Laws and Regulations for Clinical Studies of Drugs in Japan

Date of preparation: February 20, 2026

Chapter 1: Regulations pertaining to clinical studies of drugs in Japan

1. Hierarchy of the laws and regulations

1-1. Legal system

The legal system in Japan has a hierarchical structure according to the potency. The constitution is the supreme law in Japan, and all other laws and orders must follow the constitution. Below these, laws established by the Diet follow, and basic rules to be applied to the whole nation are established. To concretely operate the laws, cabinet orders are established. Below them, ministerial ordinances established by the ministers of individual ministries and agencies are positioned. Ministerial ordinances further details matters stipulated by laws and cabinet orders to stipulate procedures and standards necessary for practical operations.

Below these laws and ordinances, there are notices, notifications, and guidelines issued by administrative agencies. Although they are generally not legally binding, they play an important role in practice and supplement the interpretation and application of laws and ordinances. Furthermore, there are municipal Ordinances and regulations established by municipal governments, and they apply to regions within the scope of national laws and ordinances. As described above, the Japanese legal system forms a pyramid structure in the following order: Constitution, Laws, Cabinet Orders, Ministerial Ordinances, Notices/Notifications/Guidelines, and Municipal Ordinances and Regulations. Contents against the higher laws and regulations become invalidated. This hierarchical structure preserves consistency and order of the laws.

Only laws, cabinet orders, ministerial ordinances, guidance, and notifications issued by regulatory authorities (Ministry of Health, Labour and Welfare and Pharmaceuticals and Medical Devices Agency [PMDA]) are subject to this survey. Documents prepared by parties other than the regulatory authorities, such as academic society guidelines and voluntary standards of industry organizations, are not subject to this survey.

1-2. Regulatory authorities

The outline of the regulatory authorities in Japan is as follows:

Ministry of Health, Labour and Welfare:

It is one of the central ministries and agencies of the Japanese government, and is responsible for the formulation and implementation of policies in a wide range of areas such as medical care, public health, labor, and welfare. In the pharmaceutical regulations, individual divisions and bureaus, mainly Pharmaceutical Safety Bureau, are responsible for designing systems based on the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act), issuing administrative notifications, and making final decisions on approval, etc., and take the final responsibility for regulations on drugs, etc. in Japan. In the areas pertaining to clinical studies, the divisions and bureaus in charge of promotion of clinical trials and researches,

improvement of clinical trial environments, and R & D policies are responsible for development of the systems and policies. Based on these roles, the Ministry of Health, Labour and Welfare is positioned as an administrative body that forms the basis of the clinical trial system in Japan and supervises the direction of regulations and the final administrative judgment.

PMDA:
Pharmaceuticals and Medical Devices Agency (PMDA) is an expert organization responsible for scientific review, safety measures, and adverse health effects relief for drugs, medical devices, and regenerative medicine products according to the PMD Act and the measures of the Ministry of Health, Labour and Welfare. PMDA receives clinical trial notifications and reports on adverse drug reactions/malfunctions that occurred during clinical trials and reports to the Ministry of Health, Labour and Welfare (MHLW). In addition, it provides consultation support before the start of clinical trials and conducts scientific review before regulatory reviews. Furthermore, as a core technical agency that conducts regulatory reviews, PMDA provides the basis for the evaluation of clinical study data, establishment of appropriate indications and usage, and determination of safety measures. In this way, PMDA plays a role to support the final judgment of the Ministry of Health, Labour and Welfare as a specialized agency responsible for scientific evaluation based on clinical trial data.

2. Regulations applied to clinical studies of drugs

"Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act)" is the highest regulation among the laws and regulations related to clinical studies in Japan. Under the PMD Act, cabinet orders stipulated by the Cabinet supplement the details of the operation. Ministerial ordinances stipulated by the Ministry of Health, Labour and Welfare are positioned under them. Regulations applicable to clinical studies of drugs and their overview are as follows:

Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, 1960) (Latest revision: Issued on May 21, 2025):
This is a basic law to ensure the quality, efficacy, and safety of drugs, medical devices, and regenerative medicine products in Japan. This Act is to establish consistent regulatory frameworks from the research stage to the post-marketing stage, including product approval system, authorization of manufacturers, standards for conducting clinical studies, and post-marketing safety measures. For clinical studies, it stipulates rules related to clinical trials of drugs (in compliance with ministerial ordinance on GCP for drugs) that are conducted under the regulations to ensure the scientific nature, ethics, and protection of subjects. Hereinafter, it is referred to as the PMD Act.

Clinical Trials Act (Act No. 16, 2017) (Latest revision: Issued on February 28, 2025, enforced on May 31, 2025):
This Act was established to ensure transparency, ethics, and safety and manage conflict of interest in "clinical trials" other than clinical trials of drugs. Especially, in clinical trials of specified drugs, etc.(specified clinical researches), review by Certified Review Board, notification of research plans, monitoring/audit, and appropriate management of information on conflict of interest are obligatory

are mandatory. It also stipulates prevention of wrongful clinical trials and mandatory information disclosure to systematically support the highly reliable clinical trials.

Act on the Safety of Regenerative Medicine (Act No. 85, 2013) (Latest version: Issued on June 14, 2024, enforced on May 31, 2025):
The Act is to establish a framework for safe provision of regenerative medicine, etc. (cell-processed products, cell therapy, gene therapy, etc.) to stipulate the risk-based classification system, notification of provision plans, reviews, permission/management standards for cell processing facilities, etc. In addition, it is intended to establish compatibility between safety of subjects and patients and technical development in regenerative medicine technologies in the clinical trial stage, by requiring appropriate safety management and ethical review and imposing regulations according to risks even in pre-marketing researches.

Cabinet Order (enforcement order based on the PMD Act):
A cabinet order is to establish details and scope of application of matters stipulated by the law according to the PMD Act. It specifies details necessary for operation of law such as clinical trial system, drug classification, approval system, and post-marketing safety measures and plays a role to guarantee the effectiveness of the PMD Act.

Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs (Ministry of Health and Welfare Ordinance No. 28, 1997) (Latest revision: Enforced April 1, 2025):
The ministerial ordinance is to stipulate ethical and scientific standards to be observed when conducting clinical trials (clinical studies of drugs). It clarifies the roles and procedures of the investigator, sponsor (pharmaceutical company), institutional review board (IRB), etc. in order to protect the human rights and safety of subjects and secure the scientific validity of clinical trials and reliability of their data. It specifies matters necessary for the operation in Japan based on the international concept of ICH-GCP.

Guidance and notifications by MHLW and PMDA:
These are to supplement the interpretation and operation of the PMD Act and the Ministerial Ordinance on GCP for Drugs, etc., and show specific guidelines and precautions at the practical level. It plays a role to enhance the quality and safety of clinical trials by providing practical judgment criteria that reflect the latest scientific knowledge and international trends in a wide range of fields such as planning and implementation of clinical trials, data handling, handling of electronic systems, reporting of adverse events, and post-marketing safety measures.

ICH Guidelines (international guidelines):
The guidelines are Internationally harmonized ethical and scientific standards for pharmaceutical development, developed jointly by the regulatory authorities and the pharmaceutical industries in Japan, the US and the EU. They are provided for comprehensive requirements for clinical trial design, monitoring, quality management, document management, IRB review, etc. with a focus on the protection of subjects and assurance of data reliability. The ministerial ordinance on GCP for drugs in Japan is also based on ICH E6 (GCP), and they serve as an essential guide for international harmonization of drug development requirements.

3. Classification for consideration of applicable regulations

When conducting clinical trials of drugs involving intervention in Japan, various categories may be included to consider their applicable regulations and guidance. The uniform definition of "intervention" in clinical trials is not established by laws and regulations. However, in "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" (hereinafter referred to as the "Ethical Guidelines"), "intervention" is defined as an act of intentionally controlling factors that may affect human health for research purposes. Hereinafter, based on this, applicable regulations are to be organized.

3-1. Regulations applied to clinical trials intended for the application for marketing approval

A clinical study (clinical trial) intended for marketing approval application is conducted according to on the PMD Act and Ministerial Ordinance on GCP for Drugs in Japan. The PMD Act stipulates legal requirements for obtaining marketing approval for drugs, and a sponsor is obliged to submit a clinical trial notification to the Ministry of Health, Labour and Welfare (Article 80-2). Control and accountability of investigational product (Article 80-2, Paragraph 1), selection of investigators (Article 80-2, Paragraph 1), and assurance of study safety (Article 68) are legally required, and administrative measures or criminal punishment may be imposed when these regulations are violated (Article 72, Article 75, and Article 83 to Article 91).

The Ministerial Ordinance on GCP for Drugs sets forth detailed standards to ensure the quality and reliability of clinical trials. The sponsor is obliged to conduct monitoring and audit (Article 3 of the ministerial ordinance on GCP). The investigator is obliged to obtain informed consent from subjects (Article 4 of the ministerial ordinance on GCP), prepare case report forms (CRFs) (Article 26 of the ministerial ordinance on GCP), and appropriately store records (Article 28 of the ministerial ordinance on GCP). Prior review by the ethical review board is mandatory (Article 5 of the ministerial ordinance on GCP), and the records after completion of the clinical trial must be retained for 5 years, in principle (Article 28 of the ministerial ordinance on GCP). These regulations are essential to ensure the scientific validity and ethics of the data to be used in the application for marketing approval.

"Ethical Guidelines for Medical and Biological Research Involving Human Subjects" apply to all researches in human subject to be conducted in Japan. However, researches within the scope of other laws and guidelines are not covered. Specifically, clinical trials according to the PMD Act (clinical studies for the purpose of application for marketing approval) are not directly applicable to the ethical guidelines because they are subject to the Ministerial Ordinance on GCP for Drugs.

3-2. Regulations applied to clinical trials that are not intended for the application for marketing approval

Clinical studies not intended for the application for marketing approval are subject to the Clinical Trials Act (Articles 2, 4, 6, 9, and 12) and the Ethical Guidelines. The Clinical Trials Act was established to ensure the transparency and reliability of clinical trials in drugs, and submission of the clinical trial plan is required in those that fall under specified clinical researches (Article 2, Paragraph 3: Clinical trials involving funding from company and use unapproved drugs or off-label

use) (Article 4). Furthermore, management of conflict of interest (Article 6), implementation of monitoring and audit (Article 9), and disclosure of clinical trial plan (Article 4) are mandated. In case of violation, criminal punishment or administrative measures may be imposed (Article 12).

3-3. Laws and regulations applied to new modalities

The laws and regulations applied to clinical trials in new modalities (nucleic acid drugs, gene therapy, cell-based therapy, etc.) differ depending on whether the clinical trial is intended for marketing approval application or not, rather than the product type itself. When the trial is intended for marketing approval application, it is positioned as a clinical trial, and the PMD Act and the Ministerial Ordinance on GCP for Drugs are applied. On the other hand, if the study is conducted as a clinical trial that is not intended for marketing approval, the Clinical Trials Act is applied. If the study falls under a specified clinical research, approval from the certified review board and notification to the Ministry of Health, Labour and Welfare are mandatory.

Next, applicable laws and regulations are diverged depending on whether or not the investigational product falls under a regenerative medicine product. Regenerative medicine products are defined in the PMD Act as "human or animal cells processed through cell culture that are intended to rebuild, restore, or form the structure or function of human body or to be used to treat or prevent diseases" and "to introduce genes into human cells for use in gene therapy." If the study falls under this category and is intended for obtaining marketing approval, the Ministerial Ordinance on Good Clinical Practice for Cellular and Tissue-based Products (Ministerial Ordinance on GCP for Cellular and Tissue-based Products) will be applied, instead of the Ministerial Ordinance on GCP for Drugs. Since manufacturing processes of cellular and tissue-based products are likely to reflect quality attributes directly, it is important to control cellular and tissue-based products in accordance with Good Gene, Cellular, and Tissue-based Products Manufacturing Practice (GCTP Ordinance).

On the other hand, to a clinical trial of regenerative medicine that is not intended for application for marketing approval but intended to provide medical treatment, the Act on the Safety of Regenerative Medicine is applied, and assurance of safety according to risks is required through the submission of treatment plan and committee review, etc.

In the new modalities, measures against additional regulatory guidelines are required according to the product characteristics, regardless of the study category such as clinical trial or clinical research.

Since chemical structures and degradation characteristics of nucleic acid drugs differ remarkably from those of conventional small molecule drugs, additional measures, such as raw material control, impurity profile, and degradation product evaluation, are required for quality control and stability evaluation based on ICH quality guidelines, such as ICH Q8 (Formulation development), Q9 (Quality risk management), and Q11 (Development and manufacture of drug substances).

In gene therapy, safety evaluation on viral vector, etc. and long-term risk control associated with gene transfer are important. Therefore, in reference to domestic guidelines such as the "Guidelines for Nonclinical Studies of Gene Therapy Products," etc. presented by PMDA/MHLW and related guidelines such as ICH S6 (R1) and M3 (R2), it is necessary to evaluate the biodistribution at a non-clinical phase and plan the long-term follow-up in clinical studies.

In cell-based therapy, controls of cell-derived materials, manufacturing process, manufacturing and quality are important. Measures should be taken according to the GCTP Ordinance. In addition, to evaluate the production lot equivalence and effects of process changes, concepts of ICH quality guidelines such as ICH Q8, Q9, Q10, and Q11 should be referred to.

3-4. Ethical guidelines applied to studies which are not subject to the Clinical Trials Act

Clinical studies in which an approved drug is used within the range of approved dosage and administration, no funding is provided by any company, and "testing with a significant burden" etc. is not added for research purposes are not subject to regulations of the Clinical Trials Act. Such studies consist mainly of interventions and observations within the scope of usual medical care, or studies using existing medical information, which include so-called "observational studies" and low-risk prospective studies.

These clinical studies are conducted based on the "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" instead of the laws and regulation. The Ethical Guidelines provide basic frameworks to conduct the studies ethically conduct of research, including protection of the rights of subjects, appropriate handling of personal information, methods of obtaining an informed consent, validity of study plans, and procedures for approval by the Ethical Review Board. Although the Ethical Guidelines are not laws and regulations, they are positioned as standard codes widely applied to medical research in Japan.

3-5. Regulations on clinical trials of combination products

In Japan, products combining two or more components including drugs, medical devices, and regenerative medicine products are classified as "combination products" according to notifications/guidance of the MHLW and PMDA, based on individual product definitions of the PMD Act, and drug-eluting stents, prefilled syringes, drug-device combination products-integrated, etc. fall under this category. Based on the main indications (or main functions), PMDA will determine which product should be handled as a drugs, medical devices or regenerative medicine products. The handling of these products are organized according to the related notifications and guidance including MHLW Notification "Handling of Marketing Application for Combination Products."

In clinical trials of combination products, applicable laws and regulations as well as practical handling are determined according to the main action. In other words, clinical trial frameworks for drugs, medical devices, and regenerative medicine products will be applied to the following products, respectively: Products with drug efficacy as the main action (the framework of the PMD Act and Ministerial Ordinance on GCP for Drugs), those with mechanical/structural actions as the main action (the framework of the medical device regulations), and those with cellular effects as the main action (the framework of regenerative medicine products according to the PMD Act). Applications and reviews are mainly conducted by the relevant divisions of PMDA, and cross-functional collaborative reviews are conducted as necessary.

An Antibody-Drug Conjugate (ADC) is usually considered as a product with "pharmacological action as the main action" and handled as a medicinal product. On the other hand, for products in which the main action is exerted by a device such as drug-eluting stent, clinical studies in products as

medical devices are required, and safety and release characteristics, etc. of the drug component are also evaluated.

3-6. Phase 1 study (First-In-Human, FIH/early phase)

A phase 1 study is intended to confirm the safety, tolerability, and pharmacokinetics (and pharmacodynamics if necessary) of the study drug at an early stage and to obtain basic information on dose selection and risk management in the subsequent phases. When the study is conducted as a clinical trial for the purpose of marketing approval application, monitoring, protection of subjects, and assurance of data reliability of data by the sponsor and study site are required pursuant to the PMD Act and the Ministerial Ordinance on GCP for Drugs.

The clinical practice in the FIH/early phase is conducted based on the notification from the Ministry of Health, Labour and Welfare "Guidance for Establishing Safety in First-in-Human Studies", and key points for safety assurance, such as initial dose setting, dose escalation, treatment discontinuation criteria, adverse event monitoring, and appropriate study site system/personnel, are detailed. Regarding the handling of non-clinical safety studies of first-in-human studies at the time of submitting the clinical trial notification, the PMDA has clarified the practical concept through Q & A, etc. based on the notification to clarify the non-clinical package at the time of FIH notification.

As a result of the recent acceleration of global joint development, the MHLW Notification, "Basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan" and its Q & A by PMDA have been made public. These notifications have presented a basic principle that an additional phase 1 study in Japanese subjects are not required as a general rule for drugs in which early clinical development is preceding outside Japan, based on the consideration of individual safety evaluation and effects of ethnic differences.

3-7. Studies in orphan drugs

Clinical studies of orphan drugs in Japan are conducted in accordance with the PMD Act and the Ministerial Ordinance on GCP for Drugs, and Orphan Drug Designation system is utilized. In this system, drugs, etc. intended for use in less than 50,000 patients in Japan and at particularly high medical needs are positioned as Orphan Drugs and designated as an orphan drug by the Minister of Health, Labour and Welfare based on the opinion of the Pharmaceutical Affairs and Food Sanitation Council. The orphan drug designation itself does not guarantee approval, but if it is designated, incentives such as priority review, priority face-to-face consultation by the PMDA, reduction in application fees, extension of re-examination period, research grants, and tax preferential treatment will be given. Therefore, the orphan drug designation is commonly obtained at an early phase of clinical development.

In the field of rare diseases in which the number of patients is limited, flexible study designs such as small-scale studies, single-group designs, use of previous clinical data as a control, and use of multi-regional clinical trials are permitted. In recent years, if it is difficult to conduct an additional study in Japanese subjects with ultra-rare diseases, etc., the approval may be determined based only on data from global studies after individual scientific validity is evaluated.

3-8. Studies in children

Clinical trials in children are conducted to establish the appropriate dosage, administration method, efficacy, and safety for children, and ethical considerations and minimization of burdens are required more than those for adults. In clinical trials intended for marketing approval application, the PMD Act and the Ministerial Ordinance on GCP for Drugs are applied, and more attention is placed on the informed consent by parents, child assent, restrictions of blood sampling volume and procedures, and long-term safety observation.

The international standards of ICH E11 "Clinical Investigation of Medicinal Products in the Pediatric Population" and Appendix E11 (R1) Addendum were adopted, which provide the basic principles necessary for pediatric drug development, such as age group, ethical considerations, study design, extrapolation modeling & simulation, and pediatric drug formulation development. In Japan, ICH E11 was officially introduced in accordance with the MHLW Notification (PMSB/ELD Notification No. 1334) "Guidance on Clinical Studies of Drugs in Children," and ICH E11 (R1) was adopted as an addendum and publicized according to PSEHB/PED Notification No. 1227-5 dated December 27, 2017, "ICH E11 (R1) Addendum: Clinical Studies of Drugs in Pediatric Population."

3-9. Regulations for handling narcotics and psychotropics in clinical trials

In Japan, narcotics and psychotropics are strictly regulated in accordance with "Narcotics and Psychotropics Control Act." When handling study drugs containing narcotics in clinical trials, it is mandated that the study site should be authorized as Narcotics Handler and that physicians who treat subjects should be licensed as Narcotics Practitioner. In addition, authorization by and notification to the MHLW (Narcotics Control Department, Regional Bureau of Health and Welfare), and drug accountability are mandatory for import, storage, use, disposal, etc. of narcotics and psychotropics. To respond to these regulations, a stringent management system for the study drug is also required in clinical trials.

Chapter 2: Detailed Regulations for Clinical Studies of Drugs in Japan

This chapter organizes the relevant regulatory requirements for each of the key elements required to conduct a clinical study in Japan.

1. Approval for conducting clinical studies by the government or regulatory authorities

Ministerial Ordinance on GCP for Drugs:

According to Article 80-2 of the PMD Act and related enforcement regulations, it is necessary to submit a clinical trial notification to the regulatory authorities before starting a clinical study (clinical trial) of a drug for the purpose of approval application. In Japan, when a clinical trial is conducted in an unapproved drug or for off-label use of the drug for the purpose of application for marketing approval, all of them are managed as "clinical trials" under the PMD Act.

In Japan, there is no exemption system to simplify the procedures for the use of unapproved drugs for the purpose of clinical trials (e.g., a system corresponding to exemption from IND). When conducting a clinical trial, the submission of clinical trial notification is mandatory.

Clinical Trials Act:

In a study subject to the Clinical Trials Act, a protocol reviewed and approved by the Certified Review Board (CRB) must be submitted to the Minister of Health, Labour and Welfare before the start of the study. This notification is considered to have been submitted to the Minister of Health, Labour and Welfare by registering the study protocol in jRCT (clinical research submission/publication system).

Ethical guidelines:

No procedures including filing an application with, submission to, or approval by the government or regulatory authorities are required.

2. Approval of conducting clinical studies by IRB

Clinical studies that are conducted in Japan are characterized by the different names and requirements of review boards and review materials depending on the applicable laws and regulations.

Ministerial Ordinance on GCP for Drugs:

Clinical studies must be reviewed and approved by the IRB established by each study site, or the IRB with which the study site has concluded an engagement agreement for the review. Based on the results of the IRB review, the clinical study can be conducted at the study site after it is approved by the head of the study site.

Clinical Trials Act:
Clinical studies must be reviewed and approved by the CRB established by each study site, or the CRB with which the study site has concluded an engagement agreement for the review. Based on the results of the CRB review, the clinical study can be conducted at the study site after it is approved by the head of the study site.

Ethical guidelines:
Clinical studies must be reviewed and approved by the Ethical Review Board established by each study site, or the Ethical Review Board with which the study site has concluded an engagement agreement for the review. Based on the results of the review by Ethical Review Board, the clinical study can be conducted at the study site after it is approved by the head of the study site.

3. Conflict of interest (COI) in clinical studies

Ministerial Ordinance on GCP for Drugs:
The Ministerial Ordinance on GCP for Drugs does not require preparation of materials explaining COI with the sponsor in the requirements for study sites and investigators. Also, the responsibilities of the Institutional Review Board based on the Ministerial Ordinance on GCP for Drugs include no mandatory submission of materials concerning conflict of interest, and it is left to the individual discretion.

In addition, the company sponsoring the clinical study may voluntarily manage COI by complying with transparency guidelines stipulated by the industry organization make inquiries to physicians participating in the clinical trial about the status of acquisition of shares of the company with reference to overseas regulations, etc. The medical institution conducting the clinical trial may voluntarily accept reviews by the COI Management Committee established in the hospital according to the provisions of the medical institution.

Clinical Trials Act:
The Clinical Trials Act was established for the purpose of ensuring appropriate management of COI after the inadequacy of COI management was pointed out in past clinical studies. For this reason, the method (development of management plan, etc.) and criteria for COI management are strictly specified, and information on the COI management is also included in materials to be reviewed by CRB.

Ethical guidelines:
In Chapter 12, "management of conflict of interest" is clearly required for clinical studies conducted under the ethical guidelines. Specifically, it is stipulated that the statement of "status of conflict of interest related to funding sources and clinical studies by other institutions and conflict of interest of individual researchers" should be included in the study protocol. The study protocol, etc. containing the COI information will be confirmed by the Ethical Review Board at the time of the review, and necessary measures may be required. Unlike the Clinical Trials Act, which is a legal regulation, the Ethical Guidelines are characterized as guidelines that contribute to the proper conduct of medical researches.

4. Explanation to subjects and obtainment of consent, and multilingualization

Ministerial Ordinance on GCP for Drugs:

The Ministerial Ordinance on GCP for Drugs stipulates information that should be included in the informed consent form, and in principle, it is strictly stipulated that voluntary consent should be obtained from the subject himself/herself. In the Ministerial Ordinance on GCP for Drugs, clear explanation of the nature of the investigational product, expected efficacy, possible risks, alternative treatments, etc. are mandatory, but no provisions of explanation about the information on the funding source or conflict of interest to subjects are included. In addition, there are no provisions on multilingualization of the informed consent form.

Clinical Trials Act:

The Clinical Trials Act stipulates the informed consent form equivalent to those stipulated in the Ministerial Ordinance on GCP for Drugs and the process of obtaining a consent. It is characterized as a regulation to notify subjects of information on the COI management methods and the source of funds. There are no provisions on multilingualization of the informed consent form.

Ethical guidelines:

Unlike the Ministerial Ordinance on GCP for Drugs and the Clinical Trials Act, provisions on retrospective observational studies with no use of drugs/medical devices are included. For this reason, various options such as obtaining written consent before start of the study, orally giving a consent, recording in medical records, and utilization of opt-out are available according to the individual clinical studies. However, there are no provisions for multilingualization of the informed consent form.

It is also characterized by the complexity of the informed consent process because the process of obtaining a consent differs depending on the planned study contents, presence or absence of invasive procedures and therapeutic interventions, etc.

5. Compensation to Subjects

Ministerial Ordinance on GCP for Drugs and Clinical Trials Act:

These regulations require establishment of policy and system for handling of compensation in the event of health injuries caused by the study prior to the start of the study to reflect them in the protocol, etc., and include clear descriptions about them in the informed consent form. On the other hand, since the amount of compensation and calculation standards are not uniformly provided for in the laws and regulations, it is generally determined by the implementation body of each study (sponsor, investigator, etc.) according to the characteristics of the study, in consideration of the industry guidance by the Japan Pharmaceutical Industry Legal Affairs Association (IHOKEN), etc. In addition, the IRB and CRB are required to review that the compensation policy and system for subjects are properly established in conducting the study in accordance with each law and regulation.

Ethical guidelines:

For studies involving invasive procedures (excluding minor invasiveness) and medical practice beyond usual medical care, it is required to consider appropriate handling of compensation with reference to the guidelines provided by IHOKEN as well as the Ministerial Ordinance on GCP for Drugs and the Clinical Trials Act.

On the other hand, as represented by retrospective observational studies, etc., preparation of the compensation system is not required for studies with no risk of health injury caused by the study. In addition, in clinical trials conducted within the scope of usual medical care, a compensation system generally retained by medical institutions and companies is commonly used instead of establishing a study-specific compensation system.

6. Reporting of safety information to regulatory authorities

Ministerial Ordinance on GCP for Drugs:

Based on Article 80-2 of the PMD Act and the Ministerial Ordinance on GCP for Drugs, the sponsor or sponsor-investigator is required to report suspected unexpected serious adverse reactions (SUSARs) occurring in clinical trials to the regulatory authorities within 7 days for unknown and life-threatening events including death, or within 15 days for unknown and other serious events.

Clinical Trials Act:

During a specified clinical research in an unapproved or off-label drugs, if any unexpected serious event that is suspected to be caused by the trial occurs, the investigator is required to report diseases, etc. to the Minister of Health, Labour and Welfare according to Article 16-3 of the Clinical Trials Act. The events must be reported through jRCT, and the reporting deadline is 7 days for death or life-threatening events or 15 days for other serious events.

Ethical guidelines:

In clinical trials conducted under the ethical guidelines, persons conducting clinical trials are not required to immediately report adverse events to the regulatory authorities directly. In this case, persons conducting clinical trials must provide safety information to manufacturers, etc. Based on such information, the manufacturer must evaluate the information as part of compulsory safety management under Article 68-10 of the PMD Act, and then report it to the regulatory authorities as reporting of adverse drug reactions, etc. and take appropriate safety measures, as needed, in accordance with Article 68-2 of the PMD Act and related ministerial ordinances.

7. Protection of subjects' information (protection of personal information and protection of personal healthcare information)

Protection of Subjects’ personal information is regulated by various laws in Japan including the confidentiality obligation imposed on physicians, etc. (Article 134 of the Penal Code). Recently, appropriate management is required in accordance with the "Act on the Protection of Personal Information" (Personal Information Protection Act), and more systematic and strict management is required for definition, acquisition/use, management, provision to third parties, etc. of personal

information. The Personal Information Protection Law is not a law specialized in the conduct of clinical trials, but a framework that is applied to general handling of personal information.

