

REVIEW ARTICLE

Clinical Studies Using *in Vivo* Diagnostic Radiopharmaceuticals under the Clinical Research Law

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Abstract

The Japanese Ministry of Health, Labour and Welfare (JMHLW) introduced the Clinical Research Law¹ in April 2018. Clinical studies to evaluate pharmacokinetics or the efficacy or safety of *in vivo* diagnostic radiopharmaceuticals have to be conducted under either the Clinical Research Law or the Japanese Good Clinical Practice (GCP) guidelines. The Clinical Research Law provides stricter regulation than does the current Ethical Guideline for clinical studies, and it allows the regulatory authority to issue orders to suspend or change clinical studies. Given that a clinical study may require the same amount of time, human resources and funding resources no matter which regulatory scheme is followed, clinical investigators need to bear in mind the objectives and funding support for the planned study when choosing which legislation to adhere to. This article reviews various factors that may help determine which of the recently introduced pieces of legislation is applicable in the planning of a particular clinical study. We also aim to establish approaches to identify the appropriate law and to enable non-clinical studies to move forward to the clinical study phase.

Keywords: Clinical Trial Act, Diagnostic radiopharmaceutical, JMHLW, PET

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Until recently, the main legislation regulating clinical studies of *in vivo* radiopharmaceuticals in Japan was the “Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices” referred to as the “Pharmaceuticals and Medical Devices Law” and the “Ethical Guideline for Medical and Health Research Involving Human Subjects” or the so-called “Ethical Guideline” (1-3). The Pharmaceuticals and Medical Devices Law is binding legislation enforceable under Japanese law, while the Ethical Guideline is non-binding. In addition, the Japanese Ministry of Health, Labour and Welfare (JMHLW) in April 2018 introduced a third piece of regulation, the binding Clinical Research Law (4-6). The objectives of the Clinical Research Law are different from those of the current Pharmaceuticals and Medical Devices Law.

Some major pharmaceutical companies have not followed ethical practices in undertaking clinical studies in Japan.

JMHLW introduced this new law for clinical studies in order to avoid such misconduct. This new law can be applied to clinical studies that have different purposes from those of Clinical Trials as defined under the Pharmaceuticals and Medical Devices law. In Europe and the United States (US), clinical studies using *in vivo* radiopharmaceuticals are conducted in accordance with national good clinical practice (GCP) guidelines based on the ICH-GCP E6 (R1) recommendation, while in Japan clinical studies are conducted in accordance with the Pharmaceuticals and Medical Devices Law, the Clinical Research Law, or the Ethical Guideline.

In Japan, *in vivo* diagnostic radiopharmaceuticals (“radiopharmaceuticals”) are approved as either “drugs” or “medical devices” under the Pharmaceuticals and Medical Devices Law.

As described below, clinical studies using radiopharmaceuticals in humans can be classified into five categories

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¹This review article was written before official release of the English translation of the Clinical Research Law in June 28 2108. Although the law is officially entitled the Clinical Trials Act in English, this review uses the terminology “the Clinical Research Law”.

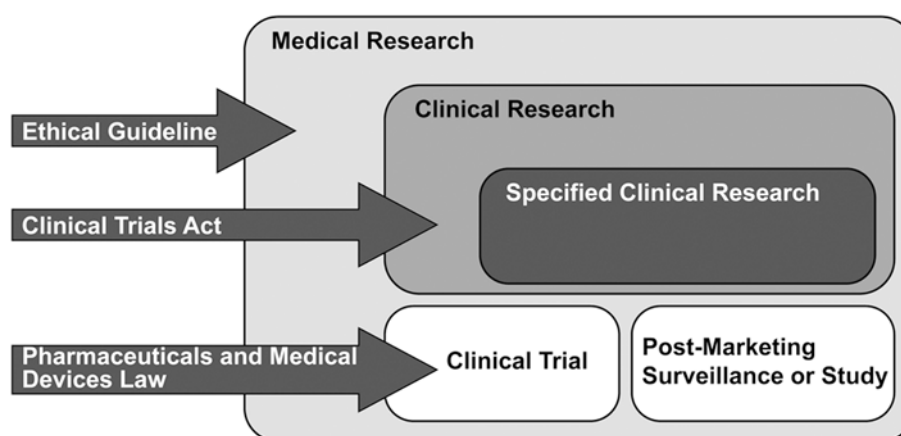


Fig. 1 Definition and scope of clinical studies.

