occurs to participants due to delays in safety reporting or notifications, the trial sponsor may be liable for damages. For information on Japan's system, refer to Attachment 4. To avoid or minimize such compensation and legal liability, the foreign sponsor and the ICCC must promptly report safety information to the regulatory authorities and notify the clinical trial sites in accordance with the law.

Section 4: Other

I. Investigational Product Label:

The trial sponsor must write the necessary information in Japanese on the container or packaging of the investigational product. (For details on items to be included or excluded, refer to Attachment 4)

However, for global studies using investigational products labeled in English for multiple countries, or for bridging studies involving unapproved drugs already approved overseas, it may be written in English if this is specified in the clinical trial protocol and approved by the IRB.

II. Document Retention:

✓ A foreign sponsor without a residence in Japan shall have the ICCC retain records concerning the manufacture of the investigational products and the results of the tests on the drug's quality, such as stability.

✓ In accordance with its purpose, the ICCC shall appropriately retain the following records or copies thereof:

i. Protocol, contracts, clinical trial reports, and other documents prepared by the foreign sponsor in accordance with this J-GCP or copies thereof

ii. Case report forms, the written notification of review results from the Institutional Review Board (IRB), and other records obtained from the heads of clinical trial sites or investigators etc. in accordance with J-GCP

iii. Records of the duties related to sponsoring and managing the clinical trial, such as monitoring and audits

iv. Data generated while conducting the clinical trial

Chapter 4: Japan’s Clinical Trial Environment and Procedures

It is important for foreign sponsors to establish a good relationship with the ICCC and have a common understanding with the ICCC before starting work to ensure that clinical trial is conducted without any delays or trouble. The necessary and major points for this are outlined below.

Section 1: Procedures with Clinical Trial sites

The following is an outline of key points to be mindful of in Japan's clinical trial procedures. To ensure the smooth progression of the clinical trial, it is recommended to agree on the procedures with the ICCC in advance.

- The clinical trial implementation contract is signed between the ICCC and the clinical trial site. It is not a contract between the foreign sponsor and the principal investigator.
- When signing a contract with a clinical trial site, the contract must meet the items stipulated in Article 13 of J-GCP (refer to Attachment 4). Additionally, depending on the clinical trial site, the contract procedure and contract format may need to comply with the site’s SOPs. It is important to agree with the ICCC on the review and approval process.
- At each clinical trial site, there are procedures such as hearings required before the initial IRB application. Many clinical trial sites use their own IRB, and the use of joint IRBs is still uncommon.
- The informed consent form must include the items stipulated in Article 51 of J-GCP (refer to Attachment 4). Some clinical trial sites may have their own template for the informed consent form.

Section 2： Clinical Trial Costs and Payments

Clinical Trial Costs:

The details of clinical trial costs in Japan and the payment procedures should be agreed upon with the ICCC in advance. Although there is a movement to introduce a benchmark-based cost calculation method aimed at increasing transparency and appropriateness of clinical trial costs in Japanese clinical trial sites, progress has been slow. Many clinical trial sites still use Japan’s unique point system to calculate clinical trial costs. The calculation method for clinical trial costs at each site should be confirmed with the ICCC at the start of the trial.

- **Clinical Trial Costs – Point System:**

Japan's unique method of calculating clinical trial-related costs was introduced following the issuance of the notification "Regarding the Contracting of Clinical Research on Pharmaceuticals and Other Products at National University Hospitals" (July 2, 1999), which initiated its operation at national university hospitals.

Since then, many clinical trial sites have adopted this method for calculating costs. Today, this system has become the standard for calculating clinical trial-related costs at most clinical trial sites in Japan. However, the calculation methods vary depending on the managing body of each clinical trial site, and the same method is not necessarily used everywhere. Since costs are calculated according to the point system, negotiating significant changes to the total amount can be challenging.

- **Clinical Trial Costs – Advance Payment System at the Time of Contract:**

In some cases, part of the research costs or the cost for managing investigational products is paid in advance to the clinical trial site at the time of contract signing. It is important to discuss this with the ICCC in advance, as this upfront payment may be nonrefundable, even if no subjects are enrolled in the trial.

- **Clinical Trial Costs – Cost-sharing System for Non-covered Services:**

In Japan, combined medical services (where both insured medical services and non-insured services are used together) are generally prohibited. If combined services are used, the patient must bear the full cost of all medical services, including those covered by insurance. However, the "cost-sharing system for non-covered services" allows insurance coverage for the shared costs of standard medical care (consultations, tests, prescriptions, hospitalization, etc.) when combined with non-insured services specified by the Minister of Health, Labour and Welfare..In clinical trials involving pharmaceuticals, the trial sponsor bears the cost of all tests and imaging examinations conducted during the trial period (from the start to the end of investigational product administration), as well as the cost of administering or injecting the investigational products and drugs similar to the investigational products. This arrangement is a rule unique to Japan that clarifies the division of costs between health insurance and corporate responsibility.

Afterword

Japan has the ICCC system that allows a foreign sponsor without a residence in Japan to request clinical trials. The Japan CRO Association published the first edition of "Basic Considerations for Utilizing the ICCC System" in 2017 for foreign sponsors. However, due to changes in clinical trial methodologies and procedures, we have now issued this revised edition.

In recent years, the number of new drugs originating from Emerging Biopharma (EBP) in countries like the United States has been increasing, but many of these drugs are not being developed in Japan, leading to a rise in the number of unapproved drugs in the country. Among these are valuable new drugs for the Japanese population. We strongly hope that foreign pharmaceutical companies, including EBPs without a residence in Japan, will utilize this ICCC system in collaboration with Japanese CROs and other organizations to promote the development of groundbreaking new drugs in Japan. We hope this report will be of assistance in that effort.