Ministerial Ordinance on GCP for Drugs:

The principles of the General Rules (11) of the Guidance on GCP for Drugs stipulate that records that may identify subjects should be protected, giving due consideration to the subjects' privacy and confidentiality. In addition, Article 2 of the same guidance stipulates that an identification code (subject identification code) should be assigned to each subject for management in order to protect the subject's confidentiality. Furthermore, Article 47 clearly states that assurances should be given to use the subject identification for data such as reports provided to the sponsor.

Clinical Trials Act:

Article 11 of the Clinical Trials Act clearly states that subjects' privacy must not be leaked to persons who are engaging or have engaged in specified clinical researches. Also, a term "subject identification code" is used in standard forms prepared by the Ministry of Health, Labour and Welfare in accordance with the Clinical Trials Act, and the subjects' personal information is coded before reporting.

Ethical guidelines:

Chapter 9 "Basic responsibilities for personal information, samples, and specimens/information from the deceased" of the Ethical Guidelines provides basic principles and responsibilities for the handling of personal information. In addition, the terminology system related to personal information used in the Guidelines classifies information as personal information, pseudonymously processed information, anonymously processed information, and information related to personal data to operate the system in alignment with the definitions in the Personal Information Protection Law.

8. Disclosure of clinical trial data (publication of registration/results)

The Japan Registry of Clinical Trials (jRCT) plays a central role in the registration of clinical trials in Japan. This system has been approved as a primary registry by the World Health Organization (WHO) to secure international transparency. jRCT is a system to centrally register and disclose information on clinical trials, clinical researches, and researches on regenerative medicine products, etc., and functions as a public database of clinical trial information accessible to patients and general public.

Ministerial Ordinance on GCP for Drugs:

Based on the revision of the Enforcement Regulations of the PMD Act (Notification dated August 31, 2020), new clinical trials starting after the revision are required to be registered in jRCT before the start of the study. Registration information should include study title, study category, study site, progress status, etc. After the registration, the information will be made public.

Clinical Trials Act:

Specified clinical researches based on the Clinical Trials Act (clinical trials that fall under those of unapproved drugs/off-label use/funded by companies, etc.) are also required to be registered in jRCT. The registration of the specified clinical research is required after approval by the Certified

Review Board (CRB) and before start of the trial. In specified clinical researches, a clinical trial notification needs to be submitted to the Minister of Health, Labour and Welfare in accordance with the provisions of the Clinical Trials Act, but the registration in jRCT will be regarded as having made the notification.

Ethical guidelines:

Among clinical researches that do not fall under the category of specified clinical researches, the registration in jRCT is required in clinical trials requiring intervention, in principle, based on the ethical guidelines. However, there are provisions that allow information not to be disclosed only if closing the information to public is permitted by the Ethics Review Board and the head of the study site for the purpose of protecting human rights and rights and interests. In other clinical trials (observational studies, etc.), disclosure of research information is required as a duty of effort.

In addition, a provision plan for regenerative medicine based on the Act on the Safety of Regenerative Medicine is also registered in jRCT. In this way, the system has been developed to visualize the status of research and provision of regenerative medicine technology to public.

Registry information to be opened to the public does not include personal information or company's intellectual property information. However, disclosure of basic information about the research and its progress increases the transparency and reliability of the research.

9. Laws and regulations on digitization of data, etc.

With the progress of digitization of clinical trials, processes of electronically recording, signing, and storing data have been increasing, which gives rise to areas that cannot be sufficiently covered by the conventional laws and regulations on "implementation of clinical trials" such as the PMD Act, GCP for Drugs, and Clinical Trials Act. In order to ensure the reliability of data associated with such digitization, the Ministry of Health, Labour and Welfare has established Guidelines for Electronic Records/Electronic Signatures (ER/ES guidelines) in Japan.

The ER/ES guidelines requires that clinical study data stored and managed electronically have the same authenticity, integrity, and reliability as those in paper records, and are applicable to all digitalized study-related data, such as eCRFs, electronic diaries, and monitoring records. This is consistent with the system validation, prevention of falsification, and securing of audit trail required by the Ministerial Ordinance on GCP for Drugs, and positioned as basic guidelines that support the electronic operation of clinical trials.

Compliance with the ER/ES guidelines is not a legal obligation for specified clinical researches that are not intended for approval application and those that are conducted under the ethical guidelines. However, since the reliability of electronic records needs to be secured in the same way, the ER/ES guidelines are often used as a practical reference, and management in accordance with the ER/ES guidelines is occasionally required at the discretion of the internal rules of the research institution or the ethics review board.

Appendix: List of laws and regulations and guidance cited in this summary
(Order of description)

1. Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, 1960) (Latest revision: Issued on May 21, 2025)
   Abbreviation: PMD Act
   https://laws.e-gov.go.jp/law/335AC0000000145
   (Article 80-2, Article 68, Article 68-10, Article 72, Article 75, etc.)

2. Clinical Trials Act (Act No. 16, 2017) (Latest revision: Enforced on May 31, 2025)
   https://laws.e-gov.go.jp/law/429AC0000000016

3. Act on the Safety of Regenerative Medicine (Act No. 85 of 2013) (Latest version: Enforced on May 31, 2025)
   https://laws.e-gov.go.jp/law/425AC0000000085

4. Cabinet Order (enforcement order based on the PMD Act)
   Enforcement Order of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices and Cabinet Order for Partial Revision of the Enforcement Order of the Act on the National Institutes of Biomedical Innovation, Health and Nutrition (Cabinet Order No. 357, 2025)
   https://laws.e-gov.go.jp/law/336CO0000000011

5. Ministerial Ordinance on Good Clinical Practice (Ministry of Health and Welfare Ordinance No. 28, 1997) (Latest revision: Enforced April 1, 2025)
   Abbreviation: Ministerial Ordinance on GCP for Drugs
   https://laws.e-gov.go.jp/law/409M50000100028

6. Guidance on "Ministerial Ordinance on Good Clinical Practice for Drugs" (Updated: April 1, 2025)
   https://www.mhlw.go.jp/web/t_doc?dataId=00tc9134&dataType=1&pageNo=1

7. ICH Guidelines
   https://www.ich.org/page/efficacy-guidelines
   (E6, E11, Q8, Q9, Q10, Q11, S6 [R1], M3 [R2], etc.)

8. Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Updated: partially revised on March 27, 2023)
   https://www.mhlw.go.jp/content/001077424.pdf

9. Handling of Marketing Application for Combination Products (Updated: partially revised on November 22, 2016)
   https://www.mhlw.go.jp/web/t_doc?dataId=00tc2324&dataType=1&pageNo=1

10. Guidance For Establishing Safety in First-in-Human Studies during Drug Development (December 25, 2020)
https://www.pmda.go.jp/files/000243439.pdf

11. Handling of Designation of Orphan Drugs (Updated: partially revised on January 16, 2024)
https://www.pmda.go.jp/files/000268405.pdf

12. Guidance on Clinical Studies of Drugs in Pediatric Population (December 15, 2000)
https://www.pmda.go.jp/files/000156072.pdf

13. Addendum to Clinical Investigation of Medicinal Products in Pediatric Population (December 27, 2017)
https://www.pmda.go.jp/files/000222107.pdf

14. Narcotics and Psychotropics Control Act (Act No. 14, 1953) (Latest revision: November 20, 2025)
https://laws.e-gov.go.jp/law/328AC0000000014

15. Use of Electromagnetic Records and Electronic Signatures for Applications for Approval or Licensing of Drugs, etc. (April 1, 2005)
Abbreviation: ER/ES guidelines
https://www.mhlw.go.jp/web/t_doc?dataId=00ta8216&dataType=1&pageNo=1

16. Act on the Protection of Personal Information (Act No. 57, 2003)
https://laws.e-gov.go.jp/law/415AC0000000057

Laws and Regulations for Clinical Studies of Medical Devices in Japan

Date of preparation: February 20, 2026

Chapter 1: Regulations pertaining to clinical studies of medical devices in Japan

1. Hierarchy of the laws and regulations

1-1. Legal system

The legal system in Japan has a hierarchical structure according to the potency. The constitution is the supreme law in Japan, and all other laws and orders must follow the constitution. Below these, laws established by the Diet follow, and basic rules to be applied to the whole nation are established. To concretely operate the laws, cabinet orders are established. Below them, ministerial ordinances established by the ministers of individual ministries and agencies are positioned. Ministerial ordinances further details matters stipulated by laws and cabinet orders to stipulate procedures and standards necessary for practical operations.

Below these laws and ordinances, there are notices, notifications, and guidance issued by administrative agencies. Although they are generally not legally binding, they play an important role in practice and supplement the interpretation and application of laws and ordinances. Furthermore, there are municipal Ordinances and regulations established by municipal governments, and they apply to regions within the scope of national laws and ordinances. As described above, the Japanese legal system forms a pyramid structure in the following order: Constitution, Laws, Cabinet Orders, Ministerial Ordinances, Notices/Notifications/Guidance, and Municipal Ordinances and Regulations. Contents against the higher laws and regulations become invalidated. This hierarchical structure preserves consistency and order of the laws.

Only laws, cabinet orders, ministerial ordinances, guidance, and notifications issued by regulatory authorities are subject to this survey. Documents prepared by parties other than the regulatory authorities, such as academic society guidelines and voluntary standards of industry organizations, are not subject to this survey.

1-2. Regulatory authorities

The outline of the regulatory authorities in Japan is as follows:

Ministry of Health, Labour and Welfare:

It is one of the central ministries and agencies of the Japanese government, and is responsible for the formulation and implementation of policies in a wide range of areas such as medical care, public health, labor, and welfare. In the pharmaceutical regulations, individual divisions and

bureaus, mainly Pharmaceutical Safety Bureau, are responsible for designing systems based on the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act), issuing administrative notifications, and making final decisions on approval, etc., and take the final responsibility for regulations on drugs, etc. in Japan. In the areas pertaining to clinical studies, the divisions and bureaus in charge of promotion of clinical trials and researches, improvement of clinical trial environments, and R & D policies are responsible for development of the systems and policies. Based on these roles, the Ministry of Health, Labour and Welfare is positioned as an administrative body that forms the basis of the clinical trial system in Japan and supervises the direction of regulations and the final administrative judgment.

Pharmaceuticals and Medical Devices Agency (PMDA):

Pharmaceuticals and Medical Devices Agency (PMDA) is an expert organization responsible for scientific review, safety measures, and adverse health effects relief for drugs, medical devices, and regenerative medicine products according to the PMD Act and the measures of the Ministry of Health, Labour and Welfare. PMDA receives clinical trial notifications and reports on adverse drug reactions/malfunctions that occurred during clinical trials and reports to the Ministry of Health, Labour and Welfare (MHLW). In addition, it provides consultation support before the start of clinical trials and conducts scientific review before regulatory reviews. Furthermore, as a core technical agency that conducts regulatory reviews, PMDA provides the basis for the evaluation of clinical study data, establishment of appropriate indications and usage, and determination of safety measures. In this way, PMDA plays a role to support the final judgment of the Ministry of Health, Labour and Welfare as a specialized agency responsible for scientific evaluation based on clinical trial data.

2. Classification for consideration of applicable regulations

When conducting clinical trials of medical devices involving intervention in Japan, various categories may be included to consider their applicable regulations and guidance. The uniform definition of "intervention" in clinical trials is not established by laws and regulations. However, in "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" (hereinafter referred to as the "Ethical Guidelines"), "intervention" is defined as an act of intentionally controlling factors that may affect human health for research purposes. Hereinafter, based on this, applicable regulations are to be organized.

2-1. Regulations applied to clinical trials that are intended for the application for marketing approval

Clinical studies intended for marketing approval application and those to confirm safety/efficacy

of an unapproved medical device or off-label use are called "clinical trials." To conduct clinical trials, compliance with the "Ministerial Ordinance on Good Clinical Practice for Medical Devices" (MHLW Ordinance No. 36) (hereinafter referred to as the "Ministerial Ordinance on GCP for Medical Devices") in principle is required based on the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act). In addition, to align with international standards, clinical trials should be conducted in accordance with ISO 14155 (the global standard for medical device clinical trials) with reference to the guidance/office memorandum issued by the MHLW and PMDA. There is a characteristic that the procedures required in the Ministerial Ordinance on GCP for Medical Devices differ depending on the entity conducting the clinical trial; a business entity or a sponsor-investigator.

In recent years, the administrative notice "Examples of points to consider and approaches for utilization of study results obtained from specified clinical research in applications for approval of medical devices and regenerative medical products" (June 5, 2024) shows the concept of effective regulatory use of results obtained from specified clinical trials.

2-1-1. Ministerial Ordinance on GCP for Medical Devices

The Ministerial Ordinance on GCP for Medical Devices is a legal regulation in Japan that stipulates standards for ethically, scientifically conducting clinical studies of medical devices in a lawful manner. The purpose of this regulation is to protect study participants' safety and rights and ensure reliability of study data. In addition, there are characteristics that clinical trial procedures, system, document types, timing of preparation, person responsible for preparation/storage, etc. should be established, and operational procedures should be specified in detail, including Japan-specific regulations on compensation requirements based on the Ministerial Ordinance.

Absolute conditions for medical device approval in Japan include clinical trial data satisfying requirements of the Ministerial Ordinance on GCP for Medical Devices, and the compliance with the Ministerial Ordinance on GCP for Medical Devices is prioritized over the compliance with the ISO shown in the section 2-1-2 below.

2-1-2. ISO 14155 (International Standard for Clinical Investigation of Medical Devices)

ISO 14155 is the international standard to appropriately conduct clinical studies (clinical trials) of medical devices in an ethical and scientific manner in order to ensure subjects' safety and improve reliability of clinical data. Unlike ICH-GCP (E6 [R3]), it is an independent standard for medical device development, but intentions of the provisions are very close to each other.

While the Ministerial Ordinance on GCP for Medical Devices is a legal regulation in Japan, there is a major difference that ISO 14155 does not include legal requirements but mainly recommendations and criteria. Also, since ISO 14155 was established on the assumption of

development of various medical devices, it is characterized by a flexible structure that can respond to the legal system and facility conditions in each country. On the other hand, since it was established based on the premise of aligning the system with that of each country, it is also characterized by the highly abstract standard. In other words, ISO 14155 is a global standard. It is advised in the GCP for medical devices to refer to ISO 14155 for information to be included in protocols, investigator's brochures, etc. The standard is widely used in Japan.

2-2. Regulations applied to clinical trials that are not intended for the application for marketing approval

A clinical study that is not intended for marketing approval application does not fall under a "clinical trial" according to the PMD Act. Such clinical studies shall be conducted in accordance with the PMD Act, the Clinical Trials Act (Act No. 16, 2017), and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Ethical Guidelines).

2-2-1. Clinical Trials Act

The Clinical Trials Act is applicable to clinical trials to verify safety and efficacy of drugs and medical devices in humans, although they are not intended for approval application. If any of the following applies, the clinical trial is subject to legal requirements as a "specified clinical research." In addition, if none of the following applies, and a clinical trial is conducted using drugs or medical devices, compliance with the Clinical Trials Act is required as a duty of effort, which is characterized by the complicated impact of the Act not only due to the objective of the clinical trial but also due to the surrounding financial environment.

(1) Clinical trials in unapproved or off-label use of medical devices
(2) Clinical trials that are funded or provided with medical devices by manufacturers (makers)

If the clinical research falls under the category of specified clinical research, the notification to the Minister of Health, Labour and Welfare, review by the Certified Review Board (CRB), monitoring, etc. are mandatory requirements. In addition, management of conflict of interest is required according to the "Guidance on the Management of Conflict of Interest in Clinical Trials Act."

There are several points to note when conducting clinical trials in unapproved medical devices in accordance with the Clinical Trials Act.

- Investigators themselves are required to import the medical devices and report to the Ministry of Health, Labour and Welfare.
- Acts of claiming indications of unapproved medical devices are prohibited.

All medical devices for which "approval," "certification," and "notification" for manufacturing and marketing have not been made are "unapproved medical devices." Even if the medical device has been approved, if the shape, specification, etc. is changed outside the scope of approval, etc., or if it is used outside the scope of approval, etc., it is handled in the same way as the unapproved medical device.

2-2-2. Ethical guidelines

The ethical guidelines are applied to general drug and medical device research that does not fall under the category of Clinical Trial Act or clinical trials, such as observational studies or studies in the usual use of approved medical devices involving no additional intervention (additional tests involving minimally invasive procedures may be included in observational studies).
According to the Ethical Guidelines, informed consent and review by Institutional Review Board (IRB) are required.

In addition, the following laws are applied as necessary in the clinical trials described above in the section 2-2:

(1) Personal Information Protection Act: Necessary for the handling of study data management and anonymization
(2) Laws related to medical service such as Medical Practitioners Act: Since acts of using medical devices apply to medical practice, regulations within its scope are applicable.
(3) Act on the Safety of Regenerative Medicine: Applicable when handling regenerative medicine

3. Regulatory classification of medical devices

3-1. Classification

Medical devices are classified into the following four classes based on the level of risk to the human body if the medical device malfunction occurs:

Classification	Summary	Example of applicable device	Necessity of clinical trial
Class I	General medical devices for extremely low risk level. Such medical devices can be marketed only by submitting a notification of manufacturing and marketing to the PMDA.	Thermometer, gauze, stethoscope	Unnecessary

Classification	Summary	Example of applicable device	Necessity of clinical trial
Class II	Controlled medical devices for relatively low risk levels Medical devices for which certification standards exist can be certified by a third-party certification body registered by the Minister of Health, Labour and Welfare.	Blood pressure monitor, ultrasound diagnostic device, MRI scanner	Medical devices for which certification standards exist: Unnecessary Other than the above, approval of the PMDA is required.
Class III	Specially controlled medical devices for risk levels that may affect life Medical devices designated by the Minister of Health, Labour and Welfare by specifying standards can be certified by a third-party certification body.	Artificial dialyzer, mechanical ventilator, catheter, artificial bone	Medical devices for which certification standards exist: Unnecessary For other than the above, approval by the PMDA is required with use of data from clinical trials.
Class IV	Specially controlled medical devices for the highest risk levels that are indispensable for life support and potentially have serious effects	Pacemaker, artificial heart valve, heart-lung machine	Approval by the PMDA is required with use of data from clinical trials.

Based on the above, the implementation of clinical trials and the submission of results from clinical trials are required only in some of the Class II, Class III, and IV medical devices that are subject to approval review by the PMDA.

3-2. Novelty-based classification of medical devices

As shown in the table below, whether or not results from clinical trials are required differs depending on the following medical device classification: new, improved, and generic medical devices.

Novelty of medical devices	Necessity of submission of clinical data (results from clinical trials)
New medical devices (medical devices with a clearly different structure from existing medical devices)	Necessary, in principle
Improved medical devices	Necessary depending on the degree of improvement
Generic medical devices	Unnecessary

Clinical trials can be omitted if equivalence to predicate devices is demonstrated. Even for improved medical devices with minor improvements such as changes in materials or appearance, clinical evaluation may be required if they have effects on the safety and performance. In addition, limited clinical evaluation or investigation may be required for moderate improvements such as additional features and software updates. When a major improvement such as structural changes or additional indications that may produce new risks is made to the medical device, clinical investigation at a clinical trial level is required. On the other hand, if new risks are unlikely to be produced, full-scale clinical trials may be unnecessary as long as there is scientific evidence of no increased risks. In such a case, the safety and efficacy are confirmed by conducting a clinical trial with a small sample size to show the actual results of use in humans. However, even if no new risks are produced, major improvements are considered to potentially change the effects on use conditions and patients. Therefore, limited clinical evaluation for approval application tends to be required more commonly.

These clinical evaluations do not necessarily require implementation of clinical trials under the PMD Act. In fact, a limited number of medical devices were approved without submission of clinical study results, and the approval with submission of overseas clinical study results and clinical evaluation reports is more common. Exploratory clinical studies are often conducted to evaluate efficacy and safety of medical devices that are developed through repeated improvements.

4. In vitro diagnostics

4-1. Handling of in vitro diagnostics in Japan

In vitro diagnostics are defined as “drugs that are intended for exclusive use in the diagnosis of diseases and not for direct use in human or animal body” and classified as drugs under the PMD Act. However, they are classified into Class I to Class III according to their effects on humans, and the review process depends on the risks of each product. Therefore, they are practically handled in the same way as medical devices.

Classification	Summary	Product example	Review
Class I	• Products have relatively low diagnostic information risk and smaller impact of the information accuracy on life support compared to the Class III items. • Reference materials for calibration and standard measurement methods are available, and self-checking is easy. • Excluding general diagnostic drugs (OTC)	Hemoglobin, total protein for hematological test, etc.	Self-certification (notification of manufacturing and marketing)
Class II	• Products that are likely to have relatively low diagnostic information risk and smaller impact of the information accuracy on life support compared to the Class III items and general diagnostic drugs (OTC)	Coagulation factors, Human chorionic gonadotrophin kits, etc.	Registered certification body (marketing certification)
Class III	• Products have relatively high diagnostic information risk and larger impact of the information accuracy on life support.	Glucose kit for self-testing, tumor marker kit for tissue testing, etc.	Ministry of Health, Labour and Welfare (marketing approval)

Class I medical devices that meet criteria for exemption from the approval/certification (criteria pursuant to Article 23-2-5, Paragraph 1 of the PMD Act) are subject to the notification system. Class II medical devices that conform to the certification criteria (those pursuant to Article 23-2-23, Paragraph 1 of the PMD Act) must be certified by a registered certification body registered by the Minister of Health, Labour and Welfare. Class III medical devices and those that do not fall under the definitions of Classes I and II above (applicability to intended use, nonproprietary name, etc.) must be reviewed by the PMDA for approval. The term "nonproprietary name" in this context is a standardized name to indicate systematically and uniformly the type of medical device, and the name, definition and code are organized based on Japan Medical Device Nomenclature (JMDN).

4-2. Clinical performance study of in vitro diagnostics

4-2-1. Required studies

Since in vitro diagnostics are not used directly on the human body, biobanks and residual samples are actively used when collecting data required for approval application. In addition, clinical performance studies may be performed using samples prospectively collected from patients. Since these studies are conducted as medical researches pursuant to the Ethical Guidelines,

clinical investigations as clinical trials are not required, but performance studies using clinical specimens are required pursuant to Article 14, Paragraph 3 of the PMD Act. In Japan, precision of reagents is evaluated using human samples, in accordance with the PMDA requirements, ISO 20916, international guidelines (GHTF/IMDRF SG5), etc.

Since clinical performance studies of in vitro diagnostics are not subject to the Ministerial Ordinance on GCP for Drugs/Medical Devices, they do not correspond to so-called clinical trials. Nor, they neither correspond to clinical researches. At present, "Guidelines for Clinical Investigation of In Vitro Diagnostics (March 30, 2015)" is published for industry by the Japan Association of Clinical Reagents Industries. However, laws and guidance, etc. to be complied with for implementation of clinical performance studies of in vitro diagnostics are still unclear, and a lack of clear rules for implementation is pointed out.

< Guidelines for Clinical Investigation of In Vitro Diagnostics (March 30, 2015) >

Key statements:

- Contract and conflict of interest management are essential for research support.
- Classification into "joint study", "contract research", "clinical trial", etc. and implementation conditions
- Scope of clinical trial, amount of provision, and upper limit of trial period (within 6 months in principle, single use only, etc.)
- Attribution and neutrality of data, arrangement of contract at the time of publication
- In the case of an investigator-initiated study, arrangement of joint study contract, etc. is needed for corporate support.

In principle, the use of the results of clinical performance studies conducted overseas is acceptable. However, it is necessary to consider the effects of racial differences, environmental factors, differences in actual clinical environments, etc. on the performance and clinical significance of the in vitro diagnostic reagent.

4-2-2. Reporting of adverse drug reactions

Currently in Japan, adverse reactions of in vitro diagnostics are required to be reported as adverse drug reactions. However, there is a problem that it is difficult to apply to the concept of adverse reactions because they are not used directly on the human body. On the other hand, outside Japan, reports on in vitro diagnostics are included in medical device malfunction reports. Therefore, the introduction of malfunction reporting system based on the characteristics of in vitro diagnostics and arrangement in accordance with medical devices are needed in Japan as in other countries

4-3. Systems for in vitro diagnostics to be required in the future

As discussed above, clinical performance studies of in vitro diagnostics are not covered by the Ministerial Ordinance on GCP for Drugs/Medical Devices, and many of them are conducted pursuant to the Ethical Guidelines. In Japan, clinical studies of in vitro diagnostics are conducted involving no intervention and using archived specimens. Therefore, it is desirable to establish the Ministerial Ordinance on GCP and guidelines for clinical performance studies that are specific to in vitro diagnostics.

In addition, the intended use of in vitro diagnostics is clearly defined as "for use in prognosis diagnosis, prediction, understanding of physiological status, determination of treatment, etc." in foreign countries, whereas in Japan, in vitro diagnostics are defined in relatively ambiguous manner as “drugs that are intended for exclusive use in the diagnosis of diseases and not for direct use in human or animal body.” However, there is an increasing need for in vitro diagnostics that are intended to obtain medically necessary and important information, such as those to determine physiological conditions (e.g., blood type and pregnancy determination) and companion diagnostics that are used to identify patients in whom the efficacy and safety of specific drugs are expected. For this reason, as in other countries, discussions to expand the definition of in vitro diagnostics and considerations to establish appropriate regulations according to the intended use and risks are required in Japan.

Chapter 2: Details on the regulations for clinical investigation

1. Laws and regulations on approval for conducting clinical studies by the government or regulatory authorities

Ministerial Ordinance on GCP for Medical Devices:

In Japan, prior to the conduct of a clinical trial, a clinical trial notification must be submitted prior to the start of the clinical trial pursuant to Article 80 of the PMD Act and Article 275 of the Enforcement Regulation of the PMD Act. In Japan, clinical investigations of medical devices corresponding to devices with new intended use are controlled as "clinical trials." Under the current circumstances In Japan, however, there is no exemption system that simplifies the procedures to use unapproved devices for the purpose of clinical trials.

Clinical Trials Act:

Prior to the start of the study, the protocol must be submitted to the Minister of Health, Labour and Welfare.

After the review and approval by the CRB, registration of the protocol in Japan Registry of Clinical Trials (jRCT) is deemed as notification.

Ethical guidelines:

After the review and approval by the Ethical Review Board, the study can be conducted upon approval by the head of the study site. No procedures including filing an application with, submission to, or approval by the government or regulatory authorities are required.

2. Compliance with ISO 14155

Ministerial Ordinance on GCP for Medical Devices:

It is specified that ISO 14155 should be consulted when preparing a protocol, investigator's brochure, and clinical study report.

Clinical Trials Act and Ethical Guidelines:

The Clinical Trials Act and Ethical Guidelines do not include statements that explicitly advise on citation of or compliance to ISO 14155. However, when conducting a global joint study, compliance to ISO 14155 may be required because there are no similar regulations to the Clinical Trials Act and Ethical Guidelines in other countries, and ISO 14155 is an international standard for conducting global clinical studies.

3. Process and laws and regulations for approval of conducting researches by Ethical Review Board and IRB

Clinical studies that are conducted in Japan are characterized by the different names and requirements of review boards and review materials depending on the applicable laws and regulations.

Ministerial Ordinance on GCP for Medical Devices:

Clinical studies must be reviewed and approved by the IRB established by each study site, or the IRB with which the study site has concluded an agreement for requesting the review. Based on the results of the IRB review, the clinical study can be conducted after it is approved by the head of the study site.

Clinical Trials Act:

Clinical studies must be reviewed and approved by the CRB established by each study site, or the CRB with which the study site has concluded an agreement for requesting the review. Based on the results of the CRB review, the clinical study can be conducted after it is approved by the head of the study site.

Ethical guidelines:

Clinical studies must be reviewed and approved by the Ethical Review Board established by each study site, or the Ethical Review Board with which the study site has concluded an agreement for requesting the review. Based on the results of the review by the Ethical Review Board, the clinical study can be conducted after it is approved by the head of the study site.

4. Laws and regulations on conflict of interest (transparency)

Ministerial Ordinance on GCP for Medical Devices:

The Ministerial Ordinance on GCP for Medical Devices does not require preparation of materials explaining conflict of interest with the sponsor in the requirements for study sites and investigators. The Guidance on Article 51 "Responsibilities of Institutional Review Board" of the Ministerial Ordinance on GCP for Medical Devices stipulates that "other materials considered necessary by the Institutional Review Board (if there is collaboration with a business entity, documents related to conflict of interest, etc.)" and is left to individual discretion.