from a legal point of view. These include “Clinical Trial” and “Post-Marketing Surveillance (PMS)” under the Pharmaceuticals and Medical Devices Law, “Specified Clinical Research” and “Clinical Research” under the Clinical Research Law, and “Medical Research” under the Ethical Guideline². One of the three regulations will be applied depending on the regulatory approval status of radiopharmaceuticals, objective of the study, study design, and funding by commercial supplier(s). From the investigator’s point of view, the appropriate selection of regulations with which a clinical study should comply becomes an important factor that may affect the feasibility of a clinical study itself, since the selected regulation relates closely to the amounts of research resources and time that will be required for the non-clinical development phase. This review provides investigators who intend to conduct clinical studies using radiopharmaceuticals with a way to identify the appropriate regulation to apply to their clinical studies. We also note points of caution in the non-clinical and clinical research phases. The information provided in this review is that current at the end of May 2018.

Definition of clinical studies

Each of the three regulations employs its own definitions of activities involved in clinical study, as follows.

Medical research: An activity conducted in humans to obtain knowledge that contributes to the improvement of public health or to the improvement of quality of life (QOL) of patients, by understanding the cause and pathology of disease. Clinical Trial and PMS as specified in the Pharmaceuticals and Medical Devices Law are excluded from the definition of Medical Research (2, 3).

Clinical research: A study to clarify the efficacy and/or safety of drugs, medical devices and regenerative medicine products in humans is defined as Clinical Research. In Clinical

Research not regarded as “Specified Clinical Research”, clinical investigators have to make reasonable efforts to comply with the Clinical Research Law. Clinical Trial and PMS defined in the Pharmaceuticals and Medical Devices Law are excluded from the definition of Clinical Research (4). **Specified clinical research:** Clinical Research especially using drugs that have not yet been approved, or using drugs for other than approved indications, is defined as Specified Clinical Research. Clinical Research financially supported by industry(s) or supplier(s) of test drugs is also included within this kind of study. In conducting Specified Clinical Research, clinical investigators shall fully observe the Clinical Research Law (4).

Clinical trial: A clinical study aiming to obtain clinical results that will be attached to the application package for approval of a drug by the JMHLW is defined as a Clinical Trial (1,7).

Post-marketing surveillance (PMS): Clinical studies conducted by pharmaceutical companies to evaluate the safety and efficacy of approved drugs after JMHLW’s approval are defined as PMS based on the Pharmaceuticals and Medical Devices Law.

To summarize the situation, Fig. 1 provides the scopes of clinical studies based on their regulatory context. The definition of Medical Research based on the Ethical Guideline includes every kind of clinical study in humans including Clinical Research, Clinical Trial, and PMS. However, the Ethical Guideline excludes Clinical Trial and PMS from the definition of Medical Research. Although there is no explicit provision in the Ethical Guideline, Clinical Research and Specified Clinical Research are also considered to be excluded from the definition of Medical Research (8).

²In order to avoid any confusion between terminologies defined in the Pharmaceuticals and Medical Devices Law and the Clinical Trials Act, “Clinical Trial”, “Specified Clinical Trial” and “Certified Review Board” defined in the Clinical Trials Act are referred to hereinafter as “Clinical Research”, “Specified Clinical Research” and “Certified Clinical Research Review Committee”, respectively.

