

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

Japan CRO Association

Policy Committee
Monitoring Working Team

Date of Issue: June 30, 2017

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Foreword

The following points are the most important to be understood and followed with regard to clinical trials conducted in Japan. The regulatory authority in Japan has expressed significant concerns regarding the following items, which must be performed without fail.

1. In any clinical trial in Japan, safety information is reported to the regulatory authority no later than 7 calendar days, in the earliest case, after first knowledge of incidence. Reporting obligations arise at the time of submitting a notification of a clinical trial plan.
2. For safety information, the date the information is obtained by a foreign sponsor or by the ICCC, whichever is earlier, is regarded as the date for obtaining initial information.
3. A foreign sponsor and the ICCC must always include items on reporting safety information in any contract between them after understanding the description above. If there is an affiliate company in Japan, the extent of its involvement must be confirmed.

In association with the guidance documents “Essential Considerations on Requesting a Clinical Trial In-Country Representative <For Foreign Sponsors> issued by Japan CRO Association, June 2017

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Chapter 1. Aim and scope of this document

As globalization of drug development progresses, companies that do not have branches or subsidiaries in Japan 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)

To take necessary measures to prevent the occurrence or spread of health hazards due to investigational products, the 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.

ICCC, in place of the foreign sponsor, conducts all the procedures for the regulatory authority, medical institutions, and so on; however, the final responsibility for the clinical trial resides in the foreign sponsor.

In contrast, along with the establishment of the Sakigake Designation System,* the need for CRO services is recently increasing from venture companies outside Japan that have little experience in drug development in Japan. Thus, it is increasingly important for ICCCs to explain the Japanese environment including regulatory requirements. This document describes the points that foreign sponsors should understand and follow, the differences in systems outside and inside Japan, and the unique regulatory requirements in Japan when a CRO enters into a contract with a foreign sponsor to perform the duties of ICCCs. We hope that this guidance document is useful for foreign sponsors.

*: Strategy of Sakigake by the Ministry of Health, Labour and Welfare (MHLW). Please refer to the following link for further information.

<http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0001.html>

While this document focuses on the considerations of clinical trials for drugs containing new active ingredients, this can also be applied to clinical trials for medical devices and regenerative products, though some of the rules differ.

Chapter 2. Items that should be checked at the time of outsourcing duties to ICCCs

When a foreign sponsor outsources duties to an ICCC, items that should be considered come down to the following two categories. If it is judged that a clinical trial that a foreign sponsor plans to outsource does not satisfy the regulatory requirements in Japan, it is necessary for foreign sponsors and the ICCC to fully discuss the foreseeable problems and measures before starting the duties.

- **Organization and system in foreign sponsors:** Foreign sponsors must have a system to be a sponsor for clinical trials, including securing professionals with adequate expertise, establishing standard operating procedures, and building processes on safety evaluation and on reporting to the regulatory authority based on the rules in Japan, as specified in J-GCP Article 4.
- **Appropriateness of conducting a clinical trial:** At the time of conducting an outsourced clinical trial, the sponsor should have completed the necessary studies including studies on the quality, toxicity, and pharmacological effects of its test drug.

Particularly in cases of foreign sponsors with little experience in drug development in Japan, studies on the Japanese population are sometimes insufficient. Thus, an evaluation needs to be performed based on the *Basic Principles on Global Clinical Trials* (Attachment 1-2), *Basic Principles on Global Clinical*

Trials (Reference Cases) (Attachment 1-3), *Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials* (Attachment 1-4), and *Guidance for Establishing Safety in First-in-Human Studies during Drug Development* (Attachment 1-5). If the studies are insufficient, consultation with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as PMDA) is recommended for the appropriateness of the Complete Clinical Data Package.

As for the timing of nonclinical safety studies enough to conduct clinical trials for pharmaceuticals, refer to ICH M3 (R2) (Attachment 1-6).

If it is difficult for foreign sponsors to examine the above-mentioned items on their own, the examination can be outsourced to a CRO.

Chapter 3. **Items that foreign sponsors need to understand when an ICCC conducts its duties**

It is important for foreign sponsors to have common grounds with the ICCC before starting duties to sufficiently understand Japanese systems and then to smoothly conduct clinical trials through building good relationships with the ICCC. Major items necessary to achieve this are described below.