In addition, the company sponsoring the clinical study may voluntarily manage conflict of interest by complying with transparency guidelines stipulated by the industry organization and make inquiries to physicians participating in the clinical trial about the status of acquisition of shares of the company with reference to overseas regulations, etc.

The medical institution conducting the clinical trial may voluntarily accept reviews by the

Management Committee of Conflict of Interest (COI) established in the hospital according to the provisions of the medical institution.

Clinical Trials Act:

The Clinical Trials Act was established because of the problem of inappropriate management of conflict of interest as a background of the development. For this reason, the method (development of management plan, etc.) and criteria for the management of conflict of interest are strictly specified, and information on the management of conflict of interest is also included in materials to be reviewed by CRB.

Ethical guidelines:

In Chapter 12, "management of conflict of interest" is clearly required for clinical studies conducted under the ethical guidelines. Specifically, it stipulates the inclusion of COI status in the study protocol and third-party evaluation of information on the conflict of interest by the Conflict of Interest Committee and Ethical Review Board in the study site. Unlike the Clinical Trials Act, which is a legal regulation, the Ethical Guidelines are characterized as guidelines that contribute to the proper conduct of medical researches.

5. Laws and regulations on explanation for consent, acquisition of consent, and multilingualization

Ministerial Ordinance on GCP for Medical Devices:

The Ministerial Ordinance on GCP for Medical Devices stipulates 18 items that should be included in the informed consent form, and in principle, it is strictly stipulated that the consent should be obtained from the subject himself/herself. The Ministerial Ordinance on GCP for Medical Devices is characterized by "Explain about the medical device must be given when it is placed into the body" due to the characteristics of medical devices, and there are no provisions requiring explanation about the information on the funding source or the conflict of interest to subjects. In addition, there are no provisions on multilingualization of the informed consent form.

Clinical Trials Act:

The Clinical Trials Act stipulates the informed consent form equivalent to those stipulated in the Ministerial Ordinance on GCP for Medical Devices and the process of obtaining a consent. It is characterized as a regulation to notify subjects of information on the COI management and the source of funds. However, there are no provisions for multilingualization of the informed consent form.

Ethical guidelines:

Unlike the Ministerial Ordinance on GCP for Medical Devices and the Clinical Trials Act,

provisions on retrospective observational studies with no use of drugs/medical devices are included. For this reason, various options such as obtaining written consent before start of the study, orally giving a consent, recording in medical records, and utilization of opt-out are available according to the individual clinical studies. However, there are no provisions for multilingualization of the informed consent form.

It is also characterized by the complexity of the informed consent process because the process of obtaining a consent differs depending on the planned study contents, presence or absence of invasive procedures and therapeutic interventions, etc.

6. Laws and regulations on compensation to subjects

Ministerial Ordinance on GCP for Medical Devices and Clinical Trials Act:

Provision of compensation to subjects prior to the conduct of the clinical study is strictly stipulated. The specific method and criteria for compensation are not included in the law. Generally, the scope and amount of compensation are determined by each entity conducting the study based on the guidance by industry organizations (e.g., The Japan Federation of Medical Devices Associations and Japan Pharmaceutical Industry Legal Affairs Association). In addition, a system where the IRB or CRB reviews that any institution to provide appropriate compensation is established to conduct clinical trials is stipulated in each law and regulation.

Ethical guidelines:

For studies involving invasive procedures (excluding minor invasiveness) and medical practice beyond usual medical care, it is advised to refer to the guidelines provided by Japan Pharmaceutical Industry Legal Affairs Association as well as the Ministerial Ordinance on GCP for Medical Devices and Clinical Trials Act.

On the other hand, for clinical investigations other than the above that are unlikely to cause any health, as represented by retrospective observational studies, etc., preparation of the compensation system is not required. In addition, in clinical trials conducted within the scope of usual medical care, a compensation system generally retained by typical medical device marketing authorization holders is commonly used instead of a study-specific compensation system.

7. Laws and regulations on reporting of safety information to regulatory authorities

Ministerial Ordinance on GCP for Medical Devices:

Pursuant to Article 80-2, Paragraph 6 of the PMD and Article 274-2 of the Enforcement Regulation,

the sponsor or sponsor-investigator must report death, serious disability, malfunction, etc. related to the use of medical devices in clinical trials to the regulatory authorities. In addition, malfunction report, etc. in a study using an unapproved medical device that is conducted pursuant to the Clinical Trials Act must be reported by the investigator to the PMDA pursuant to Article 16-4 of the Clinical Trials Act.

Clinical Trials Act:

Pursuant to Article 14 and Article 16-4 of the Clinical Trials Act and Article 56 of the Enforcement Regulation of the Clinical Trials Act, the following measures must be taken: Unexpected adverse events suspected to be caused by the conduct of the research using unapproved or off-label use of drugs, etc. must be reported within 7, 15, or 30 days in accordance with the same criteria as those for clinical trials of medical devices.

Ethical guidelines:

In clinical research that can be conducted under the Ethical Guidelines, use of the medical device is limited within the scope of approval or observational research, etc., and therefore there are no provisions that requires the entity conducting the research to directly report to regulatory authorities. For this reason, information must be shared with the manufacturer based on the procedures for post-marketing malfunction report, etc., and safety reports must be submitted to the regulatory authorities based on the medical device malfunction report in accordance with Article 68-10, Paragraph 1 of the PMD Act, being the manufacturer as the main entity.

8. Laws and regulation on protection of subjects' information (protection of personal information and protection of personal healthcare information)

Protection of Subjects' personal information is regulated by various laws in Japan, beginning with Article 134 of the Penal Code which is considered as a traditional confidentiality obligation imposed on physicians, etc. In recent years, personal information must be properly managed based on the Personal Information Protection Law which includes detailed descriptions ranging from the definition to handling of personal information. It should be noted that the Personal Information Protection Law is not a regulation specific to the conduct of clinical investigation.

Ministerial Ordinance on GCP for Medical Devices:

The principles of the General Rules (11) of the Ministerial Ordinance on GCP for Medical Devices stipulate that records that may identify subjects should be protected, giving consideration to the subjects' privacy and confidentiality. In Article 2, use of identification codes assigned to individual

subjects (subject identification code) is stipulated to protect the subjects' confidentiality. It is clearly stated in Article 67: Responsibilities of investigators (case report forms, etc.) that the subject identification codes must be used in report data.

Clinical Trials Act:

In Article 11 of the Clinical Trials Act, it is clearly stated that subjects' privacy must not be leaked to persons who are engaging or have engaged in researches. Also, a term "subject identification code" is used in standard forms prepared by the Ministry of Health, Labour and Welfare in the Clinical Trials Act, and the subjects' personal information is coded before reporting.

Ethical guidelines:

Chapter 9: Basic responsibilities for personal information, samples, and specimens/information from the deceased of the Ethical Guidelines provides basic principles and responsibilities for the handling of personal information. In addition, in the terminology system related to personal information shown in the Guidelines, definitions as personal information, pseudonymously processed information, anonymously processed information, and information related to personal data are used in alignment with the Personal Information Protection Law.

9. Laws and regulations on disclosure of clinical trial data

Ministerial Ordinance on GCP for Medical Devices:

Pursuant to Article 272-2, Paragraph 1 and Article 272-2 of the Enforcement Regulations of the PMD Act, "Disclosure of Information," it was stipulated that "when a clinical trial is conducted, matters of which the World Health Organization requires disclosure and other matters that contribute to ensuring the transparency of the conduct of the clinical trial and the people's choice to participate in clinical trials shall be disclosed in advance."

Based on this regulation, "Registration of Clinical Trial Implementation Status, etc." (PSEHB/PED Notification No. 0831-9, dated August 31, 2020) issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, requires to register information on clinical trials in jRCT when conducting clinical trials.

Clinical Trials Act:

Article 24 of the Enforcement Regulation of the Clinical Trials Act (Publication of information, etc.) requires investigators to register information on clinical trials in the database prepared by the Ministry of Health, Labour and Welfare when conducting clinical trials. In addition, achieving this publication is considered as completion of the information submission to the Minister of Health, Labour and Welfare.

Ethical guidelines:

In the Ethical Guidelines, registration in jRCT for clinical trials involving intervention are required as in Chapter 3, Part 6: Procedures related to research protocol. However, there are provisions that allow information not to be disclosed only if closing the information to public is permitted by the Ethics Review Board and the head of the study site for the purpose of protecting intellectual properties and privacy. In other clinical trials (observational studies, etc.), disclosure is advised as a duty of effort.

The Guidance on the Ethical Guidelines advises that the registration in UMIN-CTR is acceptable.

10. Laws and regulations on digitization of data, etc.

The ER/ES guidelines are to establish usage of electromagnetic records and electronic signatures in clinical studies intended for approval applications. Compliance with the ER/ES guidelines is not required in researches and clinical trials under the Ethical Guidelines that are not intended for approval application.

Appendix: List of laws and regulations and guidance cited in this summary (Order of description)

1. Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, 1960) (Latest revision: Issued on May 21, 2025)
   Abbreviation: PMD Act
   https://laws.e-gov.go.jp/law/335AC0000000145
   - Article 23-2-5, Paragraph 1: Marketing Approval of Medical Devices and In Vitro Diagnostics
   - Article 23-2-23, Paragraph 1: Certification for Marketing Specially-Controlled Medical Devices
   - Article 14, Paragraph 3: Marketing Approval for Pharmaceuticals, Quasi-Pharmaceutical Products and Cosmetics
   - Article 68-10, Paragraph 1: Reporting Side Effects
   - Article 80-2, Paragraph 6: Handling of Clinical Trials

2. Ministerial Ordinance on Good Clinical Practice for Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare No. 36, 2005) (Latest revision: Enforced April 1, 2025)
   Abbreviation: Ministerial Ordinance on GCP for Medical Devices
   https://laws.e-gov.go.jp/law/417M60000100036

3. ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice

4. Examples of points to consider and concepts in use of results from researches in the application for marketing approval of medical devices and regenerative medicine products (June 5, 2024)
   https://www.mhlw.go.jp/content/10808000/001298502.pdf

5. Clinical Trials Act (Act No. 16, 2017) (Latest revision: Enforced on June 1, 2025)
   https://laws.e-gov.go.jp/law/429AC0000000016
   - Article 11: Confidentiality Obligation
   - Article 14: Report to the Minister of Health, Labour and Welfare
   - Article 16-4: Compilation of Information and Conduct of Investigation by PMDA

6. Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Updated:

partially revised on March 27, 2023)
Abbreviation: Ethical Guidelines
https://www.mhlw.go.jp/content/001077424.pdf

7. Guidance on Conflict of Interest Management under the Clinical Trials Act (May 15, 2025)
https://www.mhlw.go.jp/content/10800000/001489048.pdf

8. Act on the Protection of Personal Information (Act No. 57, 2003) (Latest revision: Enforced on June 1, 2025)
Abbreviation: Personal Information Protection Law
https://laws.e-gov.go.jp/law/415AC0000000057

9. Medical Practitioners' Act (Act No. 201, 1948) (Latest revision: Enforced on June 1, 2025)
https://laws.e-gov.go.jp/law/323AC0000000201

10. Act on the Safety of Regenerative Medicine (Act No. 85, 2013) (Latest version: Enforced on June 1, 2025)
Abbreviation: Act on the Safety of Regenerative Medicine
https://laws.e-gov.go.jp/law/425AC0000000085

11. ISO 20916: 2019 In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice

12. IMDRF MDCE WG/N56:2019 - Clinical Evaluation
Terms in this summary: GHTF/IMDRF SG5
https://www.imdrf.org/documents/clinical-evaluation

13. Guidelines for Clinical Investigation of In Vitro Diagnostics (March 30, 2015)
https://jacri-ivd.jp/information/shiryou/798/

14. Enforcement Regulation of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance No. 1 of the Ministry of Health and Welfare, 1961) (Latest revision: Enforced on December 22, 2025)
https://laws.e-gov.go.jp/law/336M50000100001
    - Article 272-2: Disclosure of Information
    - Article 274-2: Report of Failure Information on Clinical Trials Related to Medical

Appliances or Instruments, etc.

15. Guidance on "Ministerial Ordinance on Good Clinical Practice for Medical Devices" (Partial revision: December 26, 2023)
https://www.pmda.go.jp/files/000266400.pdf

16. Enforcement Regulation of the Clinical Trials Act (Ordinance of the Ministry of Health, Labour and Welfare No. 17, 2018) (Latest revision: Enforced on November 20, 2025)
https://laws.e-gov.go.jp/law/430M60000100017
    - Article 24: Disclosure of Information, etc.
    - Article 56: Reporting of Diseases, etc. to the Minister of Health, Labour and Welfare

17. Registration of the implementation status of clinical trials (August 31, 2020)
https://www.mhlw.go.jp/content/11120000/000665717.pdf

18. Guidance on the Ethical Guidelines for Medical and Biological Research Involving Human Subjects (April 1, 2024)
https://www.mhlw.go.jp/content/001237478.pdf

19. Penal Code (Act No. 45, 1907) (Latest revision: Enforced on June 1, 2025)
https://laws.e-gov.go.jp/law/140AC0000000045/20250601_504AC0000000067
    - Article 134: Disclosure of Secrets

20. Use of Electromagnetic Records and Electronic Signatures for Applications for Approval or Licensing of Drugs, etc. (April 1, 2005)
Abbreviation: ER/ES guidelines
https://www.pmda.go.jp/files/000158308.pdf

Laws and Regulations for Clinical Investigations of Drugs in the United States

Date of preparation: February 20, 2026

Chapter 1: Regulations pertaining to clinical investigations of drugs in the United States

1. Hierarchy of the laws and regulations

1-1. Legal system

In the laws and regulations that support clinical investigations of drugs in the United States, the Federal Constitution is placed at the top, followed by the comprehensive laws related to drugs established by Congress. These laws, in the context of drug development and clinical investigations conducted in the United States, provide authorities of regulatory authorities, obligations a business entity must comply with, and justification for administrative, civil, and criminal proceedings applicable in the event of violations. The Code of Federal Regulations (CFR) puts these higher-level laws into more practical levels to stipulate specific clinical investigation procedures, protection of participants, ethical review, and application procedures in detail. These regulations are legally binding, and companies and research institutions conducting clinical investigations in the United States must plan, review, and conduct clinical investigation and manage records thereof in compliance with these regulations. If a violation is confirmed, not only administrative guidance but also suspension of clinical investigations, suspension of manufacturing/marketing, penal charge, and criminal liability may be imposed.

On the contrary to these higher-level regulations with legal force, guidance documents published by US regulatory authorities serve as aids in the interpretation of the regulations and as specific guidance for the practical operation. Although the guidance documents are not legally binding, it has a strong influence on the actual management of clinical trials and application activities as they suggest the regulatory authority's "current thinking" on how to fulfill the obligations set forth in the regulations and expected review processes. Deviations from the guidance, per se, are not a violation of the law, but additional explanations about the scientific rationale and appropriateness of alternatives are required, which may result in delay in the review and additional requirements.

1-2. Major regulatory authorities

The U.S. regulatory system for drugs consists of the federal agencies. The central agency is the U.S. Food and Drug Administration (FDA), which is a subdivision of the U.S. Department of Health and Human Services (HHS) and has the legal authority to oversee safety, efficacy, and quality of drugs. The FDA’s Center for Drug Evaluation and Research (CDER) is responsible for drug review and oversight and plays a broad role from conducting clinical trials to premarket review and pharmacovigilance.
In addition, the “Common Rule (45 CFR Part 46)” relating to protection of participants applies to federally-funded research, and the HHS’s Office for Human Research Protections (OHRP) is

responsible for its operation and oversight. This serves as common standards for ethical review and protection of participants in human research, not limited to drugs.
In addition, compliance with regulations of Health Insurance Portability and Accountability Act of 1996 (HIPAA) is required in clinical trials in drugs, and these regulations are enforced by the Office for Civil Rights (OCR).

- HHS: Department of Health and Human Services. The Federal Government's agency that governs health and welfare policies in the United States.
  - FDA: The federal agency within HHS. Responsible for safety, efficacy, and quality of food, drugs, cosmetics, medical devices, and radiation-emitting products distributed in the U.S., and for review, licensing, standard formulation, monitoring, and control thereof.
    - CDER: Drug division of the FDA. Responsible for review and approval of drugs for human use (new, generic, and OTC drugs) as well as regulation of manufacturing, labeling, and quality, and post-approval pharmacovigilance. Also responsible for evaluation/approval (Biologics License Application [BLA]), review, and oversight of therapeutic protein monoclonal antibodies and other many therapeutic proteins (e.g. cytokines, enzymes).
    - Center for Biologics Evaluation and Research (CBER): Biological product division within FDA. Responsible for review to Biologics License Application (BLA) of vaccines, blood products, cell and gene therapy, etc. and quality control and safety monitoring.
  - OHRP: Subdivision of HHS. Responsible for protecting the rights, welfare, and safety of participants (human) participating in clinical investigations conducted or funded by the Federal Government. Also responsible for operation of the Common Rule (45 CFR Part 46), which applies to all federally funded researches in human subject (including medical and social sciences).
  - National Institutes of Health (NIH): Subdivision of HHS. The primary agency that funds clinical investigations and conducts researches. Responsible for operation of ClinicalTrials.gov to require registration of clinical trials and publication of information.

2. Regulations applicable to clinical investigations of drugs

2-1. Constitution and Federal statutes

The Constitution of the United States establishes the authority of the Federal Government, and Congress serves as a base for the enactment. The following acts are related to clinical trials and researches:

- Food, Drug, and Cosmetic Act (FD&C Act):
  A basic law which authorizes FDA to review, approve, and regulate drugs, medical devices, etc.
- Public Health Service (PHS) Act:
  Although this act does not impose direct procedural requirements on clinical investigations, but provides important justification for clinical trial registration and result reporting system (ClinicalTrials.gov), measures against illicit acts in researches, and funding and support system for clinical and public health researches, etc.
- FDAAA(Food and Drug Administration Amendments Act):
  Under the act, clinical trial registration in ClinicalTrials.gov and publication of information

are required. Details are provided in 42 CFR Part 11.

- HIPAA:
  A federal law requiring assurance of privacy and security of patients' electronic health information. It requires health care providers and related business entities to appropriately manage Protected Health Information [PHI], take security measures, and notify of information leakage.

2-2. Code of Federal Regulations (CFR)

In conduct of clinical investigations and researches, FDA has established regulations in its jurisdiction in accordance with the FD&C Act, etc., and compiled them as Title 21 of CFR (mainly Chapter I: FDA). They include detailed requirements for clinical investigations and pre-marketing reviews for drugs, medical devices, biological products, and foods, etc., and systematize obligations of sponsors, principal investigator, IRB, and other persons subject to regulations and the FDA operation and procedures.
On the other hand, the Common Rule (45 CFR Part 46) contains basic rules for participant protection that apply to all human subject research conducted, supported, or otherwise subject to regulation by any Federal agency. The HHS' OHRP plays a central role to establish fundamental requirements such as IRB, informed consent, and agencies' compliance assurance, and additional protections of specific populations and IRB registration requirements, where appropriate. The same research may meet the applicable conditions of both FDA regulations and Common Rule. In such a case, requirements of the both regulations should be complied with. Although there are many conditions in common, there are differences in the handling of definitions and exemptions, etc.

- Regulations related to FDA (21 CFR)
  - 21 CFR Part 11: Electronic Records; Electronic Signatures
  - 21 CFR Part 16: Procedures for Regulatory Hearing
  - 21 CFR Part 50: Protection of Human Subjects (Informed Consent)
  - 21 CFR Part 54: Financial Disclosure by Clinical Investigators
  - 21 CFR Part 56: Institutional Review Board(IRB)
  - 21 CFR Part 58: GLP for Nonclinical Laboratory Studies
  - 21 CFR Part 312: Investigational New Drug(IND)Application
  - 21 CFR Part 314: Applications for FDA Approval to Market a New Drug
  - 21 CFR Part 320: Bioavailability and Bioequivalence Requirements
  - 21 CFR Part 601: Biologics License Application (BLA)
- Regulations related to HHS/OHRP (45 CFR Part 46)
  - Subpart A: the Common Rule (IRB, consent, federally-funded study), applicable only if funded by a federal agency
  - Subpart B: Protections for pregnant women, human fetuses, and neonates
  - Subpart C: Protections of Prisoners
  - Subpart D: Protections for Children
  - Subpart E: Requirements for registration of IRB

In addition to 21 CFR and 45 CFR Part 46, major federal regulations relating to clinical investigations and researches of drugs are as follows:

- 42 CFR Part 11

Implementation rules in Section 801 of the Food and Drug Administration Amendments Act (FDAAA) specifies details of registration of applicable clinical trials in and submission of results information to ClinicalTrials.gov, the Responsible Party, the submission deadlines, and legal consequences of failure to comply.

- 45 CFR Part 160 & 164
  As HIPAA's privacy/security rules, PHI handling standards, use and disclosure conditions, individuals' rights, security management, and notification of leakage, etc. are specified. Medical institutions and CROs collect and monitor data using PHI in accordance with these rules.

2-3. Federal guidelines and guidance

The guidance documents issued by FDA and OHRP indicate "FDA's and OHRP's current views" under the laws and CFR. Such guidance is not legally binding and may propose alternative measures which can be adopted on the premise of legal compliance. The FDA and OHRP have issued many guidance documents for clinical trials and researches of drugs. In relation to this, FDA also recommends to comply with ICH-GCP which is published as a position of guidance.

- FDA Guidance
  - Scope: FDA's jurisdiction (including drugs, medical devices, biological products, clinical trials for IND)
  - Put supplement to interpretation of 21 CFR (Parts 50, 56, 312, etc.), GCP (ICH E6) and technical requirements (electronic records and decentralized clinical trials) into practice.
  - It is almost mandatory in practice because it is directly linked to global clinical trials and new drug applications.
- OHRP Guidance
  - Federally-funded research (Common Rule application)
  - Supplement to interpretation of Common Rule (45 CFR Part 46)
  - Includes social science and public health researches outside of FDA regulations. Emphasis on ethics and protection

3. Classification for consideration of applicable regulations

When conducting clinical investigations and researches of drugs involving intervention in the United States, various categories may be included to consider their applicable regulations and guidance. The definition of Intervention is specified in the section "Clinical Trial Definition" of NIH, but regulations applicable to clinical trials are determined not based on the presence or absence of intervention, but based on the factors including the presence or absence of IND application, whether or not the investigation is intended for marketing application, involvement of funding by the Federal Government.

3-1. Regulations on clinical investigations requiring submission of Investigational New Drug (IND)

Clinical investigations requiring IND submission in the United States are regulated in an integrated manner under 21 CFR Part 312. Part 312 covers the full cycle of the IND submission, including scope and definitions, submission requirements, operational changes, safety reporting, annual

reporting, and regulatory actions.

First-In-Human studies of newly developed compounds and subsequent phase 1 to phase 3 investigations are subject to IND under the FD&C Act as a legal requirement to supply and use pre-approval drugs in clinical trials. An IND is required for a clinical investigation using an approved drug if it is reasonably determined that participant risks will be increased due to reasons such as a significant change in dose, addition of a new route of administration, use in a new patient population (e.g., high risk population), or exploratory use to evaluate an unknown effects.

The applicants submits an IND including a clinical trial protocol, pre-clinical data, Chemistry, Manufacturing and Controls (CMC) information, and labeling. FDA will review the safety and adequacy within 30 days of receipt. As a result, a measure to temporarily suspend the start or continuation of a clinical trial (Clinical Hold) may be ordered if there are concerns about the protection of participants or scientific validity.
After the start of the clinical trial, the information is required to be shared with FDA continuously through revision of the protocol for significant changes in the study contents, revision of IND to additionally submit new non-clinical/clinical information, etc., and annual report summarizing the progress of the study and safety information. For safety surveillance, under 21 CFR Part 312.32, expedited reporting of suspected unexpected serious adverse reactions (SUSAR) within 7 or 15 days is mandatory, depending on the nature of the event. A sponsor and investigator are also responsible for investigational drug management, record keeping, reporting to the regulatory authorities and IRB, and others according to their position.
The provisions on labeling to prevent misperception as a marketed drug, prohibition of promotional activities, restriction of onerous supply, etc. will apply to investigational drugs. When a serious problem occurs during a clinical investigation, FDA will take administrative measures such as suspension or discontinuation to given an opportunity for discussion or objection as necessary. In addition, expanded access to provide patients with serious diseases with investigational drugs and acceptance criteria for overseas clinical data are also specified within Part 312.

3-2. Regulations on clinical investigations subject to IND exemption (IND-exempt)

As specified in 21 CFR Part 312.2 (b), IND exemption applies to cases where the investigational drug is lawfully marketed in the United States and the purpose and conduct of the investigation is limited to the extent that no new FDA review is required.
The scope of IND exemption is particularly limited, and even for a clinical investigation using an approved drug, IND is not exempted if it includes a study design that may reasonably be expected to increase the dose, administer to a new patient population, or increase the risk. Also, IND is not exempted if the investigation is intended to be reported to FDA in support of a new indication for use or significant change in the labeling for the drug. These are summarized as the "criteria for determining IND exemption" presented by FDA, and if the sponsor is uncertain about the judgment, it is recommended to have prior consultation with the review division.
In addition, even when the investigation is subject to IND-exempt, review by IRB and compliance with informed consent are required as a requirement for exemption from IND. The provision that prohibits commercial distribution or sales promotion (Part 312.7) applies to investigational drugs.

3-3. Regulations on clinical investigations of biological products and new modalities

In the United States, unlike the category of "regenerative medicine products" in Japan, there is no independent product category in line with drugs and medical devices. Products in which human cells or tissues are used are regulated as Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) within the framework of 21 CFR Part 1271. 21 CFR Part 1271 is intended to prevent introduction, transmission, or spread of communicable diseases by HCT/Ps, and in order to realize this, requirements for facility registration and listing, eligible donors, and Current Good Tissue Practice (cGTP) are specified. If the applicable product satisfies all the requirements of 21 CFR Part 1271.10 (minimal manipulation, homologous use, etc.), IND or approval is not required, in principal, focusing on the registration as a 361 HCT/P under Part 1271, donor qualification, cGTP, etc.
On the other hand, if the HCT/P does not meet the criteria of 21 CFR Part 1271.10 (i.e., it is a 351 HCT/P), it is regulated as an existing drug, device, and/or biological product. In practice, as a biologic, the regulations on drugs such as IND (21 CFR Part 312) and BLA apply in addition to CFR Part 1271.

CBER within FDA is responsible for review and oversight of clinical investigations that use biological products or novel modalities (e.g., cell and gene therapy) in the United States. Relevant regulations include 21 CFR Parts 600 – 680 which specify requirements for manufacturing control, quality control, record control, deviation reporting, etc. from development to approval of biological products and require securing the product safety, purity, and potency. CBER reviews both the IND submitted in the clinical phases and the BLA submitted in the final phase, and the safety and efficacy data from the clinical trials is used as the rationale for the final BLA review.

3-3-1. Use of biological products

In clinical trials using biological products (e.g. vaccines, blood products, allergen products, etc.), CMC information such as identity, purity, and potency of the product, raw material and process controls, and rationales for stability are required from an early stage of IND submission.
While the investigation is ongoing, whether changes to the product characteristics or manufacturing process that are made with changes to the protocol or CMC information have an impact on the consistency or interpretation of the data from the clinical investigation should be evaluated continuously. For example, differences in product characteristics associated with lot or scale change may influence reproducibility of the evaluation or interpretation of safety signals. Therefore, a system to show the equivalence using data is important for each change.

3-3-2. Use of new modalities (cell and gene therapy, etc.)