T. Fujieda Japan CRO Association

Attachment

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Attachment 1

Guidelines and Guidance for Reference Regarding the Validity of Conducting Clinical Trials (as of February 7, 2024)

1. **J-GCP**

   Japanese version (revised on May 20, 2022): 医薬品の臨床試験の実施の基準に関する省令 | e-Gov 法令検索

   English version (May 20, 2022): 000152996.pdf (pmda.go.jp)

2. **"Basic principles for conducting phase I studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan**

   Japanese and English versions: https://www.pmda.go.jp/files/000266148.pdf

3. **"Q&A for basic principles for conducting phase I studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan"**

   Japanese and English versions: https://www.pmda.go.jp/files/000266147.pdf

4. **"Basic Principles on Global Clinical Trials"**

   Japanese version: https://www.pmda.go.jp/files/000157000.pdf
   English version: https://www.pmda.go.jp/files/000157900.pdf

5. **"Basic Principles on Global Clinical Trials (Reference Cases)"**

   Japanese version: https://www.pmda.go.jp/files/000266148.pdf
   English version (before revision): https://www.pmda.go.jp/files/000246188.pdf

6. **"Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials"**

   Japanese version: https://www.pmda.go.jp/files/000157480.pdf
   English version: https://www.pmda.go.jp/files/000157777.pdf

7. **"Guidance for Establishing Safety in First-in-Human Studies during Drug Development"**

   "Guidance for Establishing Safety in First-in-Human Studies during Drug Development Q&A"

   Japanese versions: https://www.pmda.go.jp/files/000208199.pdf
   https://www.pmda.go.jp/files/000208200.pdf

English version: https://www.pmda.go.jp/files/000208201.pdf

8. **"Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M3(R2))" (Regarding the timing of non-clinical safety studies for clinical trials)**

   "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Q&A"

   Japanese versions: https://www.pmda.go.jp/files/000156948.pdf
   https://www.pmda.go.jp/files/000156908.pdf
   English versions: https://www.pmda.go.jp/files/000156128.pdf
   https://www.pmda.go.jp/files/000156455.pdf

9. **"Development Safety Update Report (DSUR)"**

   Japanese version: https://www.pmda.go.jp/files/000156366.pdf
   English version: https://www.pmda.go.jp/files/000156623.pdf (ICH E2F)

10. **"Registration of the Status of Clinical Trials"**

    Japanese version: https://www.pmda.go.jp/files/000236406.pdf

Attachment 2

Clinical Trial Notifications (CTNs)

<Scope of Drugs Requiring a CTN>

1. Drugs with new active ingredients
2. Drugs with new routes of administration
3. New combination drugs, and drugs with new indications, effects, dosages, or usage
4. Drugs with the same active ingredients as those that have not yet passed the re-examination period for pharmaceuticals containing new active ingredients
5. Drugs expected to be classified as biological products (excluding those listed in 1 to 4)
6. Drugs produced using recombinant DNA technology (excluding those listed in 1 to 5)

* *Drugs that do not require a CTN*
Example: Bioequivalence studies (studies aimed at proving the equivalence of a test formulation with a reference formulation by comparing their bioavailability in human subjects. Studies showing equivalence based on pharmacological effects or clinical efficacy are excluded), post-marketing surveys, etc.

<Attached Documents>

- Clinical trial protocol
- (Sample case report form[*1])

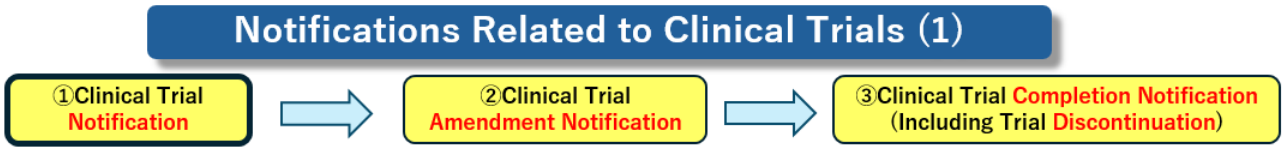
  [*1]: Submission is not required if the information to be included in the case report form can be sufficiently understood from the clinical trial protocol
- Explanation and consent forms
- Investigator's brochure for the investigational products[*2]

  [*2]: However, if the trial sponsor plans to conduct a clinical trial using multiple test drugs and cannot prepare the investigator's brochure due to reasons such as the drug being manufactured and marketed by another company, it is acceptable to submit a document containing the latest scientific information on the test drugs (e.g., package inserts, interview forms, academic papers) instead of the investigator's brochure, provided the active ingredient is already approved in Japan and the trial sponsor believes they can ensure the safety of the test drugs in the trial.
- Documents containing the latest scientific information on drugs used in the clinical trial (e.g., package inserts, interview forms, academic papers)
- Statement of reasons for determining scientific justification

- Materials related to the evaluation and control of DNA-reactive (mutagenic) impurities (for non-biological products)
- Materials related to product quality (for biological products, initial submission only)
- Final report of non-clinical safety studies (for trials involving drugs administered to humans for the first time)

Relevant Japanese Laws and Regulations Related to CTNs

- ✓ Definition of Clinical Trial (PMD Act Article 2, Paragraph 17):
  "Clinical trial" refers to tests performed in order to collect data concerning the results of a clinical study for inclusion among data submitted as part of the approval application (The term "clinical trial" is a unique legal term in Japan)
- ✓ Notification of Clinical Trial Protocols (PMD Act Article 80-2, Paragraph 2, Enforcement Regulations of PMD Act Articles 268, 269, 270, and 271)
- ✓ 30-day review (PMD Act Article 80-2, Paragraph 3)