- **Responsibilities of the ICCC:** Responsibilities of the ICCC are not limited to submitting a notification of the clinical trial plan or the Clinical Trial Notification (CTN) (see Attachment 2) and reporting adverse drug reactions to the regulatory authority. It is necessary to understand that the foreign sponsor, through the ICCC, is expected to take *necessary measures to prevent the occurrence or spread of health hazards due to investigational products*. 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* (J-GCP Article 15: Attachment 1-1).

To do this, a foreign sponsor needs to agree with the ICCC in writing on a system that is necessary for the ICCC to perform its duties and on the assignment of duties.

If a foreign sponsor has an affiliate company in Japan, it is recommended to reach a mutual agreement including the ICCC for the roles and responsibilities of the affiliate company as necessary.

- **Handling of safety information:** Obligations to report safety information arise on the day of submitting initial CTN and lasts until obtaining approval or submitting notification for discontinuation of development. Prior safety information outside Japan that is not included in the Investigator's Brochure (IB) must be reported immediately to PMDA. Therefore, it is important to establish processes including providing information to the ICCC among foreign sponsors, medical institutions, and ICCCs before submitting the CTN so that safety information is reported appropriately within the period specified by the law. The following points should be considered.

(For details, see Attachment 3, Collection, Reporting, Notification, and Definition of Seriousness for Safety Information as well as Reporting Time Frames for Safety Reports.)

- ✓ The date the information is obtained by a foreign sponsor or by the ICCC, whichever is earlier, is regarded as the date for obtaining initial information. It is reported to the regulatory authority within 7 to 15 days of this date depending on the situation.
- ✓ All safety reports to the regulatory authority in Japan require the use of a specified form. Mere translation of the Council for International Organizations of Medical Sciences (CIOMS) Form is not accepted; therefore, the information needs to be customized for reporting to the regulatory authority. Also, opinions of foreign sponsors, which are not described in the CIOMS Form, need to be reported. Therefore, the reporting procedure must be agreed upon with the ICCC so that the reports can be submitted within the reporting deadline.
- ✓ Other than individual case reports, *reports of actions outside Japan* and *drug research reports* are submitted to the regulatory authority. Therefore, the scope and the operating procedure need to be decided.

- ✓ The definition of “known” and “unknown” can sometimes differ between Japan and the country of a foreign sponsor. Events to be reported and reporting deadlines must be checked so that there is no missing report to the regulatory authorities inside and outside Japan [Enforcement Regulations for Pharmaceuticals and Medical Devices (PMD) Act Article 273/ reporting adverse drug reactions and so on related to clinical trials for drugs].

Refer to ICH E2F for the Development Safety Update Report (DSUR) [Notification 1228 No. 1 of the Evaluation and Licensing Division (ELD), Pharmaceutical and Food Safety Bureau (PFBS), Ministry of Health, Labour and Welfare (MHLW), dated December 28, 2012: Attachment 1-7].

- **Compensation and legal liability:** J-GCP Article14 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 the subject in the event of trial-related injuries (including those attributable to the duties performed by the contractor) (J-GCP: Attachment 1-1). The way of consideration for compensation and legal liability sometimes differs between outside and inside Japan; therefore, to give compensation appropriately, a system needs to be established by receiving sufficient explanation from the ICC. The main points are described below.

- ✓ A subject has the right to claim payment for damage based on legal liability from a sponsor, a medical institution, and others even after obtaining compensation based on the compensation rules of the 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 when healthy people are studied.
- ✓ Compensation is not offered for failing to offer expected effects by a drug or other benefits.
- ✓ The process of paying compensation to a subject must be clarified.
- ✓ An overview of compensation for explanation to a subject needs to be prepared beforehand and approved by the IRB.

Note: It should be sufficiently understood that “compensation” and “legal liability” have the following difference in meaning in Japan. As far as 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 the others.

- **Expenses for clinical trial — the point system:** The point table is a unique pricing tool in Japan for clinical trial-related expenses. Since the *contract of clinical studies and so on for drugs and the others in national university hospitals* (notification) (July 2, 1999) has been issued, national university hospitals have started using the pricing table. After that, many medical institutions followed, calculating expenses based on the pricing table. Currently, this system is adopted by almost all the medical institutions in Japan as a standard system for calculating clinical trial-related expenses. The calculation method differs in minor details depending upon the management of each medical institution; thus, the same pricing table is not necessarily used.
- **Expenses for clinical trial — system for medical expenses combined with treatment outside insurance coverage:** In Japan, when medical treatment covered by health insurance (insurance covered treatment) and the other treatment (treatment outside insurance coverage = self-financed treatment) are combined, it is called mixed medical treatment. The mixed medical treatment is not

allowed in principle by the regulation. If the mixed medical treatment is performed, expenses for all the medical treatment including insurance covered treatment should be paid by a patient. System to define the coverage of medical expenses combined with treatment outside insurance coverage permits insurance coverage of the expenses that are common medical treatments (such as medical examinations, tests, drug administrations, hospitalization fees) when the treatment outside insurance coverage that is designated by the Ministry of Health, Labour and Welfare is combined with insurance covered treatment.