While new modalities such as cell and gene therapy (CGT) are classified as biological products, they have characteristics including personalization, small-scale production, and high sensitivity to manufacturing processes. Therefore, the depth of CMC information required in clinical investigations, the concept of comparability evaluation, and the method of safety evaluation are more characteristic than the conventional biological products.
The IND requires submission of product-specific information according to the risks associated with the product, such as vector characteristics, cell identity, viability, differentiation and function, residual impurities, and off-target assessment at an early phase. In light of these characteristics, FDA and CBER have clarified the concepts of applying the CMC requirements in a phase-appropriate manner, and have shown a more flexible review policy for the scope of GMP in an early phase, establishment of release criteria, and comparability evaluation at the time of process

changes than the conventional products. This also makes it possible to proceed with clinical investigations of CGT that require manufacturing and prompt administration that are tailored to each patient while securing the quality and safety.
On the other hand, in the new modalities, changes in the manufacturing process have a relatively large impact on clinical outcomes. Therefore, it is essential to explain the comparability of the data before and after the changes at each phase of the investigation. FDA continues to publish guidance on concepts of change control and comparability evaluation throughout the product lifecycle, and requires to demonstrate consistency in safety, activity, and efficacy before and after the change using quality, nonclinical, and clinical data from the clinical investigation phases.
In addition, for gene therapy, etc., a long-term follow-up is generally required in a study design, and safety evaluation plan in consideration of vector persistence and delayed risks associated with gene transfer should be formulated in advance at the IND stage. These elements are finally reviewed in the BLA in an integrated manner together with the manufacturing facility and processes.

3-4. Regulations on clinical investigations of combination products

A combination product is defined by FDA as a product combining two or more components, "drugs," "devices," and "biological products," and includes an antibody drug conjugate (ADC) and products combining a drug and a dedicated device.
In a clinical investigation, FDA first determines the primary mode of action (PMOA) for a product to determine whether it should be treated as a drug, device, or biological product. According to the PMOA, either CDER, CBER, or CDRH will be the main review center and determine the applicable regulatory practice for IND/Investigational Device Exemption (IDE). Even for a combination product, a clinical investigation process for either IND (when handled as a drug or biologic) or an IDE (when handled as a device) will be selected, in general.
ADC is usually considered as a combination of "biologic and drug," and clinical investigations are conducted under the regulations on biological products.
For a product combining a drug and dedicated device (e.g., a drug with a built-in delivery system, drug plus light irradiation device, etc.), operability and safety evaluation of the device component needs to incorporated in the clinical trial design in addition to the safety and efficacy evaluation of the drug.

3-5. Phase 1 study (First-In-Human [FIH]/Early phase)

The guidance published by FDA is important as a requirement specific to phase 1 studies (early phase clinical trials) of drugs in the United States. This guidance has been formulated to clarify the minimum information necessary to ensure safety while limiting to the range necessary for the first use in human for nonclinical, CMC, and other information required particularly in early phase clinical trials among the IND components under 21 CFR Parts 312.22 – 312.23. In this guidance, FDA clarifies that the range of submission of non-clinical data and CMC information can be adjusted according to the risks to participants, considering that the requirement level more flexible than that in usual late phase clinical trials can be applicable to phase 1 studies in which the evaluation focuses on securing the safety in the first administration to participants.
In addition, manufacturing control in phase 1 studies are handled more flexibly than that in late phase studies, and FDA has issued a separate guidance called "CGMP for Phase 1 Investigational Drugs." The guidance explains it is sufficient to apply the streamlined GMP

principles to ensure the safety and quality of clinical trials at the phase 1 stage, instead of full-scale GMP that applies to commercial products. This balance ensures participant safety while avoiding excessive burden during the early development stage.

3-6. Studies in orphan drugs

Clear regulations and guidance structure are in place in the United States to support clinical investigations in orphan drug. Rare diseases are characterized by a very small number of patients, less than 200,000 patients in the United States, and often limited knowledge of the disease course and clinical presentation. Because of this background, the system based on the Orphan Drug Act is the core in the United States. When a disease under drug development is designated as a rare disease, companies under development can receive advantages such as development support and market exclusivity for a certain period. In addition, 21 CFR Part 316 was established as a regulation that embodies this system to specify the framework for orphan drug designation procedures, clinical investigation support, benefit of exclusivity period, etc.

FDA has issued several guidance documents on how to proceed with clinical trials specific to rare diseases. Of these, the latest general guidance (Rare Diseases: Considerations for the Development of Drugs and Biological Products) shows FDA's basic concepts on major issues in the development, such as study design, safety evaluation, use of external comparator, and handling of pediatric patients, reflecting issues specific to rare diseases, such as limited number of patients, disease diversity, and uncertainty in disease understanding. FDA also clarifies its policy of using 'maximum flexibility' for rare disease development, with operational considerations to advance development in areas with limited number of patients, including utilization of single-arm study and external comparator group, adjustment of statistical requirements, and simplification of the nonclinical package.

In addition, FDA's Office of Orphan Products Development (OOPD) operates a grant scheme to support clinical investigations for rare diseases. This system continues to invite application for funding programs for clinical investigations in rare diseases with unmet medical needs.

In addition, because rare diseases overlap with fields with more pediatric patients, the system has also been adjusted for Pediatric Research Equity Act (PREA), which requires clinical investigations in children, for example, that exemption from requirements is granted for designated orphan drug indications.

3-7. Regulations on clinical investigations in children

Two Federal statutes of PREA and Best Pharmaceuticals for Children Act (BPCA) play a central role in proceeding with clinical trials in children in the United States. These statutes were established by the U.S. Congress and are operated by FDA.

First, the Pediatric Research Equity Act (PREA) specifies a system requiring business entities to design and conduct clinical trials in children when a certain drug is likely to be used in children. A sponsor must submit an Initial Pediatric Study Plan (IPSP) to FDA in the application for new active ingredients or new indications. The submitted plan will be reviewed by the Pediatric Review Committee (PeRC) within FDA. In parallel with the development in adults, this system requires to obtain necessary data in the pediatric population.

Next, BPCA is a system to promote pediatric development by granting a 6-month period of pediatric exclusivity when a sponsor voluntarily conducts a pediatric study. While PREA is a mandatory system, BPCA is characterized by support to pediatric studies through incentives.

Under the BPCA, the contents of a pediatric study that FDA considers necessary are presented to the sponsor as a Written Request, and if the study is conducted according to this request, an extension of the exclusivity period will be offered.
Regarding the protection of subjects and ethical aspects, 21 CFR Part 50 Subpart D has established the provision where pediatric patients are positioned as a vulnerable participant population. In addition to the requirement of review by IRB, this provision organizes the classification of investigation risks and benefits (e.g., cases where minimal risks, direct benefits are expected, cases where important findings are obtained without direct benefits) and acceptable investigation conditions for each classification. Furthermore, it clearly specifies requirements for parental permission and assent of children and exemption from them.

3-8. Regulations on clinical trials conducted during emergency

In the United States, if a Public Health Emergency (PHE) is declared, FDA will promptly issue specific guidance aiming for balancing continuation of clinical trials and protection of participants. These guidance documents provide specific, flexible measures for operation of clinical trials during emergency. For example, during the time of COVID-19, FDA published a guidance on "Conduct of Clinical Trials for Medical Products during Public Health Emergency" (original in March 2020 and final revision on August 30, 2021). This guidance clearly indicated flexible actions for operations and their concepts required in practice, including remote monitoring, alternative evaluation methods instead of outpatient visit, adjustment of evaluation schedule, and in-home delivery of investigational drugs, on the premise of ensuring participant safety, complying with GCP, and putting the top priority on maintaining trial integrity.
Furthermore, based on the experiences from actions taken for COVID-19, FDA finalized the versatile guidance “Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies” in September 2023, in anticipation of a wide range of serious disruptive events such as infections, natural disasters, military collisions and bioterrorism natural disasters, in addition to the individual actions against pandemics. This guidance cross-sectionally organizes issues such as decision on trial continuation, remote assessments and use of digital tools, deviation recording and reporting, assessment of impact to statistical analysis and investigational drug management during supply chain disruption. It also features basic principles that can be applied with or without a PHE declaration.

3-9. Regulations on clinical investigations of controlled substances

In the United States, there are important additional requirements regulated by the Drug Enforcement Administration (DEA) in addition to the FDA regulations (IND) when handling controlled substances in clinical trials.
When a controlled substance is used in a research or clinical trial, a researchers (usually the principal Investigator) or institution must obtain a DEA Researcher Registration (DEA Form 225).

Chapter 2: Details of Regulations on Clinical Trials of Drugs in the United States

1. Approval for conducting clinical investigations by the government or regulatory authorities

An IND is usually filed to FDA to start a clinical investigation in which a new drug is administered to humans in the U.S. In principle, the safety and scientific validity are confirmed during the review period of 30 days after FDA receives the IND, and the investigation can be started if there is no notice of suspension from FDA after 30 days.

FDA may issue a Clinical Hold to suspend the start or continuation of the investigation if it determines that there are questions about the participant safety or scientific validity. Typical reasons include serious safety concerns, lack of preclinical safety margins, and critical protocol design deficiencies. To release the hold, the sponsor must resolve the concerns by submitting supplemental data or revising the protocol.

During the investigation, "whether the investigation is appropriately conducted under the conditions of approval" will be continuously inspected by expedited safety reporting (Part 312.32) and appropriate notification of protocol amendments (Part 312.30 and Part 312.31).

2. Approval for conducting of clinical trials by Institutional Review Board (IRB)

IRB review and approval are mandatory when conducting a clinical investigation under FDA regulations in the U.S. This is specified in 21 CFR Part 56, and the initial review, continuing review, and record retention by IRB are required for clinical investigations subject to FDA regulations. The roles of the IRB include protection of participants' rights, safety and well-being, and the review is conducted in accordance with FDA's regulations on informed consent (21 CFR Part 50).

The initial review will cover the protocol, informed consent form, participant information materials, participant recruitment method, compensation procedures, data management, confidentiality, etc. For federally-funded investigations, the Common Rule (45 CFR Part 46), which includes the fundamental policy of participant protection overseen by OHRP, also applies to specify the composition, review criteria, and institutional assurance of IRBs. Under the Common Rule, it is mandatory to use a single IRB (sIRB) in principle, to ensure consistency and acceleration of ethical review.

3. Conflict of interest (COI) in clinical investigations

In the U.S., the system ensures that the financial interests of researchers and institutions involved in clinical investigations do not bias the design, conduct, analysis, and reporting of clinical investigations.

21 CFR Part 54 requires applicants to submit financial interests of each clinical investigator. Such financial interests include outcome-contingent compensation, more than a certain amount of equity or stock in a sponsor (e.g., more than a certain monetary value of listed shares and private equity), and proprietary interest in the investigational product.

In federally-funded investigations, pursuant to 42 CFR Part 50 Subpart F, the research institution requires investigators to disclose their significant financial interests (SFIs) (and those of their spouse and dependent children), and reviews and manages whether they correspond to financial

conflict of interest (COI). The requirements include establishment and dissemination of institutional policies, education of researchers, periodic disclosure of financial interests, management plans and reports of financial COI (to NIH and PHS), and correction actions at the time of violation.

4. Explanation to participants and obtainment of consent, and multilingualization

4-1. Principles in informed consent

If an FDA-regulated clinical trial is conducted in the U.S., informed consent is required in accordance with 21 CFR Part 50 and applies to all FDA regulated clinical trials.
21 CFR Part 50 clarifies the basic elements to be explained to participants at the time of informed consent (the purpose, duration, and procedures of the trial, foreseeable risks and discomforts, reasonably expected benefits, disclosure of alternative treatments, confidentiality and possible FDA inspection, compensation and treatment in the event of injury, contact information, and voluntary consent and rights of consent withdraw). Depending on the nature of the trial, additional elements may be added, such as unforeseeable risks, conditions under which the investigator may terminate participation without consent, additional costs, withdrawal procedures, and notification of significant new information. FDA‘s guidance on the informed consent practice was updated in 2023 to clarify the attitude to deliver the explanation understandable for participants without coercion or undue inducement and put emphasis on the entire process.

4-2. Clinical investigations in children

In investigations in minors, requirements such as assents according to age and maturity level (expression of intention equivalent to consent) and parental consent are required in accordance with the criteria in Subpart D (additional safeguards for children).

4-3. Cases in which exemption from consent is allowed

21 CFR Part 50 includes provisions on the exemption from informed consent under strict conditions.
If the participant is confronted by a life-threatening situation necessitating the urgent use of the investigational drug and has no sufficient time to obtain a consent, the informed consent procedure is temporarily exempted on the conditions of written certification by the attending physician, expedited reporting to the IRB, etc. as an exemption from informed consent in a clinical investigation during emergency.
If all of the following conditions are met, "participation in a clinical trial without informed consent" will be permitted after prior approval by the IRB.

- The participant is life-threatening.
- Informed consent cannot be obtained (from the participant or legal representative).
- No standard of care is effective or available.
- The research is in high scientific need.
- Community consultation and public disclosure before and after the trial

These are FDA's most stringent provisions on exceptions and are rarely used in clinical trials under normal situations.

4-4. Additional requirements in federally-funded investigations

For federally-funded investigations, the provisions on informed consent in the Common Rule (45 CFR Part 46) also apply, which requires a clear presentation of “key information” at the beginning of the consent document, with greater emphasis on ease of understanding.

4-5. Multilingualization

The informed consent process in a language understandable to participants is an explicit requirement under FDA regulations, and any plans in which participants other than English speakers are enrolled are required to incorporate arrangements of translated consent forms and appropriate interpreters.

5. Compensation to participants

The U.S. Federal statutes and FDA regulations do not specify uniform requirements for a sponsor to necessarily provide compensation (medical care or monetary compensation) for research-related injury. Instead, 21 CFR Part 50 clearly specifies explanation and disclosure requirements as essential elements of informed consent: “explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs (in a research involving more than minimal risk) and, if so, where further information may be obtained.” This is not a mechanism requiring the provision of compensation, but a mechanism requiring transparency of contents and necessity of submission.
FDA's guidance on informed consent (2023) also reorganized the clarification of availability of compensation and medical treatments in the event of research-related injuries, their contents and contact information. In addition, it emphasizes on the avoidance of any wording that may lead to an exculpatory language, the use of wording that is easy to understand, and avoidance of undue inducement or coercion. Specific statements are required, including "openly disclose the fact if no compensation is available (or voluntary insurance)" and "which expenses may be incurred and who are responsible for the payment ."

Similarly, the Common Rule (45 CFR Part 46) requires elimination of undue influence and sufficient provision of information through the framework of explanation and consent. However, it does not establish the obligation to provide compensation itself. Therefore, regardless of the presence or absence of federal funding, "clarifying availability of compensation and its provision process in the informed consent form" is the basis of the actual practice.

6. Reporting of safety information to regulatory authorities

Pursuant to 21 CFR Part 312.32, the sponsor must notify FDA and all participating investigators of significant safety information from clinical trials under IND as soon as possible. The article includes definitions of adverse event (AE), serious, life-threatening, unexpected, suspected adverse reaction and provides the criteria for determining which, when, and how the information is to be delivered.

Reporting deadlines are as follows:

- Death or life-threatening "unexpected suspected adverse reaction": Prompt reporting within 7 days (subsequent supplementary information acceptable)
- Serious "unexpected suspected adverse reactions" other than the above: Prompt reporting

within 15 days

The concept of "suspected" in this context means that there is a reasonable possibility that a causal relationship to the drug is suggested and requires a judgment that goes further than that in AE. "Unexpected" adverse reactions refers to cases where the risk information is not included in the Investigator's Brochure (IB) or IND or inconsistent in terms of severity and specificity.

The sponsor collects safety information from all domestic and overseas studies and information sources, and evaluates the causal relationship in individual cases as well as risks that can be recognized for the first time from the aggregate. The guidance finalized in December 2025, "Sponsor Responsibilities-Safety Reporting Requirements and Safety Assessment for IND and BA/BE Studies" has clarified the practical concept of reporting judgment by determining "the frequency and severity beyond expectations" in aggregate evaluation, not individual cases, for foreseeable serious adverse events (e.g., disease progression and known adverse events).
The responsibilities of the principal investigator are also organized. The guidelines on practical operations, including prompt sponsor reporting of serious adverse events (21 CFR Part 312.64 [b]) and on expedited reporting to the IRB (Part 312.66), are incorporated in the guidance (2025) "Investigator Responsibilities-Safety Reporting for Investigational Drugs and Devices."

For IND-exempt bioavailability (BA)/bioequivalence (BE) studies, serious and unexpected adverse events require expedited reporting to FDA, as specified in these two guidance documents above.
On the other hand, the 7/15-Day expedited reporting per Part 312.32 does not apply to IND-exempt studies other than BA/BE studies, and reporting of "unanticipated problems" mainly by IRB is a basic rule. The establishment of the mechanism of expedited reporting from the IRB to the institution, and from the institution (as needed) to FDA is required under 21 CFR Part 56.108 (b).

7. Protection of participants' information (protection of personal information and protection of personal healthcare information)

Compliance with regulations on the protection of participants is mandatory in the conduct of clinical trials. 21 CFR Part 50 which specifies the requirement to obtain informed consent is applicable to clinical trials under FDA’s regulations, and 21 CFR Part 56 which specifies the IRB composition, review criteria, etc. specifies the IRB review criteria for clinical trials regulated by FDA and requires the initial review, approval, and continuing review by the IRB for certain studies. These criteria are used in the detailed review by the IRB for the confidentiality statement in the informed consent form (including statement of FDA inspection visibility) and handling of personal information during the study.
Additionally, for studies involving PHI, in accordance with the HIPAA Privacy Rule (45 CFR Part 164 Subpart E), HIPAA patient authorization is required in principle, and special data protection measures, such as waiver/alteration by approval of the IRB/Privacy Board are required even if authorization is not required. The regulation has organized data minimization options such as de-identification and limited data sets plus data use agreement (DUA).

8. Disclosure of clinical trial data (publication of registration/results)

In the U.S., the registration and result publication through ClinicalTrials.gov is required by the law (FDAAA 801/42 CFR Part 11). In an applicable clinical trial (ACT), registration within 21 days of participant enrollment and result submission within 12 months of the completion of data collection of the primary endpoint are required. Phase 2 and later controlled clinical investigations apply to ACT, and phase 1 investigations are excluded in principle.

Because of NIH funds and International Committee of Medical Journal Editors (ICMJE) recommendations, registration is often required in practice even in the investigations that are not subject to the laws and regulations. FDA strives to secure transparency through monitoring activities such as certification of compliance by Form FDA 3674, a Bioresearch Monitoring Program (BIMO), and other enforcement frameworks such as a Compliance Management Program (CMP). The main public registry equivalent to jRCT in Japan is ClinicalTrials.gov in the U.S., and early and accurate registry operation is essential in anticipation of global studies, applications for marketing approval, and academic presentations.

9. Laws and regulations on electronization of data, etc.

In the United States, data electronization in clinical investigations of drugs is regulated mainly by 21 CFR Part 11 which specifies handling of electronic records and electronic signatures. Part 11 is intended for storage of electronic data in a format that allows review by regulatory authorities with the reliability and integrity equivalent to those of paper media and applies to electronic records that are prepared, maintained, and submitted in accordance with the regulatory requirements among the records electronically generated and stored, such as electronic data capture (EDC), electronic case report form (eCRF), electronic signatures, and audit trail used in clinical investigations.

Appendix: List of laws and regulations and guidance cited in this summary (Order of description)

1. Federal Food, Drug, and Cosmetic Act, Section 505 and Section 745(a)
   Abbreviation: FD&C Act
   Japanese translation: Food, Drug and Cosmetic Act
   https://www.govinfo.gov/content/pkg/COMPS-973/pdf/COMPS-973.pdf

2. Public Health Service Act
   Abbreviation: PHS Act
   Japanese translation: Public Health Service Act
   https://www.govinfo.gov/content/pkg/USCODE-2011-title42/html/USCODE-2011-title42-chap6A.htm

3. Food and Drug Administration Amendments Act of 2007
   Abbreviation: FDAAA
   https://www.congress.gov/crs-product/RL34465?q=%7B%22search%22%3A%22FDAAA%22%7D&s=1&r=10

4. Health Insurance Portability and Accountability Act of 1996
   Abbreviation: HIPAA
   Japanese Translation: Health Insurance Portability and Accountability Act
   https://aspe.hhs.gov/reports/health-insurance-portability-accountability-act-1996

5. 21 CFR Part 11 — Electronic Records; Electronic Signatures
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11

6. 21 CFR Part 16 — Regulatory Hearing Before the Food and Drug Administration
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-16

7. 21 CFR Part 50 — Protection of Human Subjects (Informed Consent)
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50

8. 21 CFR Part 54 — Financial Disclosure by Clinical Investigators
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-54

9. 21 CFR Part 56 — Institutional Review Boards
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56

10. 21 CFR Part 58 — Good Laboratory Practice for Nonclinical Laboratory Studies
    https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-58

11. 21 CFR Part 312 — Investigational New Drug Application
    https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312
    - 312.2(b)
    - 312.6

- 312.8
- 312.22-23
- 312.30-33
- 312.50
- 312.53
- 312.56
- 312.57
- 312.60–68
- 312.110

12. 21 CFR Part 314 — Applications for FDA Approval to Market a New Drug
    https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314

13. 21 CFR Part 320 — Bioavailability and Bioequivalence Requirements
    https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-320

14. 21 CFR Part 601 — Applications for FDA Approval of a Biologic License
    https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-601

15. 45 CFR Part 46 — Protection of Human Subjects
    https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46
    - Subpart A: the Common Rule (IRB, consent, federally-funded study)
    - Subpart B: Protections for pregnant women, human fetuses, and neonates
    - Subpart C: Protections of Prisoners
    - Subpart D: Protections for Children
    - Subpart E: Requirements for registration of IRB

16. 42 CFR Part 11 — Clinical Trials Registration and Results Information Submission
    https://www.ecfr.gov/current/title-42/chapter-I/subchapter-A/part-11

17. 45 CFR Part 160 — General Administrative Requirements
    https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-C/part-160

18. 45 CFR Part 164 — Security and Privacy
    https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-C/part-164

19. INDs — Determining Whether Human Research Studies Can Be Conducted Without an IND Abstract Language: IND Exemption Criteria
    https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-new-drug-applications-inds-determining-whether-human-research-studies-can-be

20. 21 CFR Part 1271 – Human Cells, Tissues, and Cellular and Tissue-Based Products(HCT/P)
    https://www.ecfr.gov/current/title-21/chapter-I/subchapter-L/part-1271

21. 21 CFR Part 600-680 — Biologics
    https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F

22. Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies
https://www.fda.gov/media/72057/download

23. Current Good Manufacturing Practice for Phase 1 Investigational Drugs
Abstract Language: CGMP for Phase 1 Investigational Drugs
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-phase-1-investigational-drugs

24. 21 CFR Part 316 — Orphan Drugs
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-316

25. Rare Diseases: Considerations for the Development of Drugs and Biological Products
https://www.fda.gov/media/119757/download

26. Pediatric Research Equity Act
Abbreviation: PREA
https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea

27. Best Pharmaceuticals for Children Act
Abbreviation: BPCA
https://www.fda.gov/drugs/development-resources/best-pharmaceuticals-children-act-bpca

28. Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies
https://www.fda.gov/media/172258/download

29. 42 CFR Part 50 — Policies of General Applicability
· Subpart F: Conflict of Interest
https://www.ecfr.gov/current/title-42/chapter-I/subchapter-D/part-50/subpart-F

30. Informed Consent
Abstract Language: Practical Guidance for Informed Consent
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent

31. Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies Guidance for Industry
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sponsor-responsibilities-safety-reporting-requirements-and-safety-assessment-ind-and

32. Investigator Responsibilities – Safety Reporting for Investigational Drugs and Devices
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-safety-reporting-investigational-drugs-and-devices

Laws and Regulations for Clinical Investigations of Medical Devices in the United States

Date of preparation: February 20, 2026

Chapter 1: Regulations pertaining to clinical investigations of medical devices in the United States

1. Hierarchy of the laws and regulations

1-1. Legal system

The medical device regulations in the United States consist of a hierarchy of more than one legal systems.

(1) Federal statutes-Highest source of law

The Federal Food, Drug, and Cosmetic Act (FD&C Act) serves as the core of medical device regulation, and provisions for medical devices were organized by the Medical Device Amendments of 1976. The FD&C Act provides a basic framework of definitions, premarket reviews, post-market surveillance, penalties in the event of violations, etc. for medical devices.

(2) Code of Federal Regulations (CFR)-Regulations to implement the law

The regulations that embody the FD&C Act are incorporated in Title 21 CFR. When conducting a clinical trial of a medical device, 21 CFR Part 812 serve as the core, but the relevant provisions are also strictly stipulated, thus needing to widely deal with them according to the objectives of the investigation.

The following parts are particularly important in the field of medical devices:

- 21 CFR Part 11: Validation of electronic records and electronic signatures
- 21 CFR Part 50: Informed consent requirements
- 21 CFR Part 56: Protection of subjects/IRB requirements and IRB operations
- 21 CFR Part 803 (Medical Device Reporting): Postmarketing reporting of adverse events and malfunctions
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators): Collection and submission of financial interest of clinical investigators
- 21 CFR Part 892: Classification of radiology devices
- 21 CFR Part 807 (510 (k)): Premarket notification
- 21 CFR Part 809: Label and labeling requirements for In vitro diagnostic (IVD) products

- 21 CFR Part 812 (Investigational Device Exemption [IDE]): The core regulation for the conduct of clinical trials, including SR/NSR determination, IDE application/exemption, monitoring, recording/reporting (of unanticipated device-related adverse events, etc.), Investigator Agreement, and Financial Disclosure
- 21 CFR Part 814 (Premarket Approval): Approval system for high-risk medical devices
- 42 CFR Part 11 (ClinicalTrials.gov): Registration and results disclosure of applicable clinical trials
- 45 CFR Part 46 (Common Rule): Common rules for protection of subjects applicable to research including federal funding

These CFRs are operated by the U.S. Food and Drug Administration (FDA) and are legally binding.

(3) FDA Guidance Documents-Working Practice Standards

Although the guidance documents are not legally binding, they provide FDA's views and interpretation of regulations and practical expectations. Applicants generally prepare application documents in accordance with the guidance. Failure to follow the guidance is subject to proof of its own scientific validity. There are many types of guidance documents, and those related to the conduct of clinical trials in medical devices are summarized as shown below.

- Design Considerations for Pivotal Clinical Investigations for Medical Devices(2013, Final)
- Adaptive Designs for Medical Device Clinical Studies(2016, Final)
- Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies(2013, Final)
- Significant Risk and Nonsignificant Risk Medical Device Studies(2006, Final)
- Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies(2017, Final)
- Electronic Source Data in Clinical Investigations(2013, Final)
- Use of Electronic Informed Consent(2016, Final)
- Electronic Systems / Electronic Records / Electronic Signatures in Clinical Investigations: Q&A(2023, Draft)
- Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring(2013, Final)
- Processes and Practices Applicable to Bioresearch Monitoring (BIMO) Inspections(2025, Final)
- Financial Disclosure by Clinical Investigators(2013, Final)
- Investigator Responsibilities – Safety Reporting for Investigational Drugs and Devices(2025, Final)

1-2. Major regulatory authorities

The U.S. regulatory system for medical devices consists of the federal agencies. Food and Drug Administration (FDA), a subdivision of the U.S. Department of Health and Human Services (HHS), is the core of the system and has the legal authority to oversee the safety, effectiveness, and quality of medical devices. Center for Devices and Radiological Health (CDRH) within FDA is primarily responsible for reviewing and overseeing medical devices. Regulatory purposes for medical devices include premarket review, manufacturing and quality control, postmarket surveillance, and reporting of adverse events.

In addition, the “Common Rule (45 CFR Part 46)” relating to protection of participants applies to federally-funded research, and HHS’s Office for Human Research Protections (OHRP) is responsible for its operation and oversight. This is a uniform standard not only for medical devices, but also for ethical review of clinical trials in human and protection of participants.

■ List of main institutions:

- FDA
  - CDRH: Responsible for evaluation, approval, and postmarketing surveillance of medical devices
  - Center for Biologics Evaluation and Research (CBER): Responsible for regulations of some combination products, etc.
- OHRP: Operation and oversight of the Common Rule
- Office for Civil Rights (OCR): Enforcement of the Privacy Rule and Security Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA)

2. Classification for consideration of applicable regulations

When conducting clinical trials of medical devices involving intervention in the United States, various categories may be included to consider their applicable regulations and guidance. The definition of Intervention is specified in the section "Clinical Trial Definition" of NIH, but regulations applicable to clinical trials are determined not based on the presence or absence of intervention, but based on the factors including the presence or absence of IND/IDE, whether or not the investigation is intended for marketing application, involvement of funding by the Federal Government.