① Clinical Trial Notification	
Submission Timing (Planing to Agreement)	When administering a drug with a new active ingredient, new route of administration, or new combination ratio to humans for the first time in Japan ⇒ **30days*** In cases other than the above ⇒ **2 weeks** *: In the case of a microdose trial, approximately 30 days
Submission Unit	**Regardless of the number of investigational drugs, for each clinical trial protocol**
Target Drug(s)	New active ingredients, new administration routes, new combination drugs, new indications/effects, new dosage/administration, drugs with the same active ingredient as those undergoing reexamination, biological products, or recombinant drugs
Attachment Documents	Clinical Trial Protocol (Sample of Case Report Form) — Submission is not required if the information to be included in the case report form can be sufficiently understood from the clinical trial protocol Informed Consent Form — If the explanatory documents include videos or similar materials, it is necessary to attach them to the trial notification Investigator's Brochure (IB) or the document containing the latest scientific information on the test drug Document containing the latest scientific information on the drugs used in the clinical trial Justification document for scientifically valid reasons Documents concerning the evaluation and control of DNA-reactive (mutagenic) impurities (for non-biological products) Quality-related documents (for biological products, only for the initial submission) Final report of non-clinical safety studies (only for trials where the drug is administered to humans for the first time)

Cited from GCP Pocket References 2024 with some modifications and translations.

Notifications Related to Clinical Trials (2)

①Clinical Trial Notification → ②Clinical Trial Amendment Notification → ③Clinical Trial Completion Notification (Including Trial Discontinuation)

②Clinical Trial Amendment Notification	
Submission Timing	• Addition of test drugs: ➢ When administering a drug with a new active ingredient/new administration route/new combination ratio to humans for the first time in Japan ⇒ **More than 30 days prior to the change** ➢ For other cases ⇒ **Approximately 2 weeks prior to the change** • Addition of drugs used in the clinical trial* *: For those without sufficient accumulated safety information ⇒ **Approximately 2 weeks prior to the change** • Change in purpose or target disease ⇒ **Approximately 2 weeks prior to the change** • Minor changes ⇒ Submit a consolidated report **within 6 months after the change** • Other matters: ⇒ Submit **prior to the change**

Cited from GCP Pocket References 2024 with some modifications and translations.

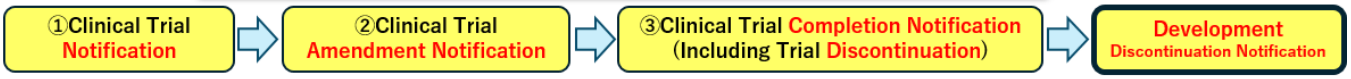
Notifications Related to Clinical Trials (3)

①Clinical Trial Notification → ②Clinical Trial Amendment Notification → ③Clinical Trial Completion Notification (Including Trial Discontinuation)

③Clinical Trial Completion Notification (Clinical Trial Discontinuation Notification)	
Submission Timing	Notify without delay at the following times: • Clinical Trial Completion Notification: Upon obtaining notification of completion from all sites and at the point of investigational product retrieval. • Clinical Trial Discontinuation Notification: Each time a clinical trial is discontinued for each submitted clinical trial notification.
Notification Items	• Number of Subjects Enrolled (Overall and by Site) • Quantity of Drugs used in the Clinical Trial (Issued, Used, Retrieved, Disposed of) (by Site) Note: For rescue medications or other drugs where predicting an appropriate quantity is difficult, estimated quantity based on the planned number of subjects. • Clinical trial change notification items that can be notified after the fact • In the case of **a Clinical Trial Discontinuation Notification**, also report the following: Date of Discontinuation Decision, Reason for Discontinuation (in detail), Subsequent Response Status

Cited from GCP Pocket References 2024 with some modifications and translations.

Notifications Related to Clinical Trials (4)