In medical treatment in clinical trials for a drug, a sponsor pays all the expenses for examination and imaging diagnosis and expenses for administering or injecting study drugs as well as the same type of drugs with the same effects as that of the study drugs through the clinical trial period (from day of starting administration of the study drug to the end of its administration).

This system, which clarifies assignment between medical insurance and responsibility of the company, is a unique rule in Japan.

➤ **Procedure of clinical trials:** Because of the unique clinical trial environment in Japan, foreign sponsors should understand such procedures by receiving prior sufficient explanation from ICCCs. An agreement in the procedure with the ICCC needs to be reached beforehand. The main points are described below.

- ✓ In performing clinical trials, the ICCC, not foreign sponsors, enters into a contract with a medical institution and not with an investigator.
- ✓ When entering into a clinical trial contract with a medical institution, the contents of the contract need to satisfy items specified in J-GCP Article 13 (refer to Attachment 1-1, J-GCP). Sometimes a medical institution asks to follow its rules including contract procedures and forms of contract. Agreement regarding procedure for the review and approval of the contract must be reached with the ICCC.
- ✓ Because of the unique handling of clinical trial expenses in Japan, agreement regarding contents and procedure for payment must be reached with the ICCC.

➤ **Clinical Trial Notification:**

- ✓ In Japan, not the approval system but the notification system is used.
- ✓ In case of CTN for drugs, which are administered to humans for the first time in Japan and with a new active ingredient, a new administration route, and a new combination for medical treatment, it will be under a 30-day investigation by PMDA as set by the law. It is necessary to answer the inquiries from PMDA within a limited time; therefore, it is desirable to establish a procedure beforehand between foreign sponsors and the ICCC for answering the inquiries including role assignment and translation works.
- ✓ Even in the Nth submission of CTN, it is necessary to answer to the inquiries from PMDA within a limited time; therefore, it is desirable to establish the similar procedure mentioned above.

➤ **Labeling of study drug:** A sponsor must indicate the following items in the Japanese language on the container or package of the study drugs:

On the package

- ✓ Statement of "For clinical trial use only"
- ✓ Name and country of the sponsor as a foreign manufacturer and name and address of the ICCC
- ✓ Chemical name or identification code
- ✓ Manufacturing number or manufacturing code
- ✓ Information on storage method, expiration date, etc., if necessary

The sponsor shall not indicate the following information in the documents attached to the study drugs, on the study drugs, or on their containers or packages (including the inner packages):

- ✓ Proposed brand name
- ✓ Proposed indications
- ✓ Proposed administration and dosage

When a study drug labeled in English is used in a multinational clinical trial, this is described in the protocol, and approval from the IRB needs to be obtained (J-GCP Article 16) (refer to Attachment 1-1, J-GCP).

When the description is in English, it is necessary to prepare another document in Japanese that explains the dissolving method of the study drug and other handling methods (refer to J-GCP for guidance).

Attachment 1

Guidelines, Guidances, and Others to Refer to for Judging the Validity of Conducting a Clinical Trial

1. J-GCP

Japanese version (Revised on January 22, 2016):

<http://law.e-gov.go.jp/htmldata/H09/H09F03601000028.html>

English version (December 28, 2012):

<http://www.pmda.go.jp/files/000152996.pdf>

2. Basic Principles on Global Clinical Trials

Japanese version: <http://www.pmda.go.jp/files/000157000.pdf>

English version: <http://www.pmda.go.jp/files/000157900.pdf>

3. Basic Principles on Global Clinical Trials (Reference Cases)

Japanese version: <http://www.pmda.go.jp/files/000157901.pdf>

English version: <http://www.pmda.go.jp/files/000208185.pdf>

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

Japanese version: <http://www.pmda.go.jp/files/000157480.pdf>

English version: <http://www.pmda.go.jp/files/000157777.pdf>

5. 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 version: <http://www.pmda.go.jp/files/000208199.pdf>