2-1. Regulations applicable to clinical trials that are intended for the application for marketing approval

Clinical investigations intended primarily for obtaining marketing authorization (in particular, Premarket Approval [PMA] of Class III medical devices) are focused on the quality of the clinical evidence and the compliance of the application format that can withstand the scientific and regulatory review by the FDA (CDRH) to which the submission is made. Regulations including 21 CFR Part 812

(IDE), Part 50 (IC), Part 56 (IRB), and Part 11 (electronic records) must be complied with when conducting a clinical trial. On the other hand, the essential elements of the structure and summary (indication, device description, alternative therapy, market history, etc.) of the clinical and nonclinical data in the PMA application are specified in 21 CFR Part 814 (particularly Part 814.20). It is important to design and operate the investigation by organizing the relationship between the implementation regulations (Part 812, Part 50, Part 56, and Part 11) and the application regulation (Part 814). While a pivotal study is often planned and conducted as a precursor to PMA, the study design clarifies the primary endpoint, statistical plans, comparator selection, and bias control with reference to the FDA guidance (Design Considerations for Pivotal Clinical Investigations). The framework of monitoring and actions against non-conformance/deviations plans prioritization of critical data/processes and central monitoring, etc. based on Risk-Based Monitoring (2013, Final) and Q & A (2023). In addition, the definition, severity, and reporting procedures for protocol deviations have been well organized in recent guidance and they are important to ensure data integrity that can withstand approval.

2-2. Regulations applied to clinical trials that are not intended for the application for marketing approval

2-2-1. IDE for the conduct of clinical trials

An application for Investigational Device Exemption (IDE) is required even if a clinical trial that is not intended for approval but intended for evaluation of the safety and effectiveness of the medical device. An IDE is an FDA exemption for the use of unapproved devices in humans, and an approved allows exemption from marketing authorization requirements (e.g., 510 (k), registrations/listings, and most parts of Good Manufacturing Practice [GMP]) and the efficient conduct of clinical trials (e.g., IDE exemption from 812.2 (c) for diagnostic devices). However, the detailed requirements for an IDE have in common regardless of the intention for marketing approval or not, and are detailed in the following sections.

2-2-2. Regulations based on risk classification

- Significant Risk (SR): IDE submission required
- Non-Significant Risk (NSR): IRB approval required in accordance with Abbreviated IDE
- Exempt: IDE exemption if the conditions such as noninvasive diagnosis are met

When conducting a clinical investigation of medical device that is not intended for approval, for a medical device corresponding to SR, a sponsor must file an application for IDE to FDA before starting the investigation, and Institutional Review Board (IRB) will make a final judgment on the risk suggested by the sponsor.

SR refers to the investigational device with the potential of serious risks to participants' health, safety, or welfare due to the following reasons under the IDE regulations: (1) implants, (2) professing life support and maintenance, (3) important uses in diagnosis, treatment, etc., and (4) other reasons. The decision as to whether or not a medical device is classified as SR is made depending not only on own

specific characteristics of the device but also on the method of use in the protocol (how to use the results, additional procedures, influence on clinical judgment).

However, if a medical device has limited risks and classified as NSR, an IDE submission to FDA is not required, but clinical trials are conducted under the IRB approval in accordance with the Abbreviated IDE.

Additionally, investigations that fall under the exempted investigation described in 21 CFR Part 812, such as use of a marketed device in accordance with its labeling and use of a diagnostic device under a specific condition without invasive procedures and energy transfer, are exempt from the IDE itself.

2-3. Classification of medical devices requiring clinical investigations

2-3-1. Classification

Classification	Summary	Example of applicable device	Necessity of submission of clinical data (results from clinical trials)
Class I	• Medical devices with the lowest risk • General Controls alone ensure safety and effectiveness. • Mostly 510 (k) exempt	Bandage, gauze, elastic bandage, examination gloves, etc.	Mostly requiring no clinical trials (mostly 510 (k) exempt and general controls only)
Class II	• Moderate risk • General Controls + Special Controls • Mostly 510 (k) required	Sphygmomanometer, syringe, catheter infusion pump, CT scanner, pregnancy testing drug, contact lens (soft, daytime wear), etc.	• Necessity and extent of clinical data are determined individually according to the characterization and claimed performance of the product item (mostly required proof of equivalence). • Subject to De Novo classification for novel medical devices lacking predicate device with low to moderate risks
Class III	• Medical devices with the highest risk device • Medical devices relating to life support or maintenance, or with serious risks • PMA required	Pacemakers, artificial heart valves, orthopedic implants (artificial joints, etc.), etc.	Submission of clinical trial results (clinical trial data) is usually required.

- 510 (k) (21 CFR Part 807): A system that requires the proof of substantial equivalence

- De Novo (21 CFR Part 860): For novel medical devices with low to moderate risks
- PMA (21 CFR Part 814): Strict approval system for medical devices with high risks

FDA has granted 510 (k) exemption for many Class I and some Class II medical devices. This is because the safety and effectiveness of the device is considered to be well understood and reasonably assured by the General Controls. However, there are general limitations to the exemption, and Class I devices designated as reserved devices or with any significant changes in the indications or technology may not be exempted. As a rule, applicability or limitations to the exemption must be confirmed with FDA Product Classification Database for each product item (product code).

In addition, De Novo classification is an application route for medical devices with low to moderate risks (equivalent to Class I/II devices) that lack predicate devices (appropriate existing devices). Although clinical trial data are not always required, FDA may require the submission of clinical data if reasonable assurance of safety and efficacy is difficult to be demonstrated only by the novelty and risk characteristics of the device and non-clinical data. The scope of the necessary data is determined flexibly according to the risks. De Novo classification establishes a new Class I/II device classification and product code and creates a predicate for future 510 (k)s.

In the US, there is no system equivalent to Notified Body (NB) in EU, but there is a system to improve the review efficiency in some medical devices with low to moderate risks by making use of third party review, investigation, and audit. In all cases, the final decision on marketing authorization is retained by FDA.

- **3P510k(3P510k/Accredited Persons):**

  A 510 (k) Substantial Equivalence (SE) or Not Substantial Equivalence (NSE) is reviewed by an FDA-recognized third party in some of the Class I/II devices, and the final decision is made by FDA. This does not apply to De Novo and PMA. This program was established based on §523 of the FD&C Act (21 U.S.C. §360m), and the applicable items are designated and disclosed by FDA.

- **ASCA(Accreditation Scheme for Conformity Assessment):**

  Specification tests certified by FDA, such as electrical safety, electromagnetic compatibility (EMC), and biocompatibility, are performed in ASCA-certified laboratories to streamline the re-verification process during the review. It is not a system for making a final decision on conformance assessment of products by a third party, but by FDA.

- **MDSAP(Medical Device Single Audit Program):**

Quality Management System (QMS) audit reports by a third-party auditing organization are accepted by FDA as a substitute for routine inspections (excluding “for cause” and pre-PMA audits, etc.).

3. In vitro diagnostic products

3-1. Handling of in vitro diagnostic products in the United States

The U.S. FDA defines in vitro diagnostic products (IVD) as “reagents, instruments, and systems used in human specimen (collection, preparation, and testing) for the purpose of the diagnosis of disease or other conditions, including a determination of the state of health” in 21 CFR Part 809, and classifies them as “medical devices” under the FD&C Act.

Classification	Summary	Example of applicable device
Class I	• Low risk • An IVD in which the safety and efficacy may be assured by General Controls alone • Mostly 510 (k) exempt	• General clinical laboratory reagents • General-purpose reagents (buffer, diluent, etc.) • Reagents for some urine pregnancy tests
Class II	• Moderate risk • General Controls + Special Controls required • 510 (k) premarket notification required mostly	• Blood glucose test systems • Immunological test systems • Rapid diagnostic testing kits for infectious diseases (influenza, etc.)
Class III	• High risk • IVD products for which a false result may directly lead to patient's life or serious health hazard • PMA required in principle	• IVD products for definitive diagnosis of serious infection such as HIV, HBV, and HCV • Companion Diagnostics • Tumor genomic profiling by NGS

In light of the compilation of technical data for an application, an IVD often is focused on analytical validity, which may obviate or limit the need for clinical performance, depending on the novelty, risk, or clinical environment, if the non-clinical data (sensitivity/specificity/reproducibility, cross-reactivity, interference/cross-reactivity, etc.) is sufficient to match the product's performance characteristics (how well the test performs in the assay). On the other hand, clinical performance studies are required for new reaction principles, intended use at high clinical risks, and result assessments directly relating to patient treatment strategies.

When conducting a clinical investigation in human to obtain clinical performance data, in principle, an IDE is applicable, and the investigated IVD is subject to IDE if it meets the following four conditions:

- Non-invasive (general low-risk procedures such as blood sampling may not be applicable)
- Does not require Invasive sampling/collection that present significant risk (e.g., cerebrospinal fluid collection)

- Do not introduce energy into a subject (e.g., radiation, ultrasound, electrical stimulation)
- Is not used as a sole diagnostic procedure without confirmation by another established diagnostic procedure

If this exemption does not apply, the IRB must determine whether the investigation has SR or NSR, and if SR is detected, the clinical investigation is conducted under the FDA approved IDE. For NSR, it is conducted under the abbreviated IDE requirements.

3-2. Clinical performance study for an IVD

3-2-1. Required studies

Clinical performance studies required for an IVD in the U.S. are those conducted to show how accurately the test can distinguish diseases in real world settings, including prospective clinical performance studies in which patient samples are prospectively collected in a clinical setting and compared with the Golden Standard method for the evaluation of Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA); retrospective studies to reproduce the actual clinical case spectrum using existing residual specimens or sample banks to confirm accuracy; bridging studies to supplement additional subgroup information and differences in use conditions; and combined usability study to confirm operability and misuse risks in combination with clinical performance in anticipation of OTC, home and POC testing. All of these studies are designed based on FDA's views on the clinical performance evaluation (PPA/NPA presentation, validity of comparison method, reproducibility of use environment), together with various clinical verifications such as prospective, retrospective, and operability evaluation to lay out the necessary clinical evidence for premarket review (IDE).

3-2-2. Reporting of adverse reactions

In the U.S., an IVD is a medical device, which is not included in the adverse drug reaction reporting system but in the Medical Device Reporting (MDR) including reporting of device malfunctions and adverse events. If the clinical performance study for an IVD is conducted under an IDE, events that correspond to adverse reactions are treated as an "unexpected adverse device effect (UADE)" and expedited reporting to FDA and IRB by the sponsor is required under 21 CFR Part 812.

Chapter 2: Details on the regulations for clinical investigation

1. Laws and regulations on approval for conducting clinical studies by the government or regulatory authorities

In the U.S., when conducting a clinical investigation of an unapproved medical device or medical device with new intended use, approval of an IDE application prior to beginning clinical investigations is required in accordance with 21 CFR Part 812 stipulated by FDA.

If the medical device used in a clinical investigation falls under the category of "SR devices," the investigation cannot be started until the sponsor submits an IDE application to FDA, and the conditions specified in 812.30 (e.g., 30 days after the receipt by FDA) are satisfied. On the other hand, for investigations of medical devices that fall under the category of "NSR devices," an IDE application to FDA is not required, but clinical investigations can be started by obtaining approval from the IRB at the study site while complying with the abbreviated IDE. For clinical investigations applicable to IDE, the protocol, subject protection, monitoring, reporting requirements, labeling, etc. must comply with requirements in 21 CFR Part 812 (e.g., labeling in 812.5, monitoring in 812.46, recording in 812.140, reporting in 812.150, etc.).

The point for which FDA requires IDE approval for the conduct of a clinical investigation of a medical device that falls under SR device is similar to the clinical trial notification system in Japan. In Japan, there are no provisions for approval, etc. because the PMDA's inspection is completed within a certain period after the notification was filed to PMDA. However, if the IDE is approved by FDA under 21 CFR 812, FDA will notify the sponsor in writing as a legally binding administrative decision (order) (812.30 (a)).

2. Compliance with ISO 14155

Clinical investigations of medical devices are conducted in the U.S. mainly in accordance with 21 CFR (e.g., Part 812). At least the major provision (21 CFR 812.28) defining GCP specifies the rules as a framework including review by the Institutional Ethics Committee (IEC)/continuing review, and informed consent, and ISO 14155 is not directly referred to.

On the other hand, FDA has published ISO 14155:2020 as Recognized Consensus Standard. While the recognized consensus standard is a framework that can be utilized in supporting data of the medical device in a form of Declaration of conformity, etc., it is not a legal basis for substituting clinical trial requirements in the United States. The conduct of clinical trials and acceptance of data are based on the requirements set forth in 21 CFR (Statement of Compliance with Part 50/Part 56/Part 812 for investigations in the United States and Statement of Compliance with GCP as defined in 812.28 for investigations outside the United States).

Therefore, ISO 14155:2020 does not replace the U.S. CFR requirements, but is consistent as a supportive framework for operation and documentation because it is consistent in many aspects with the GCP framework defined in 21 CFR 812.28 in terms of protection of participants, assurance of data reliability, monitoring, and necessity of ethical review.

3. Process and laws and regulations for approval of conducting researches by Ethical Review Board and IRB

Clinical investigations of medical devices in the U.S. are conducted under a framework based on respective legal requirements, including ethical review by the IRB (21 CFR Part 56) and FDA's IDE regulations (21 CFR Part 812). In principle, FDA-regulated clinical investigations are required to obtain IRB approval and appropriate informed consent from participants. For SR devices, FDA

requirements must also be satisfied in the FDA's IDE procedures (however, there are regulatory exceptions in the IRB review and informed consent). This is a central mechanism to protect the safety and rights of participants and to ensure the quality and reliability of clinical data to be obtained.

The IRB is an independent ethical review board responsible for protection of study participants in FDA-regulated clinical investigation. 21 CFR Part 56 specifies the IRB's composition, responsibilities, review procedures, and continuing review. In particular, 21 CFR 56.103 (excluding exceptions in 56.104, 56.105, and others) specifies that clinical investigations in which a prior submission is required to FDA (for example, those subject to Part 812) can only be initiated after the initial and continuing review by the IRB review. Additionally, 21 CFR 50.20 specifies basic rules of informed consent (requirements of subject consent except for exceptions including 50.22, 50.23, and 50.24).

In addition, the Common Rule (45 CFR Part 46) also applies if a clinical investigation is funded by the Federal government or subject to implementation, support, or regulation. 45 CFR 46.101 specifies that this policy applies to all research involving human subjects conducted, supported, or subject to regulation by any Federal department or agency (with the exception of research eligible for exemption under 46.104). In addition, 45 CFR 46.103 specifies that Compliance Assurance for research covered by this policy must be submitted to OHRP. Therefore, if a medical device clinical investigation is applicable to both the FDA regulation (e.g., 21 CFR Part 50, 56, and 812) and the Common Rule (45 CFR Part 46), a so-called dual compliance is required. The IRB confirms whether the requirements of the Common Rule in addition to the requirements under FDA regulations are met to evaluate the ethical validity of the entire research.

In clinical investigations of medical devices, the procedure is diverged by whether the device falls under SR or NSR. If the IRB considers that it falls under SR, the IRB must notify the investigator and sponsor as appropriate pursuant to 21 CFR 812.66, and the sponsor cannot start the investigation unless the sponsor follows the framework of 21 CFR 812.30 (a). If a medical device is considered to fall under NSR, an IDE application to FDA is not required in principle in accordance with the abbreviated IDE requirements of 21 CFR 812.2 (b) (except for the case when FDA requires an application under 812.20 (a)). In this case, the IRB continuously monitors the investigation through continuing review, etc.

4. Laws and regulations on conflict of interest (transparency)

In the U.S., conflict of interest (COI) of clinical investigators involved in clinical investigations of medical devices is an important issue directly affecting the reliability of study data and protection of subjects, and is strictly controlled under 21 CFR Part 54. The purpose of this regulation is to exclude the possibility that the financial interest of investigators may influence the results of clinical trials, and to ensure the transparency and reliability of clinical data to be submitted.

21 CFR Part 54 requires that sponsors (applicants) report financial conflict of interest of any clinical investigators involved in a clinical investigation that is relied on by a marketing application for a

medical device submitted to FDA (e.g., PMA, 510 (k), reclassification applications). The conflict of interest specified herein includes performance-linked compensation that may increase or decrease depending on the study results, significant payments to the sponsor company (payments of 25,000 dollars or more in total during the study period plus one year after the completion of the study, consulting fee, provision of facilities, etc.), significant ownership of stocks such as the sponsor company, and intellectual property rights such as patents, licenses, etc. related to the study device. Since these financial interests may affect the judgment of investigators, FDA considers the disclosed financial information when FDA evaluates the reliability of clinical data submitted, together with information such as study design and purpose, and information obtained from on-site inspections.

5. Laws and regulations on explanation for consent, acquisition of consent, and multilingualization

In the United States, 21 CFR Part 50 requires Informed Consent requirements for conducting clinical investigations of medical devices. Part 50 applies to FDA-regulated clinical investigations in human subjects and serves as a basic principle to protect the rights, safety and well-being of subjects, regardless of medical device, drug, or biological product.

This regulation is intended to allow participants to make an informed and voluntary decision about participation in investigation and plays a central role in medical device clinical trials conducted in the United States.

Information that participants can fully understand when participating in the investigation is required to be provided. The regulation specifies that the informed consent form and relevant documents must be provided in a language that participants can understand. Specifically, 21 CFR 50.20 states that informed consent form is required to "be provided in a language understandable to subjects or the subject's legal representative." FDA Informed Consent Guidance (August 2023) is recommended as a guide about views on the informed consent from non-English speakers, etc.

21 CFR 50.20 and 50.25 have organized that the investigator “must obtain a legally effective informed consent” before involvement of a clinical trial subject in research. In addition, they specifies that an investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The document must contain core contents, such as research objectives, foreseeable risks and discomforts, potential benefits, alternative procedures, privacy protection, compensation and treatment availability, and contact information.

Furthermore, in the U.S., the IRB will also review the appropriateness of the informed consent process in accordance with 21 CFR Part 56. The IRB is required to confirm not only the ethical nature of the study design but also whether the written information is easy to understand for subjects, unnecessarily professional, and whether the requirements for protection of subjects are met. Clinical trials cannot be started without IRB’s approval of the informed consent form by the IRB, and monitoring will be continued during the study period.

In the US, the informed consent requirements under Part 50 apply even if a medical device clinical trial is conducted under an IDE. The IDE regulations requires investigators and sponsors to monitor safety and manage labeling, and record keeping; however, informed consent is the core of subject protection, and therefore, compliance is required regardless of whether an IDE submission is required. In addition, when a UADE occurs, the contents of the consent may be revised during the study period, for example, where expedited reporting to the IRB and revision of the contents of the consent form is needed as necessary.

6. Laws and regulations on compensation to subjects

In the United States, although the handling of compensation for a research-related injury in a clinical investigation of a medical device and contents of the compensation system itself are not stipulated by Federal statutes, they are specified in the requirements of informed consent under on 21 CFR Part 50. FDA requires clear explanation of what treatment and compensation subjects can receive for injuries or disadvantages that may occur during a clinical investigation, which is a requirement of the CFR for the compensation system in the United States.

FDA's informed consent regulations under 21 CFR Part 50 require that the basic elements to be included in the consent form are an explanation as to whether any compensation and medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

In the U.S., contents of the compensation depend on the sponsor, study site, insurance policy, etc. However, FDA puts emphasis on transparency of compensation and accountability so that the participants are not disadvantaged. For this reason, it is essential to clearly state whether compensation will be provided, the scope of compensation, procedures for compensation, persons who bear medical expenses, etc. at the stage of informed consent. Failure to do so may result in the IRB not approving the informed consent form and not approving the clinical investigation.

7. Laws and regulations on reporting of safety information to regulatory authorities

Reporting of safety information on medical devices in the U.S. to regulatory authorities consists of two layers: expedited reporting and continuing review of UADE, etc. during clinical investigation and reporting of deaths, serious injuries, and serious malfunctions within the due date during the post-marketing period. Reporting subjects, due date, and formats are clearly defined, and prompt and comprehensive safety management is promoted in cooperation with the IRB, FDA, and sponsor.

7-1. Safety Reporting During Clinical Trial Conduct (Under IDE)

The IDE regulations require safety control, record keeping, and reporting in the evaluation of unapproved medical devices and those with a new intended use in humans. The sponsor must report certain safety events to both the IRB and FDA within the required timeframe. UADE is treated as a serious and unexpected device-related adverse event and requires prompt notification and correction. After review and approval of the IDE, significant deviations and significant changes are subject to

prior reporting and also require annual and progress reporting. The IRB will review the appropriateness of continuing the investigation and the necessity of revising the informed consent form through safety information.

(Reference) 7-2. Postmarketing reporting of adverse events and malfunctions (MDR: Medical Device Reporting)

Any device-related death, serious injury or malfunction (including failure or malfunction that may become serious at the time of recurrence) after the market launch must be reported to FDA in accordance with MDR (21 CFR Part 803). The scope and deadline for reporting are specified respectively for manufacturers, importers and medical institutions, and manufacturers are required to submit reports in eMDR (electronic submission).

8. Laws and regulation on protection of subjects' information (protection of personal information and protection of personal healthcare information)

- Informed consent (21 CFR Part 50)
- IRB Requirement (21 CFR Part 56)
- HIPAA Privacy Rule(45 CFR Part 164 Subpart E)

Compliance with regulations on the protection of participants is mandatory in the conduct of clinical trials. 21 CFR Part 50 which specifies the requirement to obtain informed consent is applicable to FDA-regulated clinical trials, and 21 CFR Part 56 which specifies the IRB composition, review criteria, etc. specifies the IRB review criteria for clinical trials regulated by FDA and requires the initial review, approval, and continuing review by the IRB for certain studies. Based on these standards, the IRB closely review the explanation and handling rules relating to the protection of personal information during the clinical investigation.

Additionally, for studies involving protected health information (PHI), in accordance with the HIPAA Privacy Rule (45 CFR Part 164 Subpart E), patient consent is required in principle, and data protection measures according to a waiver approved by the IRB/Privacy Board are required even if the consent is not required.

9. Laws and regulations on disclosure of clinical trial data

In the U.S., the registration and result publication through ClinicalTrials.gov is required by FDAAA 801 and 42 CFR Part 11. In a medical device investigation that falls under an applicable clinical trial (ACT), registration within 21 days of the first participant enrollment and result submission within 12 months of the completion of data collection of the primary endpoint are required. Because of National Institutes of Health (NIH) funds and International Committee of Medical Journal Editors (ICMJE) recommendations, registration is often required in practice even in the investigations that are not subject to the laws and regulations. FDA strives to secure transparency through monitoring activities such as certification of compliance by Form FDA 3674, a Bioresearch Monitoring Program (BIMO),

and other enforcement frameworks such as a Compliance Management Program (CMP). The main public registry equivalent to jRCT in Japan is ClinicalTrials.gov in the U.S., and early and accurate registry operation is essential in anticipation of global studies, applications for marketing approval, and academic presentations.

10. Laws and regulations on electronization of data, etc.

In the United States, data electronization in clinical investigations of medical devices is regulated mainly by 21 CFR Part 11 which specifies handling of electronic records and electronic signatures. Part 11 is intended for storage of electronic data in a format that allows review by regulatory authorities with the reliability and integrity equivalent to those of paper media and applies to electronic records that are prepared, maintained, and submitted in accordance with the regulatory requirements among the records electronically generated and stored, such as electronic data capture (EDC), electronic case report form (eCRF), electronic signatures, and audit trail used in clinical investigations.

Appendix: List of laws and regulations and guidance cited in this summary (Order of description)

1. Federal Food, Drug, and Cosmetic Act
   Abbreviation: FD&C Act
   Japanese translation: Food, Drug and Cosmetic Act
   https://www.govinfo.gov/content/pkg/COMPS-973/pdf/COMPS-973.pdf

2. 21 CFR Part 11 — Electronic Records; Electronic Signatures
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11

3. 21 CFR Part 50 — Protection of Human Subjects (Informed Consent)
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50

4. 21 CFR Part 56 — Institutional Review Boards
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56

5. 21 CFR Part 803 — Medical Device Reporting
   Abbreviation: MDR
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-803

6. 21 CFR Part 54 — Financial Disclosure by Clinical Investigators
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-54

7. 21 CFR Part 892 — Radiology Devices
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-892

8. 21 CFR Part 807(510(k))— Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-807

9. 21 CFR Part 809 — In Vitro Diagnostic Products for Human Use
   https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-809

10. 21 CFR Part 812 — Investigational Device Exemptions
    https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-812

11. 21 CFR Part 814 — Premarket Approval of Medical Devices
    https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-814

12. 42 CFR Part 11 — Clinical Trials Registration and Results Information Submission
    https://www.ecfr.gov/current/title-42/chapter-I/subchapter-A/part-11

13. 45 CFR Part 46 — Protection of Human Subjects
https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46

14. Design Considerations for Pivotal Clinical Investigations for Medical Devices (2013, Final)
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices

15. Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (2013, Final)
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight-clinical-investigations-risk-based-approach-monitoring

16. A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers (2023, Final)
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/risk-based-approach-monitoring-clinical-investigations-questions-and-answers

17. 21 CFR Part 860 — Medical Device Classification Procedures
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-860

18. ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice

19. FDA Informed Consent Guidance (Aug 2023)
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent

20. 45 CFR Part 164 Subpart E — HIPAA Privacy Rule
https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-C/part-164/subpart-E

21. Food and Drug Administration Amendments Act of 2007
Abbreviation: FDAAA

https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82

- Section 801

Regulatory Framework for Clinical Trials of Medicinal Products in the EU

Date of preparation: February 20, 2026

Chapter 1: Regulations governing clinical trials of medicinal products in the EU

1. Regulatory hierarchy

1-1. Legal system

The regulatory framework for clinical trials of medicinal products in the EU has a hierarchical (pyramidal) structure consisting of several layers, including regulations, directives, and guidance. As a regulation (secondary legislation) adopted on the basis of the EU Treaties (primary law), a regulation that applies directly in the Member States forms the core of clinical trial regulation, and the Clinical Trials Regulation (Regulation (EU) No 536/2014; CTR) serves as the basic regulatory framework. The CTR establishes a harmonized framework for the application, assessment, and conduct of clinical trials in the EU, ensuring both the efficient conduct of multinational trials and the protection of subjects. In addition, to ensure the transparency of clinical trial information, the CTR requires applications and the disclosure of information through the Clinical Trials Information System (CTIS).

In contrast, directives are a form of legislation that are implemented by the Member States through transposition into national law, including those establishing the regulatory framework for medicinal products in general (e.g., Directive 2001/83/EC). The regulation that applies directly to clinical trials is the CTR. However, given that clinical trial data are ultimately used for the marketing authorisation of medicinal products, requirements and concepts under relevant Directives may also be referenced.

In addition, EU guidance (e.g., Q&A documents, notices, and procedural documents) issued by the European Commission and the European Medicines Agency (EMA) supplements the interpretation and practical implementation of the CTR and related regulations. Although they are not legally binding, they are important reference materials for ensuring consistent implementation by Member State authorities and across the EU.

Furthermore, ICH guidelines (e.g., ICH E6 (GCP); ICH E8 (Design)) are used as international scientific and ethical standards for clinical trials. Although ICH is not legislation in principle, GCP compliance is a practically essential standard in the EU.

Lastly, the Declaration of Helsinki and other ethical principles are positioned at the highest level. While these are not legally binding, they influence regulatory, review, and practical decisions as fundamental principles that support the ethical conduct of clinical trials and the principles of subject protection.

1-2. National competent authorities

In the EU, the European Commission is involved in the preparation and revision of the CTR and is responsible for the formulation and coordination (establishment of provisions and implementation procedures) of the regulatory framework at the EU level. The EMA is the

coordinator for the whole regulation and maintains and operates CTIS. In the EU, one or more national competent authorities (NCAs) are established in each Member State to authorize and oversee clinical trials of medicinal products and to assess applications via CTIS. Ethics committees (ECs) independent of NCAs in each Member State are involved as needed, and their assessment is reflected in the decision on whether to conduct a clinical trial.

2. Regulations applicable to clinical trials of medicinal products

In the CTR, a clinical study is defined in Article 2(2)(1), and a clinical trial is defined in Article 2(2)(2). Clinical studies of medicinal products in the EU are first classified according to whether they fulfil the following conditions defining a clinical trial subject to the CTR.