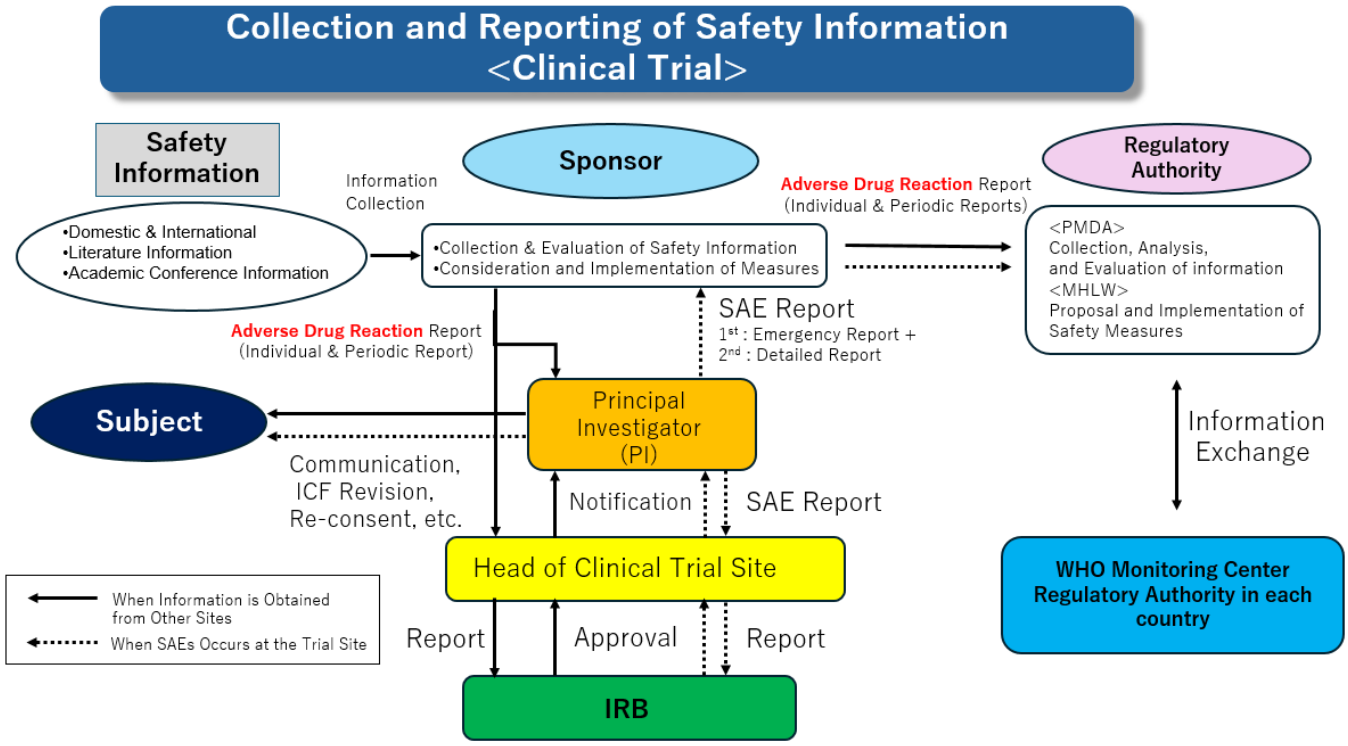


Development Discontinuation Notification	
Submission Timing	Submit a notification without delay after the decision to discontinue the development of the test drug.
Notification Items	• Date of the decision to discontinue development and specific reasons for the discontinuation. • Include in the remarks section: "There are no ongoing clinical trials for the test drug whose development has been discontinued."

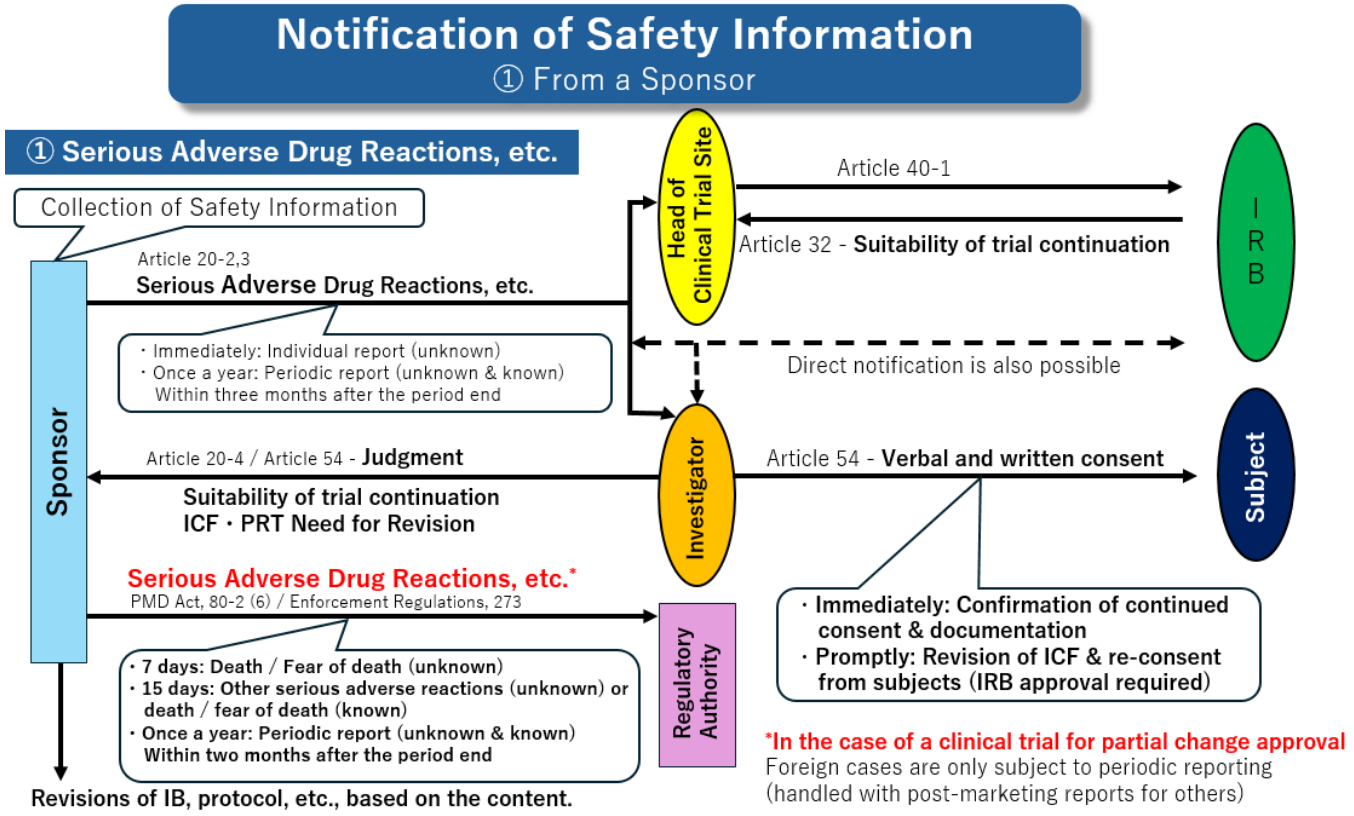
Cited from GCP Pocket References 2024 with some modifications and translations.