Japanese version: <http://www.pmda.go.jp/files/000208200.pdf>

English version: <http://www.pmda.go.jp/files/000208201.pdf>

6. Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals [ICH M3 (R2)] (timing of nonclinical safety studies for clinical trials for pharmaceuticals)

Japanese version: <http://www.pmda.go.jp/files/000156948.pdf>

<http://www.pmda.go.jp/files/000156908.pdf>

English version: <http://www.pmda.go.jp/files/000156128.pdf>

<http://www.pmda.go.jp/files/000156455.pdf>

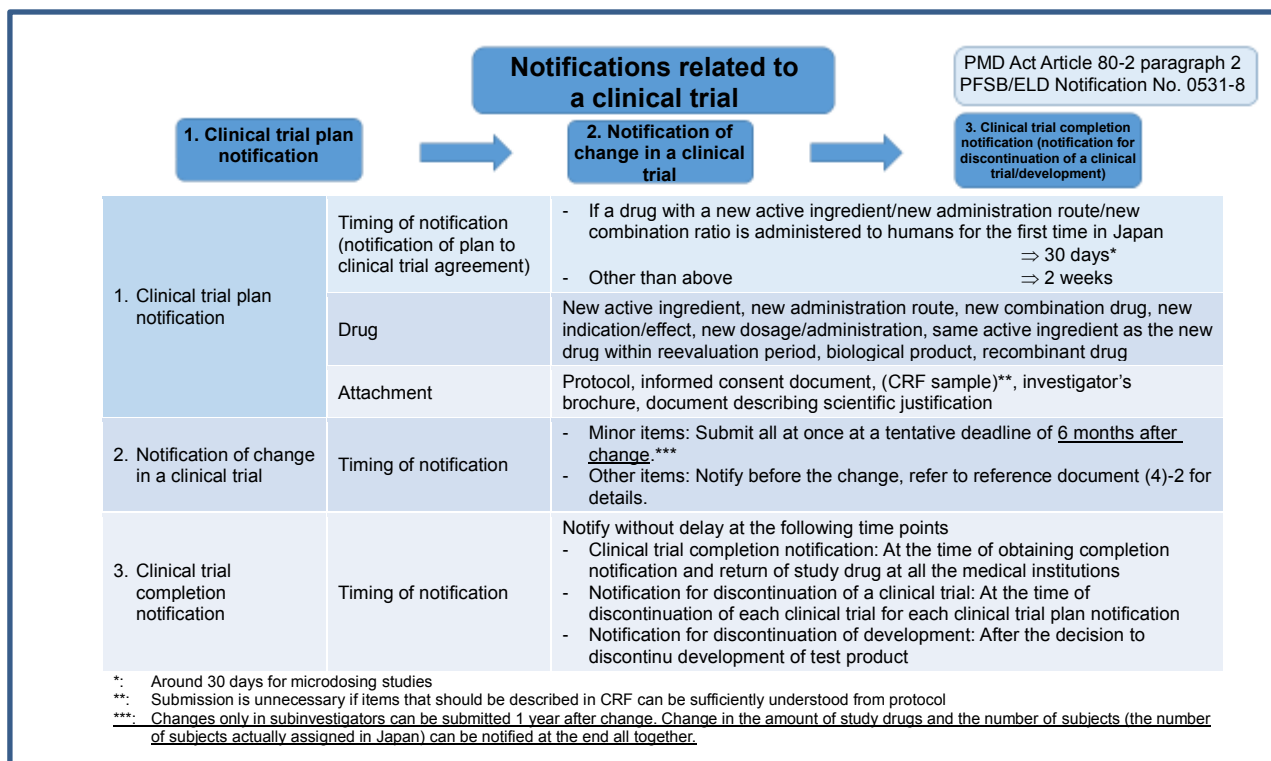
7. Development Safety Update Report (PFSB/ELD Notification 1228 No. 1, dated December 28, 2012)

Japanese version: <http://www.pmda.go.jp/files/000156366.pdf>

English version: <http://www.pmda.go.jp/files/000156623.pdf> (ICH E2F)

Attachment 2

Notifications Related to a Clinical Trial (cited and translated from GCP Pocket References 2016)