(a) The assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned.
(b) The decision to prescribe the investigational medicinal product (IMP) is taken together with the decision to include (enroll) the subject in the clinical study.
(c) Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Interventional clinical trials with medicinal products in humans fall within the scope of the CTR. Clinical trials subject to the CTR include trials to evaluate unauthorized medicinal products and trials to verify new doses, indications, administration methods, etc., of authorized medicinal products. These are classified as trials that may involve additional risks and burdens. As the CTR does not distinguish its scope of application based on the marketing classification of medicinal products (e.g., prescription medicines or OTC medicines), clinical trials conducted with products that fall under the definition of a “medicinal product” set out in Article 1(2) of Directive 2001/83/EC (Community code relating to medicinal products for human use) are subject to the CTR.

Studies not falling within the scope of the CTR are classified as non-interventional studies or observational studies. These are studies that observe, collect, and analyze data obtained as a result of normal clinical practice, rather than studies in which treatment policy or administration of medicinal products is determined by the study protocol.

Clinical trials subject to the CTR are classified as low-intervention clinical trials when certain conditions are met. If a trial qualifies as a low-intervention clinical trial, certain requirements, such as those for monitoring and IMP management, may be simplified or reduced according to the characteristics of the trial. A low-intervention clinical trial is a trial that uses authorized medicinal products and includes cases where the products are used in accordance with the authorized conditions of use or based on well-established scientific evidence. These are classified as trials with minimal additional risks and burdens associated with the intervention.

In trials involving advanced therapy medicinal products (ATMPs) or trials conducted during a public health emergency, additional regulatory requirements and guidance related to manufacturing and quality control, as well as expedited procedures, apply in addition to the CTR framework.

Under the CTR, application and assessment procedures for clinical trials are harmonized across the EU. Applications must be submitted online via CTIS. The purpose of the trial is described as part of the application information, but this is not a requirement for determining the applicability of the CTR. If it is an interventional clinical trial, it is handled in the same legal framework in principle.

CTIS serves as the common platform for the operation of clinical trial systems in the EU and European Economic Area (EEA) based on the CTR. It is positioned as the core infrastructure that enables the practical implementation of a harmonized regulatory system. CTIS simultaneously

functions as a single application portal, supports the joint assessment and supervision by the NCAs of EU Member States, and provides public access to clinical trial information to ensure transparency.

3. Classification for determining applicable regulations

When conducting interventional clinical trials or clinical studies of medicinal products in the EU, several classifications may be considered in order to determine the applicable regulations and guidance.

3-1. Regulations applicable to clinical trials subject to the CTR

In clinical trials subject to the CTR, basic requirements such as application, assessment, conduct, safety reporting, and transparency (public disclosure of information) are specified by the CTR, and these procedures are taken through CTIS. In addition, compliance with GCP is required to ensure trial quality and the protection of subjects. Cross-cutting requirements also apply, including those related to the manufacturing, quality control, and supply of IMPs (e.g., GMP), as well as personal data protection regulations applicable when handling subject information, such as the General Data Protection Regulation (GDPR).

3-2. Regulations applicable to clinical studies not falling within the scope of the CTR

Clinical studies not falling within the scope of the CTR are generally classified as non-interventional studies or observational studies, and the clinical trial application procedures through CTIS and the assessment procedures under the CTR do not apply in principle. However, even when a study falls outside the scope of the CTR, certain regulatory considerations remain necessary from the perspectives of subject protection, research ethics, and data management.
In particular, where personal data are processed, the GDPR applies. Accordingly, appropriate management is required with respect to obtaining consent, ensuring the lawfulness of data processing, secondary use of data, and cross-border data transfers. In addition, although requirements relating to ethical review and research implementation system are influenced by national systems in each Member State, appropriate review and oversight based on common EU ethical principles are expected. Furthermore, where the study is related to post-authorisation safety evaluation, it is important in practice that the study be designed and conducted in a manner consistent with the regulatory framework for medicinal products (e.g., considerations related to post-authorisation pharmacovigilance).

3-3. Regulations applicable to low-intervention clinical trials

A low-intervention clinical trial is defined in Article 2(3)(k) of the CTR. Where a trial qualifies as a low-intervention clinical trial, the streamlining of certain operational aspects for the conduct of the trial (e.g., monitoring, quality control, IMP management, and documentation) is considered possible in a proportionate manner, provided that the protection of subjects is not compromised.
Article 2(3)(k) of the CTR specifies the conditions for a low-intervention clinical trial as follows: (1) the IMPs, excluding placebos, are authorized; and (2) according to the protocol of the clinical trial, the IMPs are used in accordance with the terms of the marketing authorisation; or the use of the

IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the Member States concerned. In addition, the CTR also requires that the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.
On the other hand, with regard to the operational simplifications applicable to low-intervention clinical trials, the CTR does not set out specific implementation details (e.g., monitoring frequency) in a uniform manner. Accordingly, the application of such simplifications is expected to be based on a risk-proportionate approach, taking into account the characteristics of the trial and the level of risk to subjects, and to be designed and implemented by the sponsor on the basis of scientific evidence. When applying and conducting a trial as a low-intervention clinical trial, it is important to clearly demonstrate that the trial meets the criteria set out in Article 2(3)(k) and, where operational aspects (e.g., monitoring methods, IMP management, and the scope of documentation) are to be applied in a proportionate manner, to justify their appropriateness with supporting rationale demonstrating that subject protection and data quality can be ensured.

3-4. Trials involving advanced therapy medicinal products (ATMPs)

In the EU, ATMPs constitute a special category of medicinal products. The legal framework for ATMPs is established by Regulation (EC) No 1394/2007 (the ATMP Regulation) and Part IV of Annex I to Directive 2001/83/EC. The former provides the overall regulatory framework for ATMPs and defines tissue engineered products and combined ATMPs, while the latter sets out the definitions of gene therapy medicinal products (GTMPs) and somatic cell therapy medicinal products (sCTMPs). ATMPs comprise four product categories: GTMPs, sCTMPs, tissue engineered products (TEPs), and combined ATMPs, in which a medical device is incorporated as an integral part of the product. The ATMP Regulation also establishes a regulatory framework that includes the involvement of the EMA's specialized committee, the Committee for Advanced Therapies (CAT), among others. The determination of whether a product falls within the definition of an ATMP is carried out by the CAT within the EMA. Upon request from developers, the CAT issues a "classification recommendation."

Clinical trials involving ATMPs are applied, assessed, and conducted in accordance with the CTR as long as they fall within the scope of the CTR. In addition, because ATMPs require particularly careful management of manufacturing, quality, and biological risks, additional considerations based on ATMP-specific regulations and guidelines are required in addition to the CTR. In clinical trials involving ATMPs, it is important to be able to adequately explain the risk assessment and the scientific rationale for the trial design in light of the characteristics of the ATMP concerned.

- For gene therapy medicinal products, the "Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products" published by the EMA sets out the fundamental principles for their development and evaluation and serves as an important reference document for the planning and application of ATMP clinical trials.
- For ATMPs containing genetically modified cells (e.g., cell therapies using genetically modified cells), reference should be made to the EMA guideline (the Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells [EMA/CAT/GTWP/671639/2008 Rev.1]) or other relevant guidelines, and additional evaluation appropriate to the characteristics of the product is required from the perspectives of quality, non-clinical, and clinical development.

- Where investigational ATMPs are used, rather than ATMPs at the marketing authorisation application stage, reference should be made to the “Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials” published by the EMA. It is necessary to explain the adequacy of the data package required for the conduct of the clinical trial, taking into account the quality, non-clinical, and clinical requirements applicable to ATMP clinical trials.
- Where human-derived cells or tissues are used as raw materials (donor materials), management in accordance with Directive 2004/23/EC (the European Tissues and Cells Directive) and its implementing directives, Commission Directives 2006/17/EC and 2006/86/EC, is required with respect to donor eligibility assessment, procurement and handling, infection risk management, and traceability.
- Where the product qualifies as a genetically modified organism (GMO)—an organism in which the genetic material has been altered using genetic modification techniques—the clinical trial is conducted in accordance with the CTR. However, additional regulatory procedures, including an environmental risk assessment (ERA), may also be required under Directive 2001/18/EC (deliberate release) and/or Directive 2009/41/EC (contained use). For this reason, the assessment of GMO status and the related procedures (e.g., submission materials, review procedures, and timelines) should be planned taking into account the requirements of the relevant Member States, including the country fiches published by the European Commission.

Since ATMPs require particularly careful manufacturing and quality control, additional considerations are required with respect to the manufacturing and quality control (GMP) of IMPs. In particular, given the complexity of manufacturing processes and the need to manage product variability for ATMPs, it is important to appropriately establish manufacturing controls (such as sterility assurance, raw material management, process control, storage and transportation, and change control) in accordance with the requirements of EU GMP (EudraLex Volume 4), and to be able to explain their adequacy.

Accordingly, in clinical trials involving ATMPs, in addition to meeting the general requirements under the CTR (e.g., subject protection, informed consent, safety reporting, and transparency), it is necessary to design the application and conduct of the trial taking into account additional requirements arising from the characteristics of the product. These include additional considerations relating to quality, non-clinical, and clinical aspects under the ATMP Regulation and relevant EMA guidelines, GMP and raw material management (including human-derived materials), and ERA where the product qualifies as a GMO.

3-5. Regulations for clinical trials involving combination products

Clinical trials involving combination products composed of a medicinal product and a medical device are applied, assessed, and conducted in accordance with the CTR as long as they fall within the scope of the CTR. Where such clinical trials involve the use of a medical device that is integral to the administration or use of the medicinal product (e.g., delivery devices or inhalers), the requirements of the Medical Device Regulation (MDR; Regulation (EU) 2017/745) should also be taken into account. Articles 1(8) and 1(9) of the MDR set out how products in which medicinal products and medical devices are combined are handled.

In clinical trials involving combination products, the method of administration or use of the IMP may be closely related to the specifications or conditions of use of the medical device. Therefore,

it is important to clearly define the role of the medical device in the trial (e.g., whether it is the primary object of the investigation or used as an accessory to the administration or use of the medicinal product) as well as the intended conditions of use. In addition, the administration and use conditions should be clearly specified in the trial plan so that the evaluation of the efficacy and safety of the medicinal product is not unduly affected by differences in the conditions of use or operation of the medical device. In practice, MDCG 2019-2 (Guidance on the borderline between medical devices and medicinal products under Regulation (EU) 2017/745), issued by the Medical Device Coordination Group (MDCG) of the European Commission, as well as the Questions and Answers... regarding medicines used in combination with medical devices (EMA/37991/2019) published by the EMA, are useful references for understanding regulatory considerations and preparing for discussions with authorities.

It should also be noted that, in clinical trials involving combination products, the applicable regulatory framework (i.e., medicinal product regulation or medical device regulation) and the focus of the required evaluation may differ depending on whether the medicinal product or the medical device is the principal mode of action. Even where the trial is conducted as a trial subject to the CTR, it is important to recognize that the product may qualify as a combination product and, where necessary, to take into account additional requirements under the MDR, and to design the application and conduct of the trial ensuring consistency between the CTR application (including the trial plan and operation) and the requirements of the MDR.

3-6. Regulations for phase 1 (first-in-human / early phase) trials

Clinical trials of medicinal products corresponding to phase 1 trials are applied, assessed, and conducted in accordance with the CTR as long as they fall within the scope of the CTR. Phase 1 trials generally focus on the evaluation of safety, tolerability, and pharmacokinetics (PK), and it is therefore important to adequately design and justify the risk assessment and risk mitigation measures according to the characteristics of the trial. In particular, within phase 1 trials, first-in-human (FIH) trials require more careful identification of risks and clearer presentation of risk mitigation strategies than typical phase 1 trials. This includes aspects such as the selection of the starting dose, dose escalation strategy, safety monitoring, and stopping criteria. As a practical basis for these considerations, the EMA has published the “Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev.1),” which serves as an important reference document for risk management in phase 1 trials, including FIH trials.

In addition, in phase 1 trials, the adequacy of the non-clinical safety data package required for trial initiation is often a key issue. Therefore, such data should be prepared taking into account ICH M3(R2) (Non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals), an international guideline that sets out the timing and requirements for non-clinical safety studies.

3-7. Trials involving orphan drugs

Clinical trials involving orphan medicinal products are applied, assessed, and conducted in accordance with the CTR as long as they fall within the scope of the CTR. In addition, separate from the CTR, Regulation (EC) No 141/2000 (the Orphan Regulation) applies as the regulatory framework for the designation system and incentives for orphan medicinal products. The Orphan Regulation establishes the community procedure for the designation of orphan designation and

provides a framework for granting incentives to promote research and development in the field of rare diseases. Within the EMA, the Committee for Orphan Medicinal Products (COMP) is responsible for the designation of orphan medicinal products.
The criteria for orphan designation are set out in Article 3(1) of the Orphan Regulation. Under this provision, a medicinal product must be intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting “not more than five in 10 thousand persons” in the EU when the application is made, or, without incentives, it must be unlikely that the marketing of the medicinal product would generate sufficient return to justify the necessary investment. Furthermore, it must be shown that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.
Where orphan designation is granted, sponsors may benefit from various incentives during the development and authorisation process, including protocol assistance (scientific advice specifically for orphan medicinal products) and reductions or exemptions from regulatory fees. In addition, once the product obtains marketing authorisation in the EU, it is granted orphan market exclusivity for a period of ten years in principle, except in certain cases, and the marketing of similar medicinal products for the same indication will be limited.

3-8. Regulations applicable to clinical trials in children

For clinical trials in children (referred to as “minors” under the CTR), additional requirements specific to children are set out in Article 32 of the CTR, in addition to the general principles concerning subject protection and informed consent (Article 28 of the CTR). Article 32 of the CTR requires that, provided the scientific and ethical justification for conducting the trial in children is established, the balance between burdens and benefits must be appropriate. Specifically, where a direct benefit to the child is expected, the benefit must outweigh the risks and burdens. Where no direct benefit is expected, the risks and burdens imposed on the subject must be kept to a minimum, provided that the trial aims to obtain medical knowledge in the relevant child population. Accordingly, when designing the trial plan, it is important to incorporate ethical considerations aimed at minimizing the trial-related burden (e.g., limiting the number of blood samplings and reducing procedural invasiveness) and to ensure that the appropriateness of these measures can be justified.
With regard to the consent procedure, Article 32 of the CTR requires that informed consent be obtained from the legally designated representative (e.g., a parent or guardian). At the same time, appropriate information must be provided to the child, taking into account the child’s age and maturity, and the child’s assent must be sought. If the child expresses a wish not to participate or to withdraw, that wish must be respected. Furthermore, if the subject reaches the legal competence to give informed consent as defined in the law of the Member State concerned during a clinical trial, the subject’s own consent needs to be obtained.
In addition, for paediatric medicinal product development in the EU, the CTR applies to the conduct of clinical trials in children, a separate framework for promoting the development of medicinal products for children is established by the Paediatric Regulation (Regulation (EC) No 1901/2006). Under this regulation, the submission and approval of a Paediatric Investigation Plan (PIP) is generally required. The Paediatric Committee (PDCO) of the EMA is responsible for the review of PIPs. A PIP includes trial plans in different paediatric age groups, appropriate formulation design (e.g., easy-to-take dosage forms), and the development timeline. Clinical trials

in children must not only comply with the ethical and consent requirements under the CTR but also be consistent with the requirements set out in the PIP.

3-9. Trials conducted during a public health emergency

A “public health emergency” is a concept related to the EMA’s emergency response framework (Emergency Task Force [ETF]) and is defined in Regulation (EU) 2022/123. Under this regulation, a public health emergency refers to a situation formally recognized by the European Commission pursuant to Decision No 1082/2013/EU on serious cross-border threats to health. Accordingly, the term “public health emergency” does not refer to a general situation of “heightened social urgency” but rather to an emergency formally recognized through procedures established under EU legislation (e.g., pandemics).

Clinical trials of medicinal products conducted in connection with a public health emergency are applied, assessed, and conducted in accordance with the CTR as long as they fall within the scope of the CTR. In addition, as it is particularly important in a public health emergency to ensure both the prompt conduct of trials and the protection of subjects, the involvement of the EMA’s ETF may be considered.

In the EU, the ETF has been established within the EMA pursuant to Regulation (EU) 2022/123, which is the regulation strengthening the EMA. During a public health emergency, the ETF provides scientific input on the development of therapeutics and vaccines, as well as advice on clinical trial protocols, thereby supporting the conduct of clinical trials within the EU. Support provided by the ETF may also be coordinated with the Clinical Trials Coordination Group (CTCG), which serves as a framework for coordinating the implementation of the CTR among NCAs of EU Member States, in order to support the prompt and smooth conduct of clinical trials in the EU.

3-10. Regulations for clinical trials involving controlled narcotic drugs

Clinical trials using medicinal products containing controlled substances, such as narcotic drugs and psychotropic substances, are applied, assessed, and conducted in accordance with the CTR as long as they fall within the scope of the CTR. Substances regulated as narcotic drugs or psychotropic substances are associated with a higher risk of abuse and diversion. When establishing the trial framework, additional requirements for the storage, management, and distribution of such substances (e.g., importation, transport, storage, dispensing, and destruction) under the national laws of EU Member States must be taken into account. These requirements include licensing or notification requirements, the designation of responsible personnel, record-keeping obligations, and specific storage facility requirements. While the content of these additional requirements is broadly similar across the Member States, differences remain in authorisation procedures and operational details. Therefore, confirmation of the specific requirements applicable in each Member State is necessary.

Chapter 2: Detailed requirements for clinical trials of medicinal products in the EU

The requirements applicable to the following elements that constitute a clinical trial are summarized below. In the EU, all clinical trials of medicinal products involving an intervention fall within the scope of the CTR. Among clinical trials subject to the CTR, cases where a trial qualifies as a low-intervention clinical trial and different requirements apply are also outlined.

1. Authorisation of the conduct of clinical trials by Member States or NCAs

Where clinical trials of medicinal products conducted in the EU fall within the scope of the CTR, the assessment by NCAs required prior to the initiation of the trial is conducted through CTIS. The EMA is responsible for the operation of CTIS, while the NCAs of each EU Member State carry out the assessment. The clinical trial application (CTA) consists of a part subject to coordinated assessment among EU Member States (Part I: the scientific validity of the clinical trial and information on the quality, safety, and efficacy of the medicinal product) and a EU Member State-specific assessment part (Part II: matters such as subject recruitment and informed consent). Each Member State performs the assessment and takes its decision. When clinical trials based on the same protocol are conducted in multiple EU Member States, the CTA is structured so that Part I, which is subject to a coordinated assessment, is prepared in a unified manner, while Part II, which addresses Member State-specific requirements, is supplemented for each Member State. This allows sponsors to plan the authorisation of multinational clinical trials in a manner consistent with the CTR, while reducing the burden of preparing entirely separate applications for each Member State.

Even where a trial is applied as a low-intervention clinical trial, the authorisation procedure itself follows the Part I / Part II assessment framework conducted through CTIS. However, in the CTA it is important to demonstrate that the trial meets the criteria set out in Article 2(3)(k) of the CTR and, where operational aspects (e.g., monitoring) are to be applied in a proportionate manner, to justify the appropriateness of such approaches from the perspectives of subject protection and data quality.

In contrast, studies that fall outside the scope of the CTR are not subject to the EU-harmonized clinical trial authorisation procedure under the CTR (i.e., the CTIS application). Instead, they are managed in accordance with the national legislation of each EU Member State (e.g., ethical review procedures) as well as cross-cutting regulatory frameworks such as the GDPR.

2. Authorisation of the conduct of clinical trials by ECs

As described above, in trials subject to the CTR, the assessment conducted through CTIS is operated under a framework in which it is divided into Part I (EU-common) and Part II (Member State-specific), and ethical review by ECs is incorporated in accordance with the national systems of each EU Member State. In practice, matters directly related to the protection of subjects—such as consent documents and subject-facing materials, subject recruitment, compensation, privacy protection, and the handling of vulnerable populations—are mainly included in Part II. Therefore, the involvement of ECs constitutes the core of the evaluation concerning ethics and subject protection in Part II. It should be noted that Part II does not mean an area reviewed only by authorities; rather, based on the system of each EU Member State, ECs participate in the evaluation, and the results are reflected in the decision of the relevant Member State. Accordingly,

taking into account that the documents submitted through CTIS serve as materials for NCAs and may also serve as the basis for ethical review, it is important that they be structured so that scientific validity and the protection of subjects can be explained in an integrated manner.
The review system of ECs in the EU is not unified across EU Member States, and several forms exist based on national systems (central EC, regional EC, institutional/hospital EC, etc.). Therefore, in multinational trials, Part II documents need to be appropriately localized so as to meet the EC review requirements of each Member State. The matters reviewed by ECs include, primarily, the appropriateness of explanations to subjects and the obtaining of informed consent (comprehensibility, multilingualization, freedom to withdraw, etc.), as well as the appropriateness of subject recruitment methods, the minimization of risks and burdens, consideration for vulnerable populations, the arrangement of compensation, and the protection of personal data (notification content and data management in light of the GDPR).

3. Conflict of interest (COI) in clinical trials

In clinical trials of medicinal products in the EU, the practical management requirements for COI are formed through a combination of the CTR, ICH-GCP, the operation of ethical review and research governance in each EU Member State, and industry codes such as the EFPIA Disclosure Code. As a common approach across EU Member States, sponsors and medical institutions are required to identify the existence of COI relating to investigators and other study personnel, assess risks that may affect the scientific validity of the clinical trial, the protection of the rights and safety of subjects, and the reliability of data, and implement appropriate management measures where necessary. Specifically, it is required to identify and appropriately record and update financial relationships and other interests of investigators and study personnel, such as remuneration, lectures and consulting activities, research funding, shareholdings, and positions or secondary employment. These matters are reviewed within the framework of EC review and quality management during the conduct of the trial, thereby contributing to ensuring the transparency of trial conduct.

4. Explanation to subjects, informed consent, and multilingualization

In trials subject to the CTR, explanation to subjects and the obtaining of informed consent constitute core requirements for the protection of subjects. Under the CTR, in addition to the general requirements for obtaining informed consent, additional requirements are also provided according to subject characteristics (e.g., incapacitated subjects, minors, and pregnant or breastfeeding women) (Articles 30 to 35). In addition, the ICH-GCP sets out practical requirements for the process of obtaining informed consent (including the information to be included in the explanation and consent documents, the timing and method of obtaining consent, and documentation and record retention). Furthermore, Annex I to the CTR includes a description of subject recruitment and the procedures for obtaining informed consent as part of the information required to be submitted in a CTIS application.
Consent documents and subject-facing information materials are reviewed with the involvement of ECs in the Member State review process, and their appropriateness is assessed. In multinational trials, the multilingualization of consent documents is not merely a translation exercise; localization is required taking into account differences among the Member States in culture, healthcare delivery systems, insurance systems, and complaint contact points. In particular, the level of detail required in descriptions concerning the benefits and disadvantages

of participation in the clinical trial, alternative treatment options, handling in the event of trial discontinuation, privacy, compensation, and data disclosure differs by the Member State. Therefore, it is practical to design documentation based on a common core document (master ICF), while managing differences through Member State-specific addenda (country addendum).

5. Compensation for subjects

In trials subject to the CTR, compensation for subjects is addressed under Article 76 of the CTR, which requires EU Member States to establish systems for compensation (insurance, a guarantee, or a similar arrangement). Rather than requiring a single EU-wide approach, the specific details of compensation are left to the national laws of each Member State and to the practices of the competent authorities and ECs. In practice, the submission of proof of insurance or compensation is a mandatory requirement in the CTIS application (Part II).

For trials that qualify as low-intervention clinical trials, insurance or compensation requirements may be relaxed or simplified on the premise that the level of risk is low. However, this is not applied uniformly and depends on the practices of individual EU Member States and the judgement of ethical review.

6. Reporting of safety information to NCAs

In trials subject to the CTR, the reporting of safety information to NCAs is stipulated as a mandatory regulatory requirement, with the CTR forming the core of the framework. In addition, it is implemented in accordance with EU pharmacovigilance legislation (Regulation (EC) No 726/2004 and Directive 2001/83/EC, as amended), the relevant ICH guidelines aligned with these frameworks (e.g., ICH E2A, E2B, E2D, E2F, and E6), and related guidance issued by the EMA and the European Commission (e.g., EMA guidance on safety reporting under the CTR). Expedited reporting of suspected unexpected serious adverse reactions (SUSARs) and submission of the Annual Safety Report (ASR, corresponding to the Development Safety Update Report (DSUR)) are carried out electronically through the EU-wide pharmacovigilance database known as EudraVigilance. NCAs of each Member State access safety information through this database.

Furthermore, based on the concept of risk-proportionate safety management according to the risk level of each trial under the CTR, the methods for the collection and evaluation of AEs/SAEs may be streamlined under certain conditions. In low-intervention clinical trials, given the assumption of a lower level of risk, there is relatively greater scope for applying such streamlining. Where such streamlining is applied, it is important that the scope of data collection and procedures be clearly specified in the protocol in advance and that their appropriateness can be explained to NCAs and ECs.

Clinical trials involving advanced therapy medicinal products (ATMPs) require consideration of the potential for long-term therapeutic effects or impacts, immunological reactions, and specific risks arising from manufacturing and quality. Accordingly, from the trial design stage, it is necessary to establish a robust safety evaluation system that includes long-term follow-up and specialized assessments (the ATMP Regulation).

In trials related to a public health emergency, rapid evaluation and sharing of safety information are particularly emphasized due to the potentially significant impact on public health as a whole. While supervision by NCAs under normal circumstances (within the safety reporting framework based on the CTR) remains the basis, the framework of the ETF established within the EMA

under Regulation (EU) 2022/123 is expected to facilitate more rapid and coordinated evaluation and information sharing across the EU.

7. Protection of subject information (protection of personal data and personal health information)

In the EU, requirements concerning the protection of subject information are subject to the GDPR, which is the general law on the processing of personal data. Accordingly, regardless of whether a study falls within the scope of the CTR, clinical studies, including clinical trials, that involve the processing of personal data (particularly special categories of data such as health data and genetic data) are required under the GDPR to clarify (i) the legal basis for the processing of the data and (ii) the purposes for which the data are processed and the scope of data to be used, and to limit the processing to the minimum data necessary. Furthermore, it is necessary to appropriately inform subjects of the details of data use (including the purposes of use, recipients of the data, the retention period, and contact points for inquiries), and to establish a governance framework that includes information security management, oversight of contractors (e.g., contract research organizations (CROs) and vendors), and management of data transfers outside the EU. In addition, as subjects have certain rights under the GDPR (e.g., the right of access), it is important to prepare procedures in advance to respond to such rights.

In trials subject to the CTR, the documentation for CTA applications submitted via CTIS in accordance with the CTR (Part II: Member State-specific requirements) must include an explanation of data processing in subject-facing information documents. Accordingly, in trials subject to the CTR, clearer explanations are required regarding the description of data processing in subject-facing information documents and the status of arrangements for GDPR compliance, as part of the application and assessment process.

8. Disclosure of clinical trial data (registration and results disclosure)

In trials subject to the CTR, the disclosure of clinical trial data (registration and results disclosure) is positioned as a mandatory requirement under the CTR from the perspective of subject protection and ensuring the transparency of clinical trial. Even in multinational clinical trials, basic information on the trial is centrally managed through CTIS and made publicly accessible. After completion of the trial, results information is disclosed by preparing summary results and a layperson summary and submitting them to CTIS. The layperson summary is not merely a translation but presents organized information on the purpose of the trial, the methods, the main results, and safety-related information, in a form understandable to non-specialists. In disclosing results, while ensuring transparency, it is also necessary to appropriately protect the privacy of subjects (governed by the GDPR) and the confidential information of companies. From the study planning stage, sponsors need to prepare documentation design and data management with disclosure in mind (e.g., ensuring consistency of descriptions that can withstand public disclosure of results, approaches to anonymization, and identification of information to be disclosed).

On the other hand, for non-interventional studies not falling within the scope of the CTR, the obligations for CTIS registration and results disclosure under the CTR do not in principle apply. When determining the requirements for registration and results disclosure for studies conducted within the EU, it is important to distinguish not only whether the study is interventional but also whether it falls within the scope of the CTR, whether it was conducted under the previous regulatory framework, and whether the study is subject to transparency requirements under

another framework (e.g., post-authorisation safety frameworks).