Attachment 3:

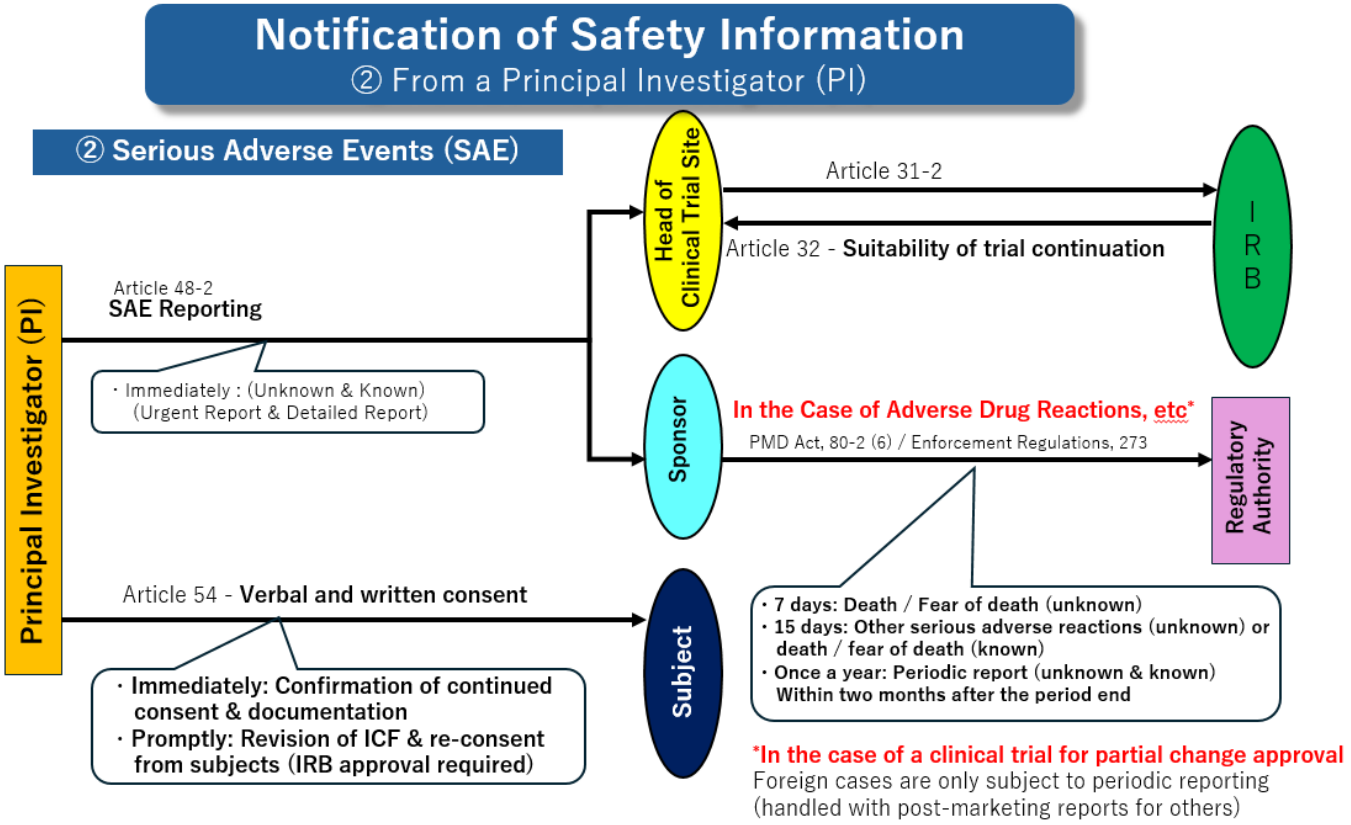
(1) Collection, reporting, and notification of safety information



Cited from GCP Pocket References 2024 with translations.