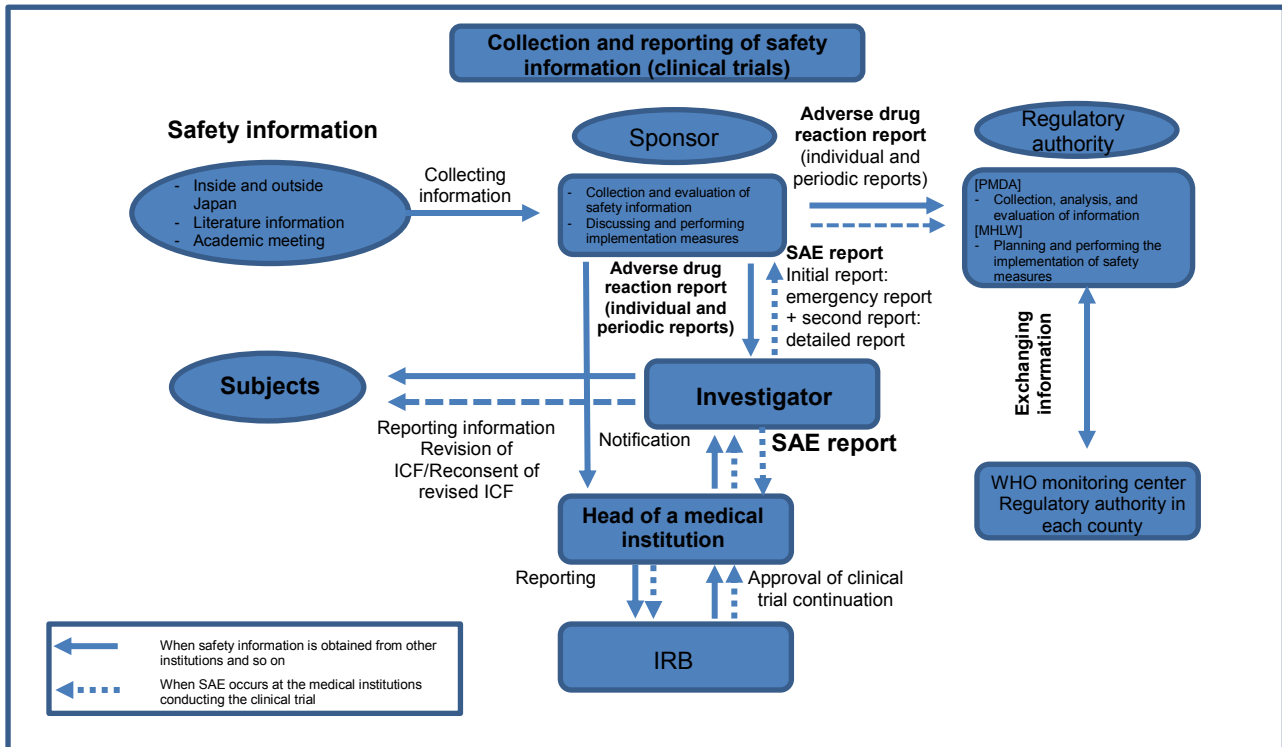
Laws and regulations related to Clinical Trial Notification in Japan

- ✓ Definition of a clinical trial [Pharmaceuticals and Medical Devices (PMD) Act Article 2 paragraph 17]
Among the data that should be submitted for approval of the application, this study aims to obtain data on the test results in a clinical study (clinical trial is a unique legal term in Japan)
- ✓ Submission of the Clinical Trial Notification (PMD Act Article 80-2, paragraph 2, Enforcement Regulations for PMD Act Articles 268, 269, 270, and 271)
- ✓ 30-day investigation (PMD Act Article 80-2, paragraph 3)