9. Regulatory framework for digitalization of data

The digitalisation of processes in clinical trials of medicinal products (e.g., electronic data capture, eSource, eTMF, and electronic signatures) is implemented within the clinical trial framework established under the CTR, and practical operations are designed and managed in accordance with ICH-GCP (ICH E6). To ensure the reliability of electronic data, it is important, in line with the record management principles required under ICH E6 and related guidance, to verify through validation that the electronic systems used operate appropriately, and to establish access control management and audit trails. In addition, source documents should be clearly identified, and rules should be established, as necessary, for the transfer or transcription of data from electronic medical records and other systems. Data integrity based on the ALCOA+ principles should also be ensured through standard operating procedures (SOPs) and related controls. With regard to electronic signatures, the eIDAS Regulation provides the legal framework for electronic signatures in the EU, and a qualified electronic signature (QES) generally has the same legal effect as a handwritten signature.

Appendix: List of laws, regulations, and guidance cited in this summary (in order of appearance)

1. Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use
   Abbreviation: CTR
   https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014R0536
   (Articles 2(2)(1), 2(2)(2), 2(3)(k), 28, 30 to 35, and 76, etc.)

2. Directive 2001/83/EC on the Community code relating to medicinal products for human use
   https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02001L0083-20190726

3. ICH E6 (R3) Guideline for good clinical practice (GCP)
   https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e6-r3-guideline-good-clinical-practice-gcp-step-5_en.pdf

4. ICH E8 (R1) General considerations for clinical studies
   https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ich-guideline-e8-r1-general-considerations-clinical-studies_en.pdf

5. Regulation (EC) No 1394/2007 on advanced therapy medicinal products
   Abbreviation: ATMP Regulation
   https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32007R1394

6. Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products
   https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-gene-therapy-medicinal-products_en.pdf

7. Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells
   https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-medicinal-products-containing-genetically-modified-cells-revision-1_en.pdf

8. Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials
   https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy-medicinal-products-clinical-trials_en.pdf

9. Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
   https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32004L0023

10. Commission Directive 2006/17/EC implementing Directive 2004/23/EC as regards technical requirements
    https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32006L0017

11. Commission Directive 2006/86/EC implementing Directive 2004/23/EC as regards traceability and notification of serious adverse reactions and events
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32006L0086

12. Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms
https://eur-lex.europa.eu/eli/dir/2001/18/oj/eng

13. Directive 2009/41/EC on the contained use of genetically modified micro-organisms
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32009L0041

14. Regulation (EU) 2017/745 on medical devices
Abbreviation: MDR
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02017R0745-20250110

15. MDCG 2019-2 Guidance on the borderline between medical devices and medicinal products under Regulation (EU) 2017/745
Abbreviation: MDCG 2019-2
https://health.ec.europa.eu/system/files/2020-09/md_mdcg_2019_2_gui_udi_dev_en_0.pdf

16. EMA – Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies regarding medicines used in combination with medical devices
Term used in this summary: EMA Q&A (EMA/37991/2019)
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-implementation-medical-devices-vitro-diagnostic-medical-devices-regulations-eu-2017-745-eu-2017-746_en.pdf

17. Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products
https://www.ema.europa.eu/en/strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational-medicinal-products-scientific-guideline

18. ICH M3(R2) Non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals
https://www.ema.europa.eu/en/ich-m3-r2-non-clinical-safety-studies-conduct-human-clinical-trials-pharmaceuticals-scientific-guideline

19. Regulation (EC) No 141/2000 on orphan medicinal products
Abbreviation: Orphan Regulation
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02000R0141-20190726

20. Regulation (EC) No 1901/2006 on medicinal products for paediatric use
Abbreviation: Paediatric Regulation
https://eur-lex.europa.eu/eli/reg/2006/1901/oj/eng

21. Regulation (EU) 2022/123 on a reinforced role for the European Medicines Agency in crisis

preparedness and management
https://eur-lex.europa.eu/eli/reg/2022/123/oj/eng

22. Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02004R0726-20220128

23. Reporting safety information on clinical trials
Term used in this summary: EMA guidance on safety reporting under the CTR
https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/reporting-safety-information-clinical-trials

24. Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data
Abbreviation: GDPR
https://eur-lex.europa.eu/eli/reg/2016/679/oj/eng

25. Regulation (EU) No 910/2014 on electronic identification and trust services for electronic transactions in the internal market (eIDAS)
https://eur-lex.europa.eu/eli/reg/2014/910/oj

Regulatory Framework for Clinical Investigations of Medical Devices in the EU

Date of preparation: February 20, 2026

Chapter 1: Regulations governing clinical investigations of medical devices in the EU

1. Regulatory hierarchy

1-1. Legal system

The regulatory framework for clinical investigations of medical devices in the EU has a hierarchical (pyramidal) structure composed of multiple layers, including regulations, Member State legislation (national laws), and guidance.

At the highest level are regulations that apply directly as EU law, and the Medical Device Regulation (MDR; Regulation (EU) 2017/745) constitutes the core regulatory framework for medical devices, including clinical investigations. The MDR establishes harmonized requirements across the EU for the safety and performance of medical devices and also sets out certain requirements for the conduct of clinical investigations (subject protection, ethical and scientific considerations, applications and notifications, and reporting). In addition, the regulatory framework incorporates a system design based on the submission and sharing of information (including its phased implementation) through the European Database on Medical Devices (EUDAMED), with the aim of ensuring transparency of clinical investigation information and facilitating cooperation among authorities.

In contrast, Member State legislation (national laws) constitutes a body of law established by each Member State to complement EU regulations and plays an important role particularly in areas where the MDR leaves the setting of additional requirements to the Member States (e.g., “other clinical investigations” under Article 82 of the MDR). Accordingly, while the MDR serves as the core regulatory framework common across the EU, in practice compliance must also take into account differences among the Member States (such as application portals, ethics review practices, and additional procedural or documentation requirements).

In addition, EU guidance (e.g., Q&A documents, notices, and procedural documents) issued by the European Commission and the Medical Device Coordination Group (MDCG) supplements the interpretation and practical implementation of the MDR and related regulations. Although they are not legally binding, they are important guidance materials for ensuring consistent implementation by Member State authorities and across the EU.

Furthermore, ISO standards (e.g., ISO 14155), etc. are used as international scientific and ethical standards for clinical investigations. Although ISO standards are not legislation in principle, in the context of clinical investigations of medical devices, they are regarded as a practical common framework for ensuring that investigations are appropriately designed, conducted, documented, and reported, and they contribute to shaping regulatory expectations. Moreover, when conducting clinical investigations, other relevant legislation in addition to the MDR (e.g., the General Data Protection Regulation (GDPR) relating to the protection of personal data) must also be taken into account, and cross-cutting compliance is required with respect to the handling of subject information or other related matters.

1-2. Competent authorities

The European Commission is involved in the framework of the MDR and other related legislation, and it organizes and coordinates the regulatory framework across the EU. In particular, with regard to clinical investigations of medical devices, Article 73 of the MDR provides that the European Commission has a role in organizing and maintaining an electronic system, in cooperation with the Member States, for applications and information exchange. The MDCG is established under Article 103 of the MDR and is composed of representatives of the competent authorities (CAs) of the Member States, with the European Commission acting as chair. Guidance documents approved by the MDCG are not legally binding but are positioned as documents that provide a common understanding for the practical implementation of the MDR.

The authorisation procedures for clinical investigations are operated with the involvement of the Member States in which the clinical investigation is to be conducted. The sponsor submits an application to the Member State(s) where the clinical investigation is planned to be conducted (Article 70 of the MDR), and the application documentation must include the documents specified in Annex XV, including the clinical investigation plan. In practice, the “sponsor” is often the manufacturer; however, the MDR specifies the applicant as the “sponsor,” and this is not limited to companies.

Furthermore, clinical investigations are subject to scientific and ethical review, and ethical review is conducted by an ethics committee (EC) in accordance with national laws (Article 62 of the MDR). The Member States are required to ensure that the procedures for ethical review are operated in a manner consistent with the authorisation procedures for clinical investigations under the MDR (Article 62 of the MDR).
In comparison with the implementation of “common portal-type” systems, such as the Clinical Trials Regulation (CTR) and the Clinical Trials Information System (CTIS), a key characteristic for medical devices is that authorisation decisions are made at the Member State level. For the MDR, on the other hand, an EU-level electronic system for clinical investigations (Article 73) is planned. However, due to delays in the establishment of EUDAMED (the clinical investigations and performance studies module), which is one of the electronic systems provided for under Article 73, applications and information submissions have instead been handled through national procedures in each Member State during the transition period, as described in MDCG 2021-1 Rev. 1. In the recent revision (Regulation (EU) 2024/1860), step-by-step implementation of EUDAMED is underway, and a shift toward full-scale operation of the electronic system is expected in the future.

- Medicinal products: National competent authorities (NCAs) + (common platform such as CTR and CTIS)
- Medical devices: Member States concerned (authorisation procedures in each Member State) + the European Commission (Article 73: electronic systems) + the MDCG (Article 103)

2. Classification for determining applicable regulations

When conducting clinical investigations of medical devices in the EU, several classifications may be considered in order to determine the applicable regulations and guidance.

2-1. Regulations applicable to clinical investigations intended for CE marking

The regulatory framework for clinical investigations of medical devices in the EU is centered on EU regulations such as the MDR. In addition, EU legislation that applies in a cross-cutting manner as necessary (e.g., regulations concerning personal data protection) and non-binding guidance issued by the MDCG support practical implementation. MDCG guidance consists of non-legally binding recommendations, but it is referenced as providing a common understanding of the practical implementation of the MDR and related regulations (including expectations regarding documentation and procedural approaches).

EU essential legislation constitutes the top-level legal framework for the uniform regulation of the safety, performance, and market distribution of medical devices and consists of two regulations: Regulation (EU) 2017/745 (MDR) and Regulation (EU) 2017/746 (*In Vitro* Diagnostic Medical Device Regulation, IVDR). While these regulations set out a common framework at the EU level, operational procedures (such as application assessment and ethical review) are implemented within the frameworks of the individual Member States.

In situations where clinical data are collected for the purpose of CE marking (conformity assessment), which corresponds to the marketing authorisation application process, several key compliance requirements apply under the framework of the MDR. These include the preparation of a clinical investigation plan (CIP), an investigator's brochure (IB), safety reporting, and the reporting and disclosure of results after completion of the investigation. In addition, these compliance requirements are further specified as recommended requirements in the final guidance by the MDCG. Clinical investigations intended for CE marking are carried out in accordance with Article 62 and Annex XV of the MDR and require prior approval by the competent authority of the relevant Member State and an ethics committee. The MDR also establishes obligations for reporting following completion of the investigation.

For *in vitro* diagnostic medical devices subject to the IVDR, guidance on performance studies has been developed. The assessment concerns the need for performance evaluation rather than "clinical investigations," and performance studies must be conducted in accordance with the applicable requirements.

- Regulation (EU) 2017/745 (MDR)

A comprehensive regulation governing medical devices and applicable to medical devices in general.

- Regulation (EU) 2017/746 (IVDR)

A regulation governing *in vitro* diagnostic medical devices, applicable to *in vitro* diagnostic medical devices (such as test kits and diagnostic software). Under the IVDR, the regulatory focus is on determining whether "clinical performance evaluation," rather than "clinical investigation," is required.

2-2. Regulations applicable to clinical investigations not intended for CE marking

Even for clinical research that is not intended for CE marking, if a systematic clinical investigation involving a medical device falls within the definition of a clinical investigation under the MDR, Article 82 of the MDR applies. Clinical investigations subject to Article 82 of the MDR

are required to comply with certain provisions of Article 62 of the MDR, including those relating to the protection of the rights, safety, and dignity of subjects and ethical review. In addition, the Member States shall set out additional requirements (including procedural requirements) for such investigations. Depending on the Member State, notification or other regulatory procedures may therefore be required.

However, not all clinical research involving medical devices falls within the definition of a clinical investigation under the MDR. Under the MDR, a clinical investigation is defined as a systematic investigation involving human subjects, undertaken to assess the safety or performance of a device. Therefore, even when a medical device is used in clinical research, if its purpose is not to assess the safety or performance of that device, it may not be subject to the clinical investigation procedures under the MDR (Chapter VI and Annex XV of the MDR).
Specifically, even if the evaluation is not for CE marking such as post-market clinical follow-up (PMCF) after obtaining CE marking, the notification procedure may be applied depending on the type of investigation (with or without CE mark, within or outside the scope of intended use, presence or absence of additional invasive or burdensome procedures, etc.) (e.g., framework under Article 74 of the MDR). This approach is similar to the regulatory framework under the Japanese Clinical Trials Act and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects.

Accordingly, even in clinical research not intended for CE marking, the protection of subjects and compliance with ethical requirements remain important considerations. However, the applicable procedures (including any additional requirements established by the Member States) vary depending on the intended purpose of the investigation (whether Article 62(1) of the MDR applies) and on its type (e.g., Articles 74 and 82 of the MDR).

2-3. Classification of medical devices requiring clinical investigations and the approach to determining the need for clinical investigations

For medical devices subject to the MDR, classification rules are defined in Annex VIII of the MDR. Based on factors such as invasiveness, duration of use, and the part of the body contacted, medical devices are classified into the following four basic classes.

2-3-1. Classification under the MDR and the need for clinical investigations

Class	Overview	Need for Clinical Investigation
Class I	Low-risk devices (e.g. bandages, non-invasive measuring devices)	Generally not required; literature data or equivalence may be used as alternatives.
Class IIa	Moderate-risk devices (e.g. infusion pumps, ultrasound diagnostic devices)	Generally not required; however, a clinical investigation is required if equivalence cannot be adequately demonstrated.
Class IIb	High-risk devices (e.g., long-term invasive devices such as ventilators and long-term indwelling catheters)	Often required.
Class III	Highest-risk devices (e.g., heart valves, implantable devices)	Generally required; exemptions are exceptional.

Among these classes, clinical investigations are generally required for class III devices and implantable devices. For certain class IIb devices (for specific use), a clinical investigation may also be required depending on the device. For classes I, IIa, and IIb (for general purposes) devices, clinical evaluation is generally considered sufficient, and a clinical investigation is not required in principles. However, if the available clinical evidence is insufficient, a clinical investigation is required.
Even for class III implantable devices, a clinical investigation may exceptionally be waived if the manufacturer demonstrates that the device is a modified version of its own existing device and is technically, biologically, and clinically equivalent, or if sufficient clinical data or evidence based on a well-established technology are already available. In such cases, the justification and conditions are determined on a case-by-case basis.

Note: Role and involvement of notified bodies

Under the MDR, a notified body (NB) is a third-party conformity assessment body designated by a Member State. It assesses whether a medical device complies with MDR requirements and issues certificates where applicable. An NB does not replace “authorisation” by a competent authority; rather, it acts as a third party involved in the manufacturer’s conformity assessment process.
Devices handled by NBs are those for which third-party assessment is required under conformity assessment procedures (e.g., Annexes IX to XI) under the MDR. Where third-party assessment is not required, the manufacturer ensures conformity through a declaration of conformity and affixes the CE marking under its own responsibility. When an NB is involved in the conformity assessment, its identification number is affixed alongside the CE marking.

Device classification is determined by the manufacturer in accordance with Annex VIII of the MDR. If the manufacturer and the NB disagree on the application of the classification rules, the competent authority makes the final determination.

In relation to clinical evidence, the NB reviews the technical documentation and clinical evaluation as part of the conformity assessment to confirm that sufficient clinical evidence is available. For class III devices and implantable devices (e.g., implantable pacemakers/defibrillators, mechanical heart valves, and cerebral/spinal nerve stimulators), clinical investigations are generally required. However, exemptions may apply under the limited conditions set out in Article 61(4) to (6) of the MDR. A typical example of such an exemption is where a manufacturer claims equivalence with an improved version of its own previously marketed device. In such cases, the demonstration of equivalence must be endorsed by the NB, as explicitly required. In addition, the framework also assigns the NB a role in confirming the adequacy of the post-market clinical follow-up (PMCF) plan. Accordingly, for class III devices and implantable devices, decisions on the need for clinical investigations, possible exemptions, and equivalence claims may be considered based on the NB’s assessment, in light of relevant guidance.

Accordingly, through the conformity assessment procedures, the NB verifies conformity as an independent third party from the perspectives of technical documentation, clinical evaluation, and post-market surveillance, and is positioned as the practical assessment body in the CE marking process.

3. *In vitro* diagnostic medical devices

3-1. Handling of *in vitro* diagnostic medical devices in the EU

In the EU, an *in vitro* diagnostic medical device is treated as a type of a medical device and is designated as an *in vitro* diagnostic (IVD). IVDs are regulated by the IVDR. The IVDR defines reagents, instruments, devices, systems, software, etc. intended to be used in vitro for the examination of specimens derived from the human body for the purpose of providing information on physiological or pathological states, genetic predisposition, or responses to treatment as IVDs, and also includes specimen receptacles within the scope of IVDs. The IVDR also provides definitions and positioning of accessories, self-testing devices, point-of-care testing (POCT), companion diagnostics (CDx), and, as a special category, laboratory-developed tests (LDTs) developed and used within clinical laboratories.

IVDs are classified into four classes A to D, determined based on the intended purpose and the level of public risk (public health risk). Performance evaluation consists of three elements: scientific validity, analytical performance, and clinical performance. In conformity assessment, the specified procedures apply to class B, C, and D devices. Class A devices are generally subject to self-declaration, although when they are placed on the market in a sterile condition, a notified body is involved only with respect to aspects related to sterilization.

Class	Overview	Examples
Class A	Minimal risk, no public impact	Products for general laboratory use (general reagents such as buffer solutions, test tubes, specimen receptacles)
Class B	Low to medium risk, low public risk	Many IVDs (e.g. chemistry, immunology, and pregnancy tests)
Class C	High risk, moderate public risk	Many infectious disease tests (e.g., COVID-19 self-tests), genetic tests, companion diagnostics, etc.
Class D	Highest risk, high public risk	Tests for pathogens with major implications for blood transfusion, transplantation, and public health (e.g., HIV, HBV, HCV)

Based on the three elements of performance evaluation—scientific validity, analytical performance, and clinical performance—devices of class B and above require assessment by an NB.
Under the IVDR, “scientific validity” refers to evidence demonstrating that the analyte or marker that the IVD is intended to measure is scientifically associated with the disease, pathological process, physiological state, or clinical condition related to the device’s intended purpose.

3-2. Clinical performance studies of IVDs

3-2-1. Studies to be performed

Performance studies are conducted within the framework of Chapter VI of the IVDR. In particular, studies in which invasive sample-taking is done for the purpose of the performance study, interventional clinical performance studies, or studies in which the conduct of the study involves additional invasive procedures or other risks for subjects of the study shall be designed,

conducted, recorded, and reported in accordance with Article 58 and Articles 59 to 77 (which specify the requirements for conducting performance studies), and Annex XIV (which sets out detailed procedures and documentation requirements), in addition to meeting the requirements set out in Article 57 of the IVDR and Annex XIII (which sets out the general requirements for performance evaluation). Such studies require designated procedures, including application to and authorisation by the competent authority and ethical review. Depending on the type of performance study, notification to the competent authority may be required; for example, performance studies involving CDx using only left-over samples.

3-2-2. Reporting of adverse events

During the conduct of a clinical performance study, safety reporting is required under Article 76 of the IVDR, including the reporting of serious adverse events (SAEs) and device deficiencies (DDs). MDCG 2024-4 outlines the reporting procedures, including cases where the electronic system based on Article 69 of the IVDR (i.e., EUDAMED and its modules) is not operational or is not fully functional. It specifies the reportable events, reporting timelines, and reporting formats, and provides a performance study summary safety reporting form as an appendix.

Chapter 2: Detailed requirements for clinical investigations

1. Regulatory framework for the authorisation of clinical investigations by national competent authorities

In the EU, the conduct of clinical investigations of medical devices is governed by the provisions of Chapter VI (Articles 62 to 82) and Annex XV of the MDR. These provisions aim to ensure that clinical investigations protect the rights and safety of subjects while appropriately managing the generation of data necessary to demonstrate the performance, clinical benefit, and clinical safety of medical devices.

Most clinical investigations under the MDR require application to and authorisation by the CA of the Member State before the investigation begins. This authorisation procedure applies not only to unauthorized devices but also to CE-marked devices investigated for a new intended purpose. The purpose of the authorisation is to ensure that subjects are not exposed to unnecessary risks at the stage when the investigation is conducted. A key consideration is whether the potential risks arising from the investigation are justified in relation to its scientific value. The competent authorities comprehensively evaluate factors such as the investigation methodology, target population, safety management measures, and known risk information of the device, and grants authorisation only when it determines that appropriate protective measures are in place.

In addition, under the EU regulatory framework, the conduct of a clinical investigation requires not only authorisation by the competent authority but also approval by an ethics committee. This is an essential element for the protection of subjects, and the outcome of the ethical review also serves as an important factor in the authority's assessment for authorisation.

1-1. Examples of the interface between the MDR and Member State legislation (Germany / the Netherlands)

As a Regulation, the MDR applies directly in the Member States. Accordingly, the fundamental requirements for clinical investigations (the protection of rights, ethical principles, scientific validity, investigation plan, information and informed consent, safety reporting, and communication of results at the end of the investigation) are defined within a common EU framework. However, the conduct of clinical investigations requires "concrete institutional arrangements" at the Member State level, such as healthcare delivery systems, the design of research ethical review systems, the allocation of responsibilities among administrative bodies, language requirements, application portals, and review procedures. These aspects cannot be fully addressed by the MDR alone. Consequently, the common requirements set out in the MDR are further specified through national implementing laws, domestic research regulations, and procedural guidance issued by competent authorities, forming a "two-layer" regulatory structure consisting of EU-wide rules and Member State-specific implementation. To understand this interface, this section presents the regulatory systems of Germany and the Netherlands as representative examples and outlines how the rules of the MDR are incorporated into national laws and translated into practical procedures.

1-1-1. Germany: A structure in which the common framework of the MDR is implemented in national law by the MPDG and procedures are clarified through the operation of authorities

In Germany, the Medizinprodukterecht-Durchführungsgesetz (MPDG) serves as the national implementing law that "implements" the system for clinical investigations under the MDR in a form

that can be operated domestically. While the MDR provides common principles and procedural frameworks for clinical investigations, elements such as the authority responsible for receiving applications, the allocation of ethical and scientific reviews, document submission methods, requirements for change management, domestic legal obligations of each actor (e.g., sponsors and principal investigators), and responses to violations must be designed within national systems by the Member States. The MPDG complements these “nationally regulated areas” and embeds the requirements of the MDR into the German legal framework, thereby enabling clinical investigations to be conducted through administrative procedures.

The practical effect of this interface is that “procedural pathways are clearly organized within the national system according to the type of clinical investigation.” In other words, clinical investigations that support conformity assessment, such as those involving non-CE-marked devices or those investigating off-label uses of CE-marked devices, generally require authorisation by the competent authority before their start, whereas certain clinical investigations involving CE-marked devices (e.g., investigations corresponding to PMCF under specified conditions) require only notification rather than authorisation. In addition, for cases classified as “other clinical investigations,” procedures and requirements are determined within the framework of the MPDG, taking into account the common requirements set out in the MDR. In this way, starting from the EU-wide framework established by the MDR, the MPDG provides the structure of national procedures (such as which authority is responsible, which category applies, whether authorisation or notification is required, when submission is required, and the applicable requirements), allowing sponsors to determine which regulatory pathway their clinical investigation falls under.

Furthermore, in operational practice after the start of the investigation, the management of safety reporting (SAEs, device deficiencies, etc.) and substantial modifications required by the MDR is implemented through national laws and regulatory practice. The MDR presents the principles and obligations for modifications and safety reporting, but in practice, procedural elements such as what is determined to be “serious,” which authority must be notified, the required format, and the applicable timeline need to be defined. The German system ensures the feasibility of applications, notifications, modifications, and safety reporting by incorporating the MDR provisions through the MPDG and implementing procedures presented by the authorities. Accordingly, the German system can be understood as a three-layer structure, “MDR (common requirements) → MPDG (national implementation) → authorities’ practice (clarification of practical procedures),” through which EU-wide rules and national systems are connected.

1-1-2. The Netherlands: A two-layer structure in which the MDR’s three frameworks (Art 62/74/82) form the basis and the WMO and related legislation complement the review system and procedures

In the Netherlands, the basic framework for clinical investigations presented by the MDR serves as the starting point, while areas that must be regulated domestically are complemented by the Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen, WMO) and related legislation. Under the MDR, the regulatory framework for clinical investigations can broadly be organized into multiple categories, including at least the following: (i) clinical investigations supporting conformity assessment (generally under Article 62), (ii) clinical investigations involving CE-marked devices (Article 74), and (iii) other clinical investigations (Article 82). In the Netherlands, this “MDR-based categorization” serves as the basis, while the WMO and related legislation provide the organization of the review system and the specification of national procedures (including the acceptance of applications, the positioning of review bodies,

national requirements for the protection of research subjects, and the handling of research involving specific populations).
The key point of this two-layer structure is that “the MDR defines the common requirements—what must be met—while the WMO and related legislation define the operation of the system—who conducts the review and how the procedures are carried out.” In other words, the MDR sets out EU-wide requirements concerning ethics, scientific validity, and safety, whereas the design of the review system (such as the role of central review bodies, the placement of ethics committees, the allocation of review responsibilities, and the scope of additional procedures or documentation required at the national level) may differ between the Member States. In the Netherlands, these elements are established through the WMO and related national laws, thereby enabling the MDR provisions to be implemented within the Dutch research system. In particular, because the MDR leaves room for the Member States to introduce additional requirements for “other clinical investigations” under Article 82, the role of national laws in supplementing the MDR becomes relatively more important. In this area, the WMO and related legislation serve as the institutional framework that connects the abstract provisions of the MDR with practical procedures.

2. Conformity with ISO 14155

Clinical investigations of medical devices in the EU are governed by the MDR as the legal framework. However, in the practical conduct of clinical investigations, the international standard ISO 14155 is regarded as an important reference standard. Although ISO 14155 is not a legally binding regulation, it is widely recognized as a “practical standard” for meeting the requirements of the MDR and serves as an essential reference for conducting clinical investigations in accordance with the MDR.

First, ISO 14155 is positioned as an international GCP for clinical investigations of medical devices to ensure subject safety, data reliability, and ethical conduct. The standard provides specific guidance for the design, conduct, monitoring, recording, and reporting of clinical investigations, and serves to ensure common understanding and consistency among stakeholders such as sponsors, principal investigators, ethics committees, and competent authorities. The scope of ISO 14155 covers not only pre-market clinical investigations but also post-market clinical follow-up, and by applying the relevant principles according to their nature, it provides a framework for ensuring the quality of clinical data throughout the medical device lifecycle.

When discussing the status of ISO 14155:2020 as a harmonized standard under the MDR, caution is required. More precisely, its status as a harmonized standard (i.e., the presumption of conformity) depends on whether the standard is cited in the Official Journal of the European Union (OJEU). As the citation status in the OJEU may be updated, it is necessary to check the latest list published in the OJEU. This is because the legally binding MDR and the international standard ISO 14155:2020 do not fully coincide, and some requirements may differ. In situations where both the legal requirements of the MDR and the operational standards of ISO 14155 apply, the principle is clear that the provisions of the MDR, which have legal force, always take precedence.

[Positioning of Amendment A11:2024 (MDR compliant)]
Amendment A11:2024 is a revision added to EN ISO 14155:2020 (GCP for clinical investigations of medical devices) and is organized for the purpose to clarifying its connection with the clinical

investigation requirements under the MDR in the EU. A11:2024 does not replace the overall approach of the standard but adds corrections and supplements to EN ISO 14155:2020 in order to align it with the EU regulatory framework.
The practical significance of A11:2024 is that, when clinical investigations are conducted with reference to ISO 14155, it makes it easier to explain the relationship with the “requirements of the MDR (in particular MDR Annex XV: Clinical Investigations)” and to apply both consistently. Specifically, through the maintenance and update of Annex ZA, which shows the correspondence between the standard and the legislation, it clarifies which requirements of EN ISO 14155 relate to which requirements of the MDR, making it easier to explain clinical investigation plans, monitoring procedures, recording and reporting procedures, and subject protection systems in relation to MDR requirements.
However, the addition of A11:2024 does not automatically make the standard a “harmonized standard under the MDR.” In general, the status of a harmonized standard in the EU (i.e., presumption of conformity through voluntary use of the standard) depends on whether the standard is cited in the OJEU by the European Commission. Therefore, A11:2024 should be understood as an institutional development that clarifies the correspondence with the MDR and prepares for possible future operation as a harmonized standard.