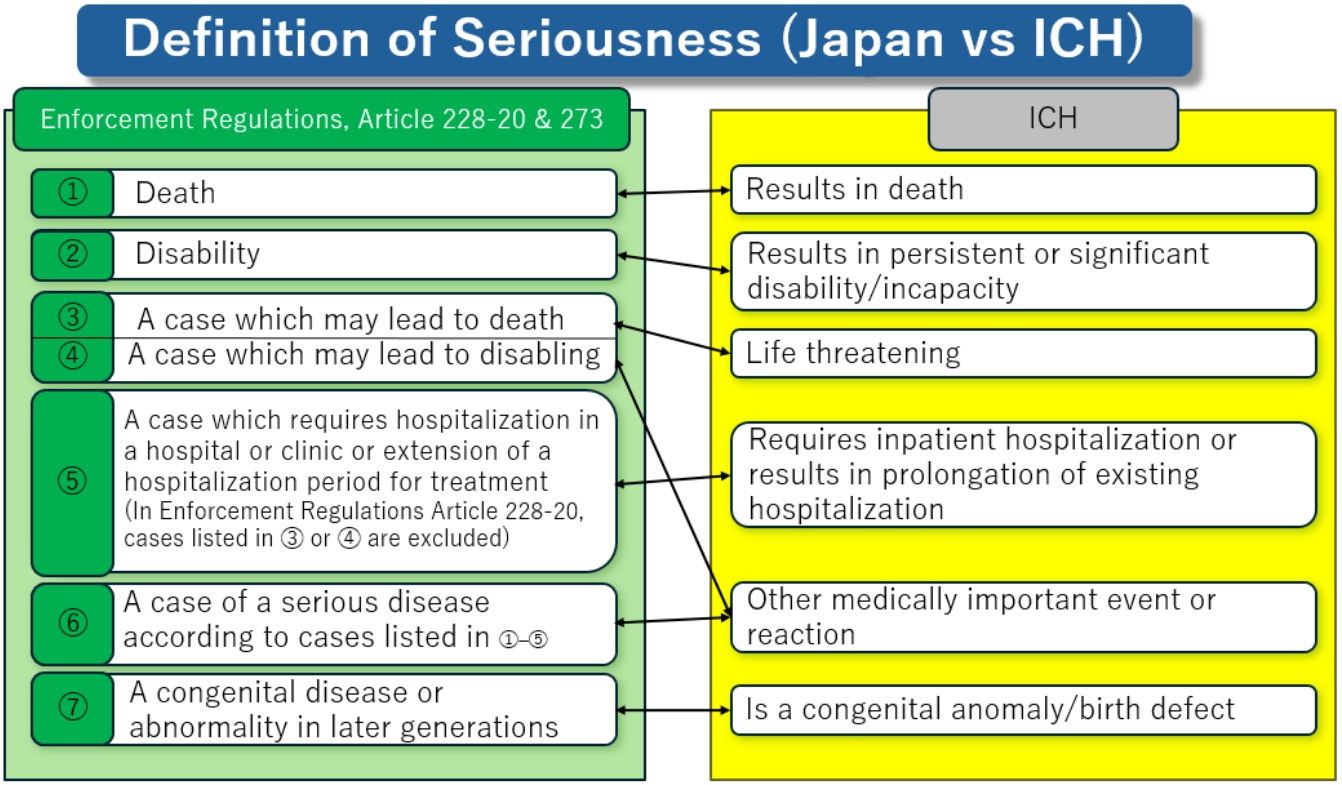


Cited from GCP Pocket References 2024 with some modifications and translations.



Cited from GCP Pocket References 2024 with translations.

(2) Definition of seriousness in safety information



Cited from GCP Pocket References 2024 with translations.

(3) Reporting deadlines for safety information

Handling of Regulatory Reporting of Safety Information in Clinical Trials

Source of Safety Information	Target *1	Reporting Required
Targeted clinical trial	Test drug	○
	Drug used in the clinical trial*2 other than the test drug	○
Clinical trials conducted overseas other than the targeted clinical trial *3	Test drug	○
	Drug used in the clinical trial*2 other than the test drug	○ (If the drugs used in the clinical trial includes the test drug)
Post-marketing cases overseas *3	Test drug	○ (Excluding cases where the safety judgment regarding subject protection in the trial is considered not to be affected)
	Drug used in the clinical trial*2 other than the test drug	×
Research reports	Test drug	○ (Excluding those that are deemed not to affect the evaluation of the efficacy and safety of the test drug in the targeted disease)
	Drug used in the clinical trial*2 other than the test drug	×
Measures reports	Test drug	○
	Drug used in the clinical trial*2 other than the test drug	○ (Only for measures to prevent the occurrence or spread of a hazard in health caused by the combined use of the test drug)

*1: Includes drugs considered to have identical ingredients to drugs used in the clinical trial.
*2: Comparators, concomitant drugs, rescue drugs, etc., as specified in the clinical trial protocol for evaluating the efficacy and safety of the test drug.
*3: In the case of a clinical trial for partial change approval, foreign are only subject periodic reporting (handled with post-marketing for others).

○: Target to reporting requirements
×: Not target to reporting requirements

Cited from GCP Pocket References 2024 with some modifications and translations.

1. Reporting Requirements to Regulatory Authorities for Adverse Drug Reactions during Clinical Trials (Enforcement Regulations Article 273)

(1) Domestic Clinical Trial Case

	Predictability	Seriousness	Domestic Clinical Trial Case Non-amendment	Amendment *
Test drug	Unknown	Death. A case which may lead to death	Individual (within 7 days) Periodic (annually)	Individual (within 7 days) Periodic (annually)
		Other serious case	Individual (within 15 days) Periodic (annually)	Individual (within 15 days) Periodic (annually)
	Known	Death. A case which may lead to death	Individual (within 15 days) Periodic (annually)	Individual (within 15 days) Periodic (annually)
		Other serious case	Not required Periodic (annually)	Not required Periodic (annually)
Drugs used in the clinical trial other than the test drug	Unknown	Death. A case which may lead to death	Individual (within 7 days) Periodic (annually) a	Individual (within 7 days) Periodic (annually) a
		Other serious case	Individual (within 15 days) Periodic (annually) a	Individual (within 15 days) Periodic (annually) a
	Known	Death. A case which may lead to death	Individual (within 15 days) Periodic (annually) a	Individual (within 15 days) Periodic (annually) a
		Other serious case	Not required Periodic (annually) a	Not required Periodic (annually) a

*: This is limited to clinical trials used for partial change approval applications concerning the addition, modification, or deletion of the usage, dosage, or indications/effects.
a: For drugs used in the clinical trial other than the test drug, report them collectively by test drug. Additionally, submit i. The Summary of the Development Safety Update Report (Attachment Form 1) and ii. The List of Occurrences of Serious Adverse Drug Reactions in Japan (Attachment Form 2). Submission of iii. the Development Safety Update Report (DSUR) is not required.