Attachment 3

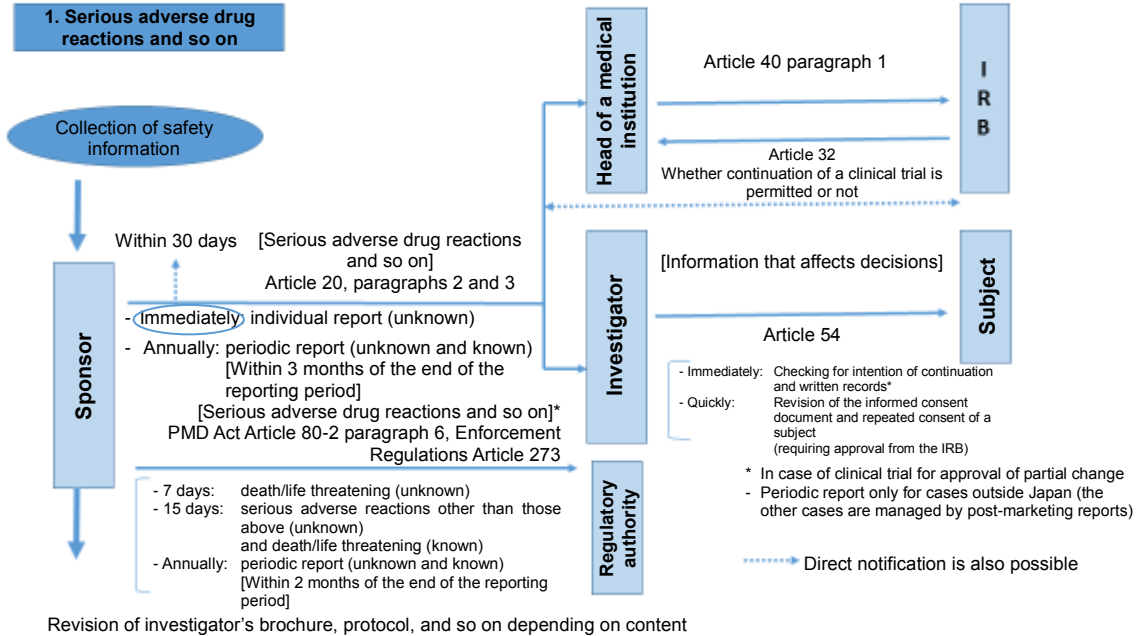
Collection, Reporting, and Notification of Safety Information; Definition of Seriousness for Safety Concerns; and Reporting Deadline for Safety Reports

(Cited and translated from GCP Pocket References 2016)



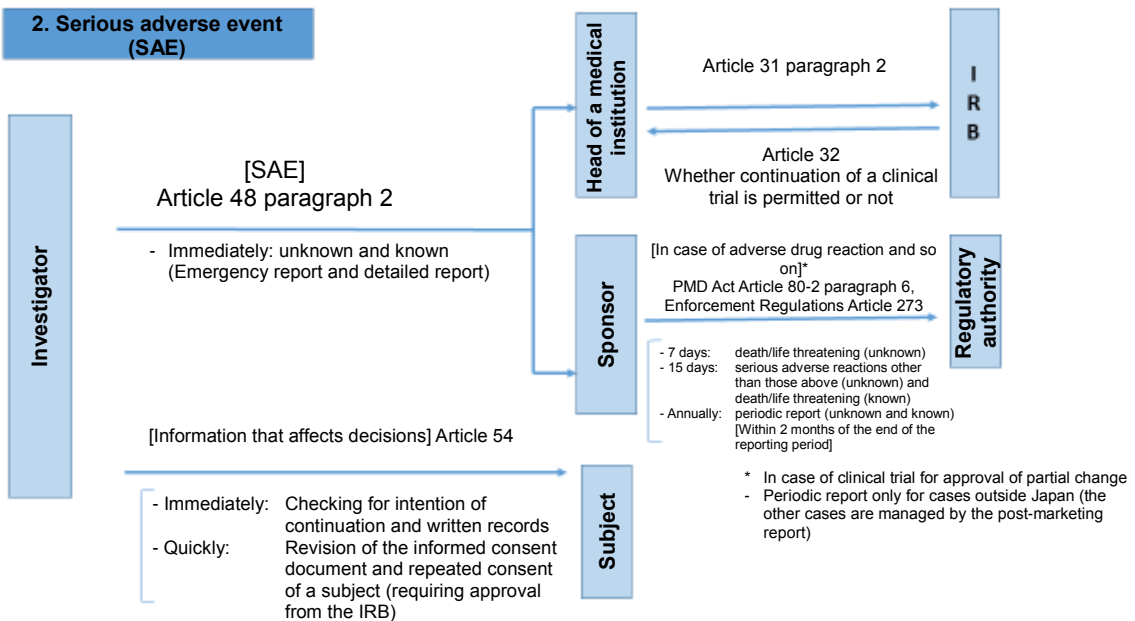
Notification of safety information 1. From a sponsor