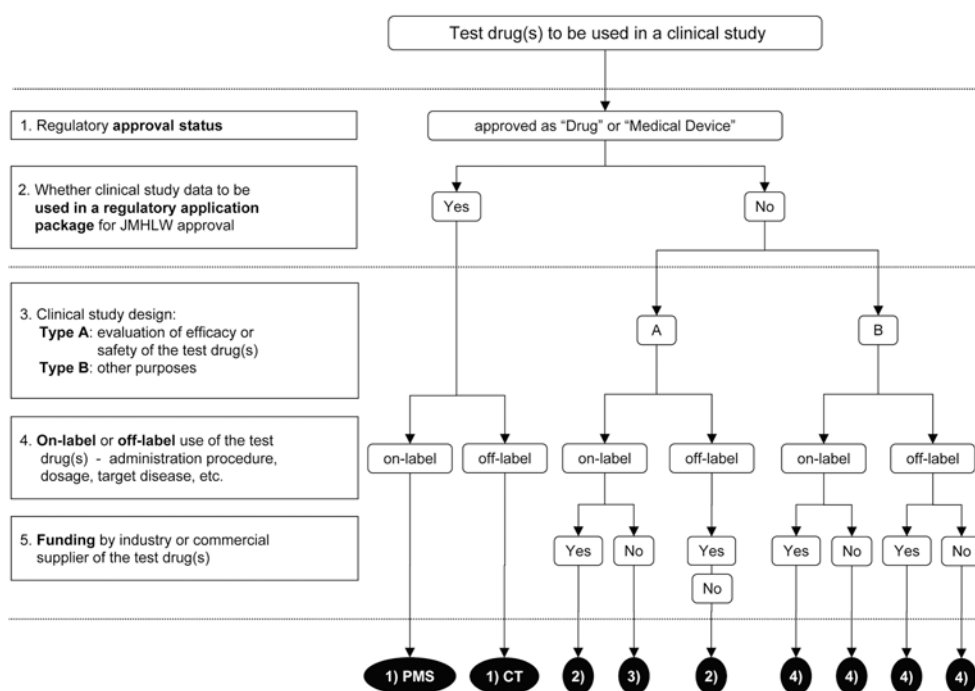


Fig. 2 Flow chart to determine applicable regulations from the investigators' viewpoint: Approved drugs and medical devices.

Applicable Law:

- 1) Pharmaceuticals and Medical Device Law - "Clinical Trial (CT)", "Post-marketing Surveillance or Study (PMS)"
 - 2) Clinical Research Law - "Specified Clinical Research"
 - 3) Clinical Research Law - "Clinical Research"
 - 4) Ethical Guideline - "Medical Research"
- CT: clinical trial, PMS: post marketing study

How to select the applicable law for conducting clinical studies using radiopharmaceuticals

The regulation applied to a clinical study using a radiopharmaceutical(s) on humans depends on several aspects of the study such as the approval status of the radiopharmaceutical(s) being used. Fig. 2 is a flow chart for selecting the applicable law for clinical studies using approved test drug(s). Fig. 3 shows how to select the applicable laws for clinical studies involving unapproved test drug(s). The first and second steps will determine whether or not the study needs to comply with the Pharmaceuticals and Medical Devices Law. The next four steps, from third to sixth, will determine whether or not the study needs to comply with the Clinical Research Law. If a planned study does not match either of the two laws, the Ethical Guideline should be applied instead.

In Figs. 2 and 3, the first step to be considered in the flow chart is whether or not the drug being used for the study has been approved. The second step is to consider whether or not the clinical study data that will be obtained are intended to be used as part of the package for application for JMHLW approval. The third step is to consider whether or not the study is designed to evaluate the efficacy and/or safety of the drug being used for the study. The fourth step is to consider whether on-label or off-label instructions will be followed in terms of

administration procedure, dosage, or target disease. The fifth step is to check whether or not the study is being funded by industry or by the supplier of the drug being used for the study. The sixth step is to select the type of radiopharmaceutical to be used in the clinical study. By following these 6 steps, researchers can determine the appropriate law to apply to their clinical studies.