Cited from GCP Pocket References 2024 with translations.

(2) Cases in Clinical Trials Conducted Overseas

	Predictability	Seriousness	When using the test drug		When not using the test drug	
			Non-amendment	Amendment #, b	Non-amendment	Amendment
Test drug	Unknown	Death. A case which may lead to death	Individual (within 7 days) Periodic (annually)	Not required Periodic	—	—
		Other serious case	Individual (within 15 days) Periodic (annually)	Not required Periodic	—	—
	Known	Death. A case which may lead to death	Individual (within 15 days) Periodic (annually)	Not required Periodic	—	—
		Other serious case	Not required Periodic (annually)	Not required Periodic	—	—
Drugs used in the clinical trial other than the test drug	Unknown	Death. A case which may lead to death	Individual (within 7 days) Periodic (annually) c	Not required Periodic c	Not required	Not required
		Other serious case	Individual (within 15 days) Periodic (annually) c	Not required Periodic c	Not required	Not required
	Known	Death. A case which may lead to death	Individual (within 15 days) Periodic (annually) c	Not required Periodic c	Not required	Not required
		Other serious case	Not required Periodic (annually) c	Not required Periodic c	Not required	Not required

#: For unknown foreign cases, utilize the information reported within the post-marketing safety measures framework.
b: Even in the case of amendments, an annual periodic report on the test drug is required.
c: In periodic reports, for drugs used in the clinical trial other than the test drug, submit i. Summary of the Development Safety Update Report (Attachment Form 1) and ii. List of the Occurrence Status of Serious Adverse Drug Reactions etc. in Japan (Attachment Form 2). Submission of iii. the DSUR is not required.

Cited from GCP Pocket References 2024 with translations.

(3) Cases Arising from Use Overseas (Excluding Use in Clinical Trials)

	Predictability	Seriousness	Non-amendment	Amendment
Test drug	Unknown	Death. A case which may lead to death	Individual (within 7 days) Periodic (annually)	Not required # Periodic(annually)
		Other serious case	Individual (within 15 days) Periodic (annually)	Not required # Periodic(annually)
	Known	Death. A case which may lead to death	Individual (within 15 days) Periodic (annually)	Not required # Periodic(annually)
		Other serious case	Not required Periodic (annually)	Not required # Periodic(annually)
Drugs used in the clinical trial other than the test drug	Unknown	Death. A case which may lead to death	Not required	Not required
		Other serious case	Not required	Not required
	Known	Death. A case which may lead to death	Not required	Not required
		Other serious case	Not required	Not required

#: For unknown foreign cases, utilize the information reported within the framework of post-marketing safety measures.

Cited from GCP Pocket References 2024 with translations.

(4) Research Report

	Content	Domestic	Foreign
Test drug	-Risks of cancers, other serious diseases, disabilities, or death -Significant changes of the occurrence trend of adverse drug reactions, etc. -Lack of previously approved efficacy or effects	15 days [d]	15 days [d]
Drugs used in the clinical trial other than the test drug		—	—

d: Excluding those deemed to have no impact on the assessment of efficacy and safety of the test drug on the target disease in the clinical trial.

Cited from GCP Pocket References 2024 with translations.

(5) Foreign Measures Report

	Content	Domestic	Foreign
Test drug	-Measures to prevent the occurrences or spread of a hazard in health and hygiene (suspension of manufacturing, import, or sales, the collection, abandonment, etc.)	15 days [e]	15 days
Drugs used in the clinical trial other than the test drug		15 days [e, f]	15 days [f]

e: When conducting a clinical trial for the purpose of applying for partial changes to approval matters, or after the trial has been completed and the application for such partial changes is in preparation or under submission, and measures are taken for the same active ingredient of the drug marketed domestically, which is considered to affect the content of the trial or the application.
f: Only measures taken to prevent the occurrence or spread of a hazard in health when the approved drug is used in combination with the test drug.

Cited from GCP Pocket References 2024 with translations.

2. Notifications to the Principal Investigator and Head of Clinical Trial Site for Adverse Drug Reactions etc. during Clinical Trial regarding Drugs used in the Clinical Trial (J-GCP Article 20-2,3)

Predictability	Seriousness	Domestic Case (Domestic Clinical Trial*)	Foreign Case* (Foreign Clinical Trial, Foreign Post-Marketing Spontaneous Reports, etc.)
Unexpected (Unknown)	Death. A case which may lead to death	Individual (Immediately) Periodic (annually)	Individual (Immediately) —**
	Other serious case	Individual (Immediately) Periodic (annually)	Individual (Immediately) —**
Expected (Known)	Death. A case which may lead to death	— Periodic (annually)	— —**
	Other serious case	— Periodic (annually)	— —**

*: For domestic clinical trial cases or foreign cases, who are subject to regulatory reporting under 1. (1) to (3).
**: For foreign cases, the periodic reports, such as the DSUR, should include the evaluation and opinion based on the cumulative assessment of serious adverse drug reactions, etc. collected in foreign clinical trials.

Cited from GCP Pocket References 2024 with translations.

Attachment 4

(1) Compensation and legal liability

Compensation and legal liability: J-GCP Article 14 states that the person who intends to sponsor a clinical trial shall beforehand take necessary measures such as purchasing insurance in preparation for compensation to subjects in the event of trial-related injuries (including those attributable to the duties performed by the contractor) The way of considering compensation and legal liability sometimes differs inside and outside Japan; therefore, to give compensation appropriately, a system needs to be established after receiving sufficient explanation from the ICCC. The main points are described below.