1. Serious adverse drug reactions and so on

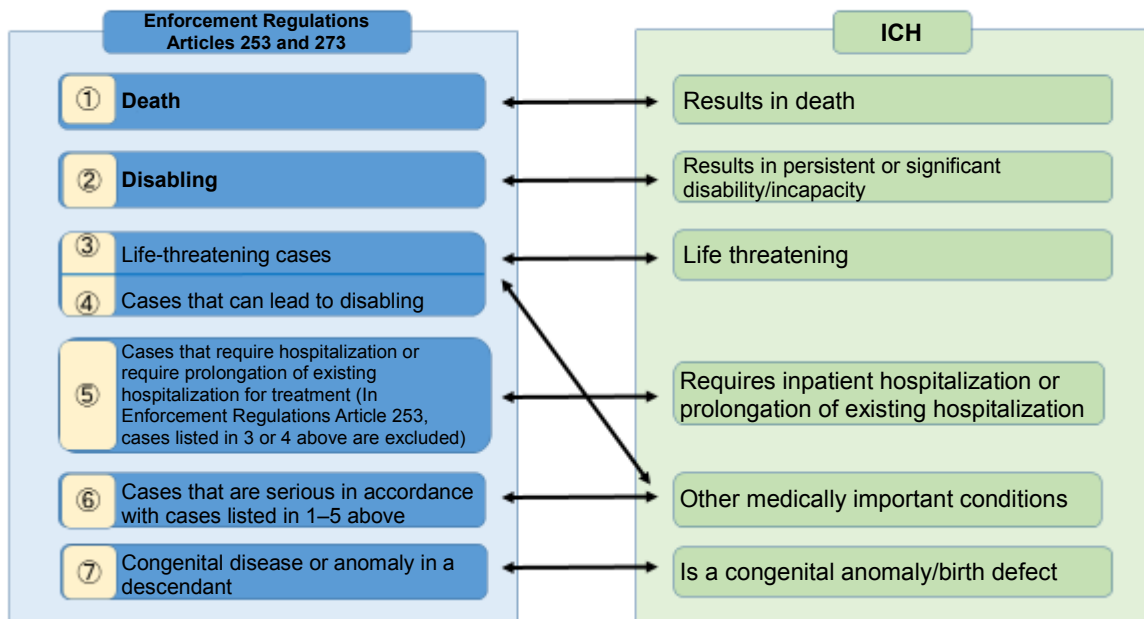


Notification of safety information 2. From an investigator

2. Serious adverse event (SAE)



Definition of Seriousness (Japan vs. ICH)



Safety Report: Reporting Time Frames

1. Reporting items to the regulatory authority (Regulations Article 273)

New active ingredient

| Expectedness | Seriousness | Cases inside Japan (clinical trials in Japan) | Cases outside Japan (clinical studies outside Japan, post-marketing spontaneous reports outside Japan, and so on) |
|-------------------------|---------------------------------|---|--|
| Unexpected (unknown) | Fatal or life-threatening cases | Individual (no later than 7 calendar days after first knowledge) Periodic (annually) | Individual (no later than 7 calendar days after first knowledge) Periodic (annually) |
| | Other serious cases | Individual (no later than 15 calendar days after first knowledge) Periodic (annually) | Individual (no later than 15 calendar days after first knowledge) Periodic (annually) |
| Expected (known) | Fatal or life-threatening cases | Individual (no later than 15 calendar days after first knowledge) Periodic (annually) | Individual (no later than 15 calendar days after first knowledge) Periodic (annually) |
| | Other serious cases | - Periodic (annually) | - Periodic (annually) |

The date the information is obtained by a foreign sponsor or by the ICC, whichever is earlier, is regarded as the date for obtaining initial information.

2. Notification items to investigators and heads of medical institutions
(GCP Ordinance, Article 20 paragraphs 2 and 3)

| Expectedness | Seriousness | Cases inside Japan (clinical trials in Japan) | Cases outside Japan (clinical studies outside Japan, post-marketing spontaneous reports outside Japan, and so on) |
|-------------------------|------------------------------------|--|--|
| Unexpected (unknown) | Fatal or life-threatening cases | Individual (immediately) Periodic (annually) | Individual (immediately) -* |
| | Other serious cases | Individual (immediately) Periodic (annually) | Individual (immediately) -* |
| Expected (known) | Fatal or life-threatening cases | - Periodic (annually) | - -* |
| | Other serious cases | - Periodic (annually) | - -* |

*: Opinions and so on based on the total evaluation of accumulated cases for serious adverse drug reactions and others in clinical studies outside Japan are described in the Development Safety Update Report.