Variations in clinical studies

There are various designs for clinical studies involving radiopharmaceuticals. Certain studies may require careful consideration given the lack of clarity and experience with respect to the enforcement of the Clinical Research Law. The authors propose the following cases which include examples of certain point to consider.

- 1) In a clinical study where only the *pharmacokinetics* of an approved radiopharmaceutical are being investigated in human subjects, the study conforms with the definition of Clinical Research (9).
- 2) In a clinical study where the approved radiopharmaceutical is being used based on approved indications only to visualize the *physiological or pathological condition* of subjects and is not being used to stratify or randomize patient allocation, the study may be considered "Medical

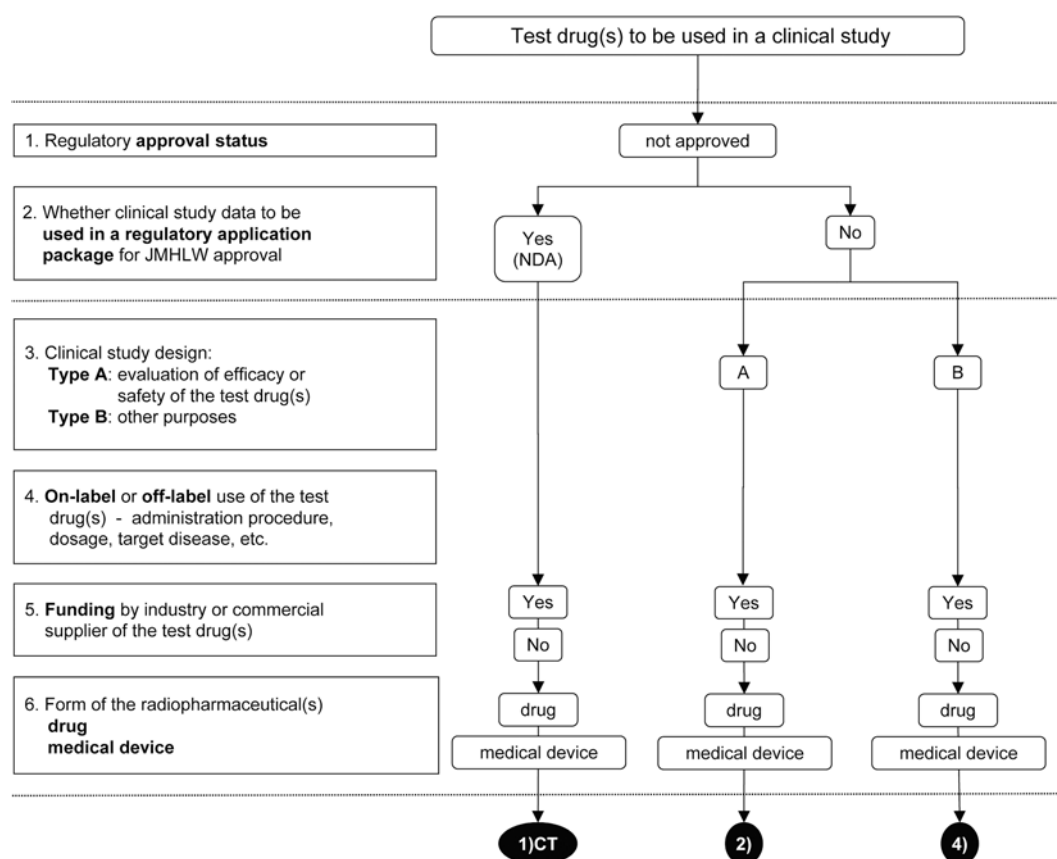


Fig. 3 Flow chart to determine applicable regulations from the investigators' viewpoint: Unapproved drugs and medical devices.