- ✓ A subject has the right to claim payment for damages based on legal liability from the trial sponsor, the clinical trial site, and others even after obtaining compensation based on the compensation rules of the trial sponsor.
- ✓ Compensation consists of three parts: medical fee, medical allowance, and payment for compensation.
- ✓ A subject can receive compensation when the causality between the conduct of a clinical trial and the health damage is not reasonably excluded.
- ✓ Compensation for absence from work is not covered; however, this does not apply in studies with healthy people.
- ✓ Compensation is not offered for a drug failing to offer the expected effects or other benefits.
- ✓ Prepare compensation procedures and clarify the process for paying compensation to a subject.
- ✓ An overview of compensation for the explanation to subjects needs to be prepared beforehand and approved by the IRB.

Note: It should be sufficiently understood that “compensation” and “legal liability” have the following differences in meaning in Japan. As far as the Japan CRO Association surveyed, no English translation clearly differentiates between “compensation” and “legal liability.” Therefore, when a foreign sponsor discusses with concerned parties in Japan, the meaning of the words in the context needs to be clarified. In this document, each word is used according to the following meaning:

Compensation: To make up the loss due to damage, when something caused damage during a legal activity.

Legal liability: To make up the loss due to damage when an illegal activity caused damage to others.

(2) Investigational products label (J-GCP Article 16)

A sponsor shall indicate the following information in the Japanese language on the container or package of the investigational products:

(1) Statement of “For clinical trial use only”

(2) Name and address of the sponsor (if the sponsor resides outside Japan, name of the sponsor and name of

the country where the sponsor is located, and name and address of the ICCC)
(3) Chemical name or identification code
(4) Manufacturing number or manufacturing code
(5) Information on storage method, expiration date, etc., if necessary

The sponsor shall not indicate the following information in the documents attached to the investigational products, on the investigational products, or on their containers or packages (including the inner packages) except when a clinical trial using investigational products that are not supplied in such a state that the subject, investigators etc., or clinical research coordinators cannot distinguish the test drug from the comparator or an expanded clinical trial is conducted.

(1) Proposed brand name
(2) Proposed indications
(3) Proposed administration and dosage

(3) Contents to be included in the Informed Consent Form (ICF) (J-GCP Article 51)

When providing written information, the investigators etc. shall give each subject the written information that should include the following information:

(1) That the clinical trial involves research
(2) The objectives of the clinical trial
(3) The name and contact information of the investigator
(4) Clinical trial design
(5) The expected benefits to the subject's physical and mental health from using the investigational product (or that there is no intended clinical benefit to the subject, if applicable), and the potential disadvantages to the subject
(6) Description of alternative procedure(s) or course(s) of treatment
(7) Duration of the subject's participation in the clinical trial
(8) That the subject may withdraw from the clinical trial at any time
(9) That the subject's refusal of or withdrawal from participation in the trial does not cause any disadvantage to the subject
(10) That the monitors, auditors, and IRB etc. are given direct access to the source documents on the condition that confidentiality of the subject is fully secured
(11) That the subject's identity will be kept confidential
(12) The contact information of the medical institution in the event of trial-related injury
(13) That necessary treatment is available to the subject in the event of trial-related inju
(14) Description of compensation in the event of any trial-related injury
(15) Type of the IRB reviewing/deliberating the appropriateness of the clinical trial, etc., matters

reviewed/deliberated by each IRB, and other matters concerning the IRB involved in the clinical trial

(16) Description of the clinical trial expenses to be borne by subjects, if any

(17) Other necessary matters concerning the clinical trial

(4) Contents of contracts with clinical trial sites (J-GCP Article 13)

A clinical trial contract shall be concluded by means of a document specifying the following information:

(1) Date of concluding the contract

(2) Name and address of the person who intends to sponsor a clinical trial

(3) Name(s) and address(es) of the contractor(s) and the scope of the duties outsourced, if all or any of the duties are outsourced pursuant to the preceding article

(4) Name(s) and address(es) of the medical institution(s)

(5) Name(s) and title(s) of the person(s) in charge of the contract from each party

(6) Name(s) of the investigator(s)

(7) Duration of the clinical trial

(8) Description of the control/accountability of drugs used in the clinical trial

(9) Description of record (and data) keeping

(10) Description of notifications given by the sponsor and the personnel of the medical institution in accordance with this Ministerial Ordinance

(11) Description of maintenance of the confidentiality of the subjects

(12) Description of the expense for the clinical trial

(13) Statement that the medical institution conducts the clinical trial in compliance with the protocol

(14) Statement that the medical institution will provide the sponsor with direct access to the records (including documents) specified in Article 41, Paragraph 2[*1], upon request by the sponsor

(15) Statement that the sponsor may cancel the contract if it is found that the medical institution has violated this Ministerial Ordinance, the protocol, or the relevant contract, resulting in interference with the proper conduct of the clinical trial (excluding cases stipulated in Article 46[*2])

(16) Description of compensation to the subject in the event of trial-related injuries

(17) Other matters necessary to ensure that the clinical trial is conducted properly and smoothly

*1: (1) Source documents

(2) The contract or Approval Document, informed consent forms, written information and other documents prepared by persons engaged in the clinical trial at the medical institution in accordance with this Ministerial Ordinance, or their copies

(3) The protocol, documents obtained from the IRB etc. pursuant to Article 32, Paragraphs 1 through 3, and other documents obtained in accordance with this Ministerial Ordinance

(4) Records of trial-related duties such as control/accountability of drugs used in the clinical trial

*2: When the investigator has failed to comply with the protocol in order to eliminate immediate hazards to subjects or for other inevitable medical reasons