Applicable Law:

- 1) Pharmaceuticals & Medical Device Law – “Clinical Trial (CT)”, “Post-marketing Surveillance or Study (PMS)”
 - 2) Clinical Research Law – “Specified Clinical Research”
 - 3) Clinical Research Law – “Clinical Research”
 - 4) Ethical Guideline – “Medical Research”
- CT: clinical trial

Table 1 Regulations applicable to the chemistry, manufacturing and control (CMC) of investigational products and their non-clinical studies

| Clinical study type | Ethical Guideline | Clinical Research Law | | Pharmaceuticals and Medical Devices Law |
|--|--|---|-----------------------------|---|
| | | Clinical Research | Specified Clinical Research | Clinical Trial, PMS |
| Chemistry, manufacturing and control (CMC) of test drug(s) | No explicit provisions to specify the CMC of test drug(s) required before entering Medical Research phase | Notification to ensure the quality of test drug (s) before entering Clinical Research phase (14) | | GMP for Investigational Products for quality standards (7) |
| Non-clinical Studies | No explicit provisions to specify non-clinical study items required before entering Medical Research phase | No explicit provisions to specify non-clinical study items required before entering Clinical Research phase | | ICH-M3 (R2) Guidance and Micro-dose Clinical Trial Guidance (10,11) |

Research”. However, it is recommended that investigators consider the study design from a broader perspective. Where a study aims to evaluate the safety and/or efficacy of therapeutic intervention including therapeutic drug(s) based on information obtained through imaging with radiopharmaceutical (s), the applicable law should be

determined based on the objectives and design of the study.

- 3) When an approved radiopharmaceutical used as a standard measurement and an unapproved radiopharmaceutical used for testing purposes are administered to human subjects in a comparative study, for evaluating the safety

and/or efficacy of unapproved drug, such a study can be performed as either Specified Clinical Research or a physician-sponsored Clinical Trial. It should be noted that the Clinical Research Law does not clearly specify which non-clinical data package should be used for an unapproved drug that is being reviewed by the Certified Clinical Research Review Committee. On the other hand, the Pharmaceuticals and Medical Devices Law requires investigators to prepare the non-clinical data package in compliance with the Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) for investigational products, and in accordance with ICH-M3(R2) Guidance, Micro-dose Clinical Trial Guidance, etc. (10-12). The applicable law should be determined based on the potentially high risk of the unauthorized drug and research resources that will be needed for compiling the non-clinical data package.

It is recommended that investigators consult the Pharmaceuticals and Medical Devices Agency (PMDA) if they have any questions about the choice of relevant law.

Specified clinical research

Particular attention should be paid to the “Specified Clinical Research” because the types of clinical studies involved need to fully comply with the Clinical Research Law. The principal investigator is required to prepare a set of documentation that includes such things as the research protocol, case report forms, informed consent form, and standard operating procedures (6). The study plan should be reviewed by the Certified Clinical Research Review Committee accredited by the JMHLW, which is similar to the Institutional Review Board (IRB) defined in the GCP. After review, the study plan needs to be submitted to the JMHLW with the review report of the above committee. Under the Ethical Guideline, oversight of Medical Research is not within the purview of the JMHLW, whereas under the Clinical Research Law, the JMHLW has the authority to monitor and instruct with regard to Clinical Research, and if necessary, to issue an order to stop or change the protocol of the Clinical Research.

The Clinical Research Law also obligates the drug or medical device company to establish an agreement with the institution and principal investigator when it financially supports Specified Clinical Research involving its own drug (s). The company must provide annual disclosure of any funding to investigators conducting the above-mentioned Specified Clinical Research. Both clinical investigators and industries should follow conflict of interest procedure in accordance with the JMHLW notification (13).

Conclusions

In Japan, clinical studies to evaluate the pharmacokinetics,

efficacy, or safety of *in vivo* diagnostic radiopharmaceuticals have to be conducted under either the Pharmaceuticals and Medical Devices Law or the Clinical Research Law from April 2018 or the Ethical Guideline. Clinical investigators need to carefully determine the applicable law relevant to a planned clinical study bearing in mind the objectives of the study, study design, and any funding by companies.

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Conflicts of interest

None.

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