Therefore, in the conduct of clinical investigations, it is important to reference EN ISO 14155:2020+A11:2024 as the practical basis for clinical investigation operations, while designing the investigation to meet the requirements set out in the Articles and Annexes of the MDR as the highest-level binding requirements (through a gap assessment and the establishment of supplementary measures). This approach helps ensure subject protection and data reliability, while improving the ability to demonstrate compliance with the clinical investigation requirements of the MDR.

3. Ethics committee (EC)/ IRB approval process and regulatory framework

Before initiating a clinical investigation of a medical device in the EU, the MDR requires both authorisation by the competent authority of the Member State and ethical review by an ethics committee (EC). The procedures under the MDR are divided into authorisation, notification, etc., depending on the type of clinical investigation (Articles 62, 74, or 82) and national procedures.

First, Article 62 of the MDR clearly states that clinical investigations must undergo both scientific and ethical review. Clinical investigations must be designed under the fundamental principle that “the rights, safety, and dignity of subjects prevail over all other interests,” and must undergo review by an ethics committee (EC) and obtain approval before the start of the investigation.
In the EU, ethics committees (EC) perform a role similar to that of IRBs in the United States. However, because legal systems differ among EU Member States, ethical review is conducted by independent bodies operating under the national laws of each Member State.
Ethics committee (EC) review is an important entry point for determining whether a clinical investigation may proceed. The ethics committee (EC) evaluates all documents related to the ethics of the investigation, including the clinical investigation plan, subject information materials, informed consent documents, risk–benefit assessment, information on the investigational device, and the qualifications of the investigator. If ethics committee (EC) approval is not obtained, a clinical investigation cannot begin even if authorisation has been granted by the competent authority.

The MDR does not specify the order of review between authorisation by the competent authority and ethical review by an ethics committee (EC). However, in some Member States, ethics committee (EC) review is legally required to be completed first.

[Reference: Overview of ethics committee (EC) approval and CA authorisation systems in Germany and the Netherlands (before the start of clinical investigations)]

In clinical investigations of medical devices in the EU, it is generally required to obtain ethical approval by an ethics committee (EC) and regulatory authorisation by the competent authority (CA) before the start of the investigation (or to complete the required procedures depending on the type of investigation). However, the specific design of these systems (such as the allocation of review responsibilities, the order of review, and the involvement of central bodies) is defined within the national laws and systems of each Member State.

(1) Germany: A regulatory structure in which CA authorisation follows ethics committee (EC) approval

In Germany, obtaining "ethics committee (EC) approval" prior to the start of a clinical investigation is positioned as an important element of the system, with "authorisation by the CA (or completion of the required start conditions depending on the type)" following in sequence. The formal name of the ethics committee is "Ethik-Kommission (ethics committee)" in German, and it functions as the body responsible for ethical review under national laws (including the MPDG, the national implementing law of the MDR) and the domestic system. The CA is the competent authority designated by the Member State, and in Germany, a framework has been adopted in which "the federal higher authority" performs review and supervision as the CA. Accordingly, in Germany, the regulatory process can be understood as follows: (i) determine the category of clinical investigation under the MDR framework and national requirements; (ii) prepare the documentation for submission to the ethics committee (EC) and obtain ethics committee (EC) approval; (iii) submit an authorisation application to the CA or complete the required procedures; and (iv) start the clinical investigation after obtaining ethics committee (EC) approval and meeting the CA start conditions. The detailed procedures prior to the start of the investigation are supplemented by national implementing laws such as the MPDG.

(2) The Netherlands: A structure in which the approval system is organized through the MDR frameworks (Art 62/74/82) and national laws (WMO etc.), with a central framework acting as the entry point for the purpose of CE marking

In the Netherlands, the attributes of a clinical investigation are first organized under the MDR frameworks (Articles 62, 74, and 82), and the systems for ethical review (EC approval) and national procedures (CA authorisation or other required procedures) are defined under national laws (including the WMO). An important country-specific feature is that, for clinical investigations conducted for the purpose of obtaining or extending CE marking (conformity assessment) (generally corresponding to Article 62 and Article 74(2)), the central organization, the Central Committee on Research Involving Human Subjects (CCMO), acts as the institutional entry point, carrying out formal checks of submitted information (e.g., validation) and allocating the responsible review body. The official Dutch name of the CCMO is "Centrale Commissie Mensgebonden Onderzoek." The CCMO is positioned as the central body of the review system under national laws. It is involved in the review as a designated review body depending on the

research category. It also plays a role in the framework for the accreditation and operation of MREC/METC committees. After this, an accredited ethics committee (MREC/METC, etc.) or the CCMO grants ethics committee (EC) approval (ethical approval), and the investigation proceeds to start after authorisation by the CA or completion of the required procedures. Accordingly, the Dutch system is not one in which “a single central ethics committee (EC) approves all investigations.” Rather, “for investigations intended for CE marking, the central framework (CCMO) is involved in the entry procedures, and the investigation starts after ethics committee (EC) approval and CA authorisation have been obtained (or the required procedures have been completed).”

(3) Common key points of the regulatory systems

In both countries, the key points of the pre-start system are the following: (a) determination of the category of clinical investigation (the MDR framework and its application to national laws); (b) preparation of the documentation used for ethics committee (EC) approval and CA authorisation (or required procedures); (c) design of informed consent and subject protection measures (compensation, personal data protection, etc.); (d) version control of submitted documents; and (e) confirmation that the start conditions (ethics committee (EC) approval, CA authorisation / non-objection / receipt of notification, etc.) are fulfilled.

4. Regulatory framework for conflicts of interest (transparency-related)

In the EU, in the areas of clinical investigations, review, evaluation, and advice on medical devices, the management of conflicts of interest (COI) is regarded as an important element for ensuring transparency and the neutrality of review. In particular, the COI of the review side (those involved in evaluation, advice, and review) is expressly addressed in the MDR from the perspectives of independence and transparency. In other words, the Member States are required to ensure that persons involved in the verification, evaluation, and decision-making related to clinical investigation applications have no conflicts of interest, are independent of sponsors and investigators, and are not subject to undue influence. In addition, for EU-level review and advisory bodies (such as the MDCG and expert panels), mechanisms are required for the preparation, updating, and publication of declarations of interests, as well as for the management and prevention of potential COI. These are COI management measures designed to ensure the neutrality of regulatory review.

In contrast, regarding COI management on the implementation side (investigators and institutions conducting clinical investigations), the MDR requires financial disclosure by individual investigators as part of the application documentation (Annex XV), but it does not directly specify detailed procedures for evaluation criteria or management methods.
COI on the implementation side is managed through review by ethics committees (EC), national laws of the Member States, and international standards such as ISO 14155, with the aim of ensuring the ethical and scientific validity of clinical investigations, minimizing bias, and protecting subjects. In other words, EU COI management can be understood as a combined structure: the MDR directly requires strong independence and transparency on the review side, while on the implementation side, the MDR ensures “transparency (disclosure),” and the “actual management” of COI relies on ethical review and national systems.

5. Regulatory framework for information provision, informed consent, and multilingualization

The MDR explicitly sets out the requirements for informed consent in Article 63, and requires that clinical investigations be conducted in accordance with recognized ethical principles under the "General requirements / ethical principles" in Annex XV. On this basis, the clinical investigation plan, the patient information sheet (PIS), and the informed consent form (ICF) are prepared as a set and reviewed by the ethics committee (EC), taking into account the provision of sufficient information and consent based on free will, as well as special considerations for vulnerable subjects (including minors, adults with limited decision-making capacity, and pregnant women, as provided in Article 64 and subsequent Articles). In practice, subject-facing documents such as the PIS/ICF are submitted for ethical review.
ISO 14155 is an international standard that operationalizes GCP for clinical investigations of medical devices and sets out operational requirements, such as ethics, scientific validity, subject protection, and informed consent. The MDR states in Recital 64 that it is important for the rules on clinical investigations to be consistent with well-established international guidance or standards such as ISO 14155, and in practice ISO 14155 is widely used as a reference framework for planning, conducting, recording, and reporting clinical investigations.

In the EU, the language used for documents and information in clinical investigations of medical devices is not a single EU-wide language; in practice, it follows the requirements set by each Member State and relevant institution where the investigation is conducted. The MDR requires that clinical investigations be conducted within a framework in which "the rights, safety, and dignity of subjects take precedence," and provides that ethical review is carried out by ethics committees (ECs) established under Member State legislation. Accordingly, documents used for PIS/ICF, review, and submission must, in practice, be presented in a language that can be understood in the relevant Member State. Although the MDR does not list detailed language requirements in its provisions, ethical review is entrusted to the legislation and practices of the Member States, and Recital 64 refers to alignment with international ethical principles (such as the Declaration of Helsinki). On this basis, explanations and consent in a language that subjects can understand are assumed in practice.

Supplement: Specification of language requirements by Member State—examples from Germany and the Netherlands

As noted above, the MDR does not set out detailed language requirements in its provisions. However, the operational use of language is specified through the regulatory frameworks of the Member States and through the published requirements for ethical review and application procedures (such as templates, checklists, and operational requirements for application portals). This section outlines how the language requirements for PIS/ICF are implemented in regulatory systems and practices, using Germany and the Netherlands as examples.

(1) Germany

In Germany, a framework based on the MDR and the MPDG has been established in which applications are submitted through BfArM's application information system (DMIDS). In practice, DMIDS is designed on the basis of a German-language environment, and German functions as the de facto working language at the entry point of the review process.

For informed consent documents (patient information sheet and consent form), the national framework of ethics committees (AKEK) provides model texts (Mustertexte) of “information and consent” for clinical investigations of medical devices and related materials. Applicants are expected to prepare their documents with reference to these materials. In line with the intent of the MDR, patient information should be “comprehensive yet concise and clear, and should be understandable to the subject (or legal representative).” When translations are involved, it is emphasized that the documents should not be simple literal translations but should be prepared in meaningful German that meets national quality requirements. Accordingly, in Germany, German is used as the basic language for institutional and application procedures, while the design of subject-facing documents (including appropriate translation where necessary) ensures in practice that subjects can understand the information.

(2) The Netherlands

In the Netherlands, research conducted under the WMO requires review and approval by an accredited ethics committee (MREC) or the central committee (CCMO). The informed consent process is based on verbal and written explanations and written consent as the basic requirements.

Regarding language use, the requirements related to subject Information sheets and informed consent forms published by the CCMO provide that review committees generally “review only the Dutch-language version of the information sheet and consent form.” At the same time, to ensure that participants can fully understand the explanation and make an informed decision, it is specified that “information documents in a language that the participant can understand must be prepared” for participants whose Dutch is insufficient.

Translation is in principle the responsibility of the sponsor. Although submission of the translated documents themselves is not mandatory, the requirements are specifically designed, including cases in which translation certification may be required when foreign-language versions are prepared. In addition, not only written documents but also verbal explanations must be provided in a language that the participant can understand. Accordingly, the Netherlands can be characterized as having a system in which the review language (Dutch) and the participant-facing language (a language that the participant can understand) are distinguished, with translation responsibility and certification requirements clearly defined within the regulatory framework.

6. Regulatory framework for compensation for subjects

Regarding compensation for subjects in clinical investigations of medical devices in the EU, Article 69 of the MDR requires the Member States to ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical investigation are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose. The same Article also requires that such arrangements be appropriate to the nature and the extent of the risk of the investigation concerned, and that the sponsor and the investigator make use of the system referred to in the form appropriate for the Member State in which the clinical investigation is conducted. Accordingly, when conducting multinational clinical investigations in the EU, the specific requirements for compensation systems are defined by the national laws and practices of each Member State. Therefore, it is important in practice to arrange insurance or equivalent arrangements in accordance with the requirements of each Member State in which the clinical investigation is conducted and to prepare the necessary documentation.

7. Regulatory framework for safety reporting to competent authorities

In clinical investigations in the EU, safety reporting is operated under a two-layer structure: it is defined as a legal obligation under Chapter VI of the MDR, and MDCG 2020-10/1 specifies definitions, scope, reporting routes, and interim operational procedures.

The MDR requires clinical investigations to be designed, conducted, recorded, and reported under the principle that "the rights, safety, and dignity of subjects take precedence," and places safety monitoring during the investigation and reporting to authorities as essential, with assessment and oversight by the competent authorities of the Member States and review by ethics committees (ECs).

The specific reporting items, submission routes, and report formats are described in MDCG 2020-10/1 as standard practice, clarifying what information the sponsor must report, to whom, when, and how. MDCG 2020-10/1 also defines the scope, terminology, and categories of safety information, organizes events that may occur during a clinical investigation into categories such as adverse event (AE), adverse device effect (ADE), serious adverse event (SAE), serious adverse device effect (SADE), and unanticipated serious adverse device effect (USADE), and requires sponsors to identify, assess, and report them to the competent authorities of the Member States through the specified timelines and routes.

The timing of safety information reporting is broadly divided into expedited reporting (e.g., USADE or serious events involving death, life-threatening conditions, hospitalization, or severe dysfunction of subjects, where device-related involvement is suspected or confirmed) and periodic tabulation and evaluation (including annual safety evaluation and compilation for the final report). MDCG 2020-10/1 outlines the reporting flow to the authorities and provides examples of the minimum information items (including recent measures taken for subject protection, corrective actions related to the device, and evaluation of whether the investigation should continue), focusing in particular on "immediately reportable events" that are subject to expedited reporting.

8. Regulatory framework for protection of subject information (protection of personal data and healthcare information)

Protection of subject information (protection of personal data and healthcare information) in clinical investigations of medical devices in the EU is structured as a layered framework. The GDPR provides the cross-cutting foundation, while the MDR clinical investigation framework and ISO 14155 add operational requirements on top of it. The GDPR is a horizontal regulation aimed at ensuring both the protection of personal data of individuals (data subjects) in the EU and the free movement of such data.

The GDPR adopts a two-step structure, requiring both a legal basis for processing (Article 6) and conditions for the processing of special categories of data (Article 9). Processing of data concerning health is prohibited in principle (Article 9(1)) but is permitted only when specific conditions are met, such as explicit consent (Article 9(2)(a)) or exceptions for scientific research purposes (Article 9(2)(j)).

The role of the MDR is to establish the legal framework under which clinical investigations are conducted with "the rights, safety, and dignity of subjects as the highest priority." Article 62 of the MDR requires review by an ethics committee (EC), and Annex XV sets out ethical principles aligned with the Declaration of Helsinki as general requirements, broadly defining the framework for subject protection, including the handling of sensitive information.

ISO 14155 specifies confidentiality and privacy protection at the operational level. Its ethics provisions require subject confidentiality, data protection, and appropriate document management, alongside prohibitions on undue inducement and additional protections for vulnerable populations. It also requires that data protection procedures and allocation of responsibilities be specified in the clinical investigation plan.

9. Regulatory framework for disclosure of clinical investigation data

In the EU, information on clinical investigations of medical devices is registered and disclosed in EUDAMED. EUDAMED is the official database operated by the European Commission and includes mechanisms to publish information on clinical investigations/performance studies (CI/PS) in order to enhance transparency. The system is currently being introduced module by module, and the CI/PS module is expected to become mandatory after audit and publication in the Official Journal. (Modules for “actor registration,” “UDI/device registration,” “NB/certificates,” and “market surveillance” have already been confirmed as functional and will become mandatory for use from May 28, 2026.)

10. Regulatory framework for digitalization of data

The reliability of electronic records is operationalized by ISO 14155, which requires procedures to be established in the CIP and SOPs for system validation (qualification), access control, audit trails, the location of source data and transcription rules, and data integrity based on ALCOA++. Electronic signatures are governed by the eIDAS Regulation, under which a qualified electronic signature (QES) has the same legal effect as a handwritten signature.

Appendix: List of laws, regulations, and guidance cited in this summary (in order of appearance)

1. Regulation (EU) 2017/745 on medical devices
   Abbreviation: MDR
   https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02017R0745-20250110
   - Article 73 (Electronic system on clinical investigations)
   - Article 103 (Medical Device Coordination Group)
   - Article 70 (Application for clinical investigations)
   - Annex XV (Clinical investigations)
   - Article 62 (General requirements regarding clinical investigations conducted to demonstrate conformity of devices)
   - Article 82 (Requirements regarding other clinical investigations)
   - Chapter VI (CLINICAL EVALUATION AND CLINICAL INVESTIGATIONS)
   - Article 74 (Clinical investigations regarding devices bearing the CE marking)
   - Annex VIII (Classification rules)
   - Annex IX (Conformity assessment based on a quality management system and assessment of the technical documentation)
   - Annex X (Conformity assessment based on type examination)
   - Annex XI (Conformity assessment based on product conformity verification)
   - Article 61 (Clinical evaluation)
   - Article 63 (Informed consent)
   - Article 69 (Damage compensation)

2. ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice
   Abbreviation: ISO 14155

3. Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data
   Abbreviation: GDPR
   https://eur-lex.europa.eu/eli/reg/2016/679/oj/eng
   - Article 6 (Lawfulness of processing)
   - Article 9 (Processing of special categories of personal data)

4. MDCG 2021-1 Rev.1 Guidance on harmonised administrative practices and alternative technical solutions until EUDAMED is fully functional
   Abbreviation: MDCG 2021-1 Rev. 1
   https://health.ec.europa.eu/document/download/ea0369a7-d86c-465e-9a54-0c0dfb01bc84_en
   - Article 103

5. Regulation of the European Parliament and of the Council of 13 June 2024 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards a gradual roll-out of Eudamed, the obligation to inform in case of interruption or discontinuation of supply, and transitional provisions for certain in vitro diagnostic medical devices

Abbreviation: Regulation (EU) 2024/1860
https://eur-lex.europa.eu/eli/reg/2024/1860/oj

6. Regulation (EU) 2017/746 on in vitro diagnostic medical devices
Abbreviation: IVDR
https://eur-lex.europa.eu/eli/reg/2017/746/oj/eng
   - Chapter VI (CLINICAL EVIDENCE, PERFORMANCE EVALUATION AND PERFORMANCE STUDIES)
   - Article 57 (General requirements regarding performance studies)
   - Annex XIII (Performance evaluation, performance studies and post-market performance follow-up)
   - Article 58 (Additional requirements for certain performance studies)
   - Articles 59–77
   - Annex XIV (Interventional clinical performance studies and certain other performance studies)
   - Article 76 (Recording and reporting of adverse events that occur during performance studies)
   - Article 69 (Electronic system on performance studies)

7. Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices
Abbreviation: MDCG 2024-3
Term used in this summary: Final guidance by the MDCG
https://health.ec.europa.eu/document/download/690de85a-ac17-45ea-bb32-7839540c25c4_en?filename=mdcg_2024-3_en_0.pdf

8. Guidance on content of the Investigator's Brochure for clinical investigations of medical devices
Abbreviation: MDCG 2024-5
Term used in this summary: Final guidance by the MDCG
https://health.ec.europa.eu/document/download/ee7ee8eb-841a-4085-a8dc-af6d55ebf1bd_en?filename=mdcg_2024-5_en.pdf

9. Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745
Abbreviation: MDCG 2020-10/1
Term used in this summary: Final guidance by the MDCG
https://health.ec.europa.eu/document/download/0537d335-7eed-4087-b65d-3c2bd8c72c1a_en?filename=md_mdcg_2020-10-1_guidance_safety_reporting_en.pdf

10. Guidance on the publication of the clinical investigation reports and their summaries in the absence of EUDAMED
Abbreviation: MDCG 2024-15
Term used in this summary: Final guidance by the MDCG
https://health.ec.europa.eu/document/download/0e076d19-62dc-4ff9-83f2-be6072a45993_en?filename=mdcg_2024-15_en.pdf

11. Questions & Answers regarding performance studies of in vitro diagnostic medical devices under regulation (EU) 2017/746
    Abbreviation: MDCG 2025-5
    Term used in this summary: Guidance on performance studies
    https://health.ec.europa.eu/document/download/f22f559b-dee5-43b4-9595-3ccdcca9f7ad_en?filename=mdcg_2025-5_en.pdf

12. Safety reporting in performance studies of in vitro diagnostic medical devices under Regulation (EU) 2017/746
    Abbreviation: MDCG 2024-4
    https://health.ec.europa.eu/document/download/5cc894e0-331d-4fa2-8ab3-cdd4437c48fc_en?filename=mdcg_2024-4_en.pdf

13. Regulation (EU) No 910/2014 on electronic identification and trust services for electronic transactions in the internal market (eIDAS)
    https://eur-lex.europa.eu/eli/reg/2014/910/oj

Regulatory Framework for Clinical Trials of Medicinal Products in the UK

Date of preparation: February 20, 2026

Chapter 1: Regulations governing clinical trials of medicinal products in the UK

1. Regulatory hierarchy

1-1. Legal system

The regulatory framework for clinical trials of medicinal products in the UK has a hierarchical structure similar to that of Japan but differs in that the UK does not have a written constitution. The highest level consists of Acts of Parliament, with the “Medicines and Medical Devices Act 2021” forming the legal basis for clinical trials.

The next level consists of statutory instruments, which set out detailed provisions under delegated legislation. The “Human Medicines Regulations 2012” stipulate the comprehensive rules for medicinal products for human use, while clinical trial regulation is mainly set out in the “Medicines for Human Use (Clinical Trials) Regulations 2004.” These regulations were substantially amended in 2024 and 2025 and will be fully enforced on April 28, 2026, aiming to improve procedural efficiency and transparency.

Below this level are guidance issued by the regulatory authority. Although these are often not legally binding, they are important guidance that must be referenced in practice. The guidance includes practical interpretations and operational measures for clinical trial planning, conduct, monitoring, amendment procedures, and compliance with GCP.

In addition, guidance is provided for research ethics committees (RECs) and the Integrated Research Application System (IRAS), describing application procedures, model sponsor agreements, and the details of the integrated review process. These complement legislation and guidance and provide the practical framework required for the conduct of clinical trials in practice.

In addition, local policies of National Health Service (NHS)* Trusts also exist and support operational practice at the site level, provided that they do not conflict with national legislation.

In this way, the UK legal system forms a hierarchical structure: Acts of Parliament → statutory instruments → regulatory authority guidance → IRAS and ethical review guidance → NHS local policies. Compliance with GCP in clinical trials is also legally required under the 2004 Regulations and related guidance, with a strong emphasis on alignment with the international standard, ICH-GCP.

*NHS:

This is a public healthcare system intended to provide healthcare services to all UK residents free of charge in principle. It provides a comprehensive range of services, including hospitals, clinics, emergency services, and community healthcare, and is also responsible for employing healthcare professionals and implementing healthcare policy. Most clinical research is conducted in NHS facilities, and in such cases, R&D approval and site agreements with the relevant NHS Trust are required.

1-2. Main regulatory authorities

The main regulatory authorities in the UK are outlined below.

- **Medicines and Healthcare products Regulatory Agency (MHRA)**
  It operates under the Department of Health and Social Care and is responsible for reviewing clinical trial authorisation (CTA), conducting GCP inspections, and issuing guidance for clinical trials of investigational medicinal products (CTIMPs).
- **Health Research Authority (HRA)**
  It is established as a non-departmental public body and is responsible for the ethics and governance of medical research.
- **Research Ethics Committee (REC)**
  It is established under HRA and conducts ethical review of research including clinical trials.

2. Regulations applicable to clinical trials of medicinal products

The main regulations applicable to the conduct of clinical trials of medicinal products in the UK are as follows.

- **Medicines and Medical Devices Act 2021**
  Legislation providing a comprehensive framework that enables the regulatory system for medicines, medical devices, and related products in the UK to be updated in a flexible and timely manner. It aims to establish a UK-specific regulatory environment following the UK's withdrawal from the EU. The Act also provides for the establishment of a "Commissioner for Patient Safety" to enhance patient safety and forms the legal basis for rapid regulatory updates and improved access to innovative therapies.
- **Human Medicines Regulations 2012**
  The principal regulations governing the entire lifecycle of medicines in the UK, including manufacture, sale, distribution, advertising, clinical trials, and pharmacovigilance. Reflecting EU law, these regulations establish a comprehensive framework to ensure the quality, safety, and efficacy of medicines and set out the medicines licensing system, requirements for clinical trial conduct, standards for manufacturing and distribution (GMP/GDP), and temporary authorisation measures in emergencies (e.g., Regulation 174).
- **Human Medicines (Amendment etc.) (EU Exit) Regulations 2019**
  Legislation enacted in 2019 to ensure that the Human Medicines Regulations 2012 and other EU-based medicines laws could continue to operate independently in the UK following its withdrawal from the EU. Because the EU centralized authorisation system no longer applies in the UK, functions previously relying on the European Medicines Agency (EMA), including marketing authorisation and variation assessment, GMP/GDP oversight, and pharmacovigilance, were transferred to the UK authority, MHRA. The legislation also introduced a framework to convert medicines centrally authorized in the EU at the time of exit into UK marketing authorisations (UK MAs) under equivalent conditions. In addition, it adjusts provisions on marketing authorisation, import controls, the handling of products from the European Economic Area (EEA), the handling of GMP/GDP certificates, and the recognition of prescriptions issued in the EEA, reflecting the UK's operation as a third country outside the EU. It further establishes UK-specific pharmacovigilance requirements, such as the appointment of a UK qualified person for

pharmacovigilance (QPPV) and a UK contact point, and also provides for data and market exclusivity and the continued application of incentives for orphan and pediatric medicines.

- **Human Medicines (Amendment) (Modular Manufacture and Point of Care) Regulations 2025**
  Regulations amending the Human Medicines Regulations 2012 to introduce a regulatory framework for new types of medicines manufactured at the place where the patient receives treatment (point of care, POC), including ultra-short-shelf-life and highly personalized medicines. To complement the conventional fixed manufacturing model, the regulations provide a framework to appropriately manage distributed manufacturing across multiple sites, such as hospitals. They establish a hub-and-spoke quality management system centered on a central “control site” (a core site responsible for the quality system and key responsibilities), aimed at ensuring appropriate safety, quality, and efficacy while enabling broader access to advanced therapies.
- **The Medicines for Human Use (Clinical Trials) Regulations 2004**
  The principal legislation regulating CTIMPs in the UK, implementing the EU Clinical Trials Directive 2001/20/EC into domestic law. The regulations require CTA authorisation and a favourable opinion from a REC before a clinical trial can be conducted and define requirements for the design, conduct, subject protection, GCP compliance, and regulatory oversight of clinical trials. They also establish comprehensive provisions covering the lifecycle of a clinical trial, including trial initiation and completion, reporting of serious breaches, and the responsibilities of sponsors and investigators.
- **The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025**
  The amendments to the above Medicines for Human Use (Clinical Trials) Regulations 2004 aimed at modernizing the UK clinical trial framework while enhancing international alignment and competitiveness. The amendments introduce measures such as the clarification of terminology, a risk-based approach to trial modifications, enhanced transparency, and closer coordination between RECs and MHRA (through the formalization of the combined review process). These changes represent a regulatory reform intended to strengthen the UK’s position as a globally competitive country for conducting clinical trials.
- **UK Policy Framework for Health and Social Care Research**
  A policy framework that sets out common principles and standards of good practice for research conducted in the fields of health and social care across the UK. The framework consolidates the previously separate regional Research Governance Frameworks and establishes 19 principles supporting high-quality research, including the safety of research participants, transparency, ethical conduct, and risk-proportionate research management. It applies to research funders, sponsors, researchers, research organizations, and care providers, and serves as the foundation of research governance in the UK.

For reference, the basic terms and their definitions under the respective regulations are provided below.

<u>Medicinal Product</u>

- Defined in the Human Medicines Regulations 2012
- Any substance or combination of substances presented as having properties of preventing or treating disease
- Any substance or combination of substances intended to restore, correct, or modify a

physiological function by exerting a pharmacological, immunological, or metabolic action, or to make a medical diagnosis

Clinical Trial

- Defined in the Medicines for Human Use (Clinical Trials) Regulations 2004
- Any investigation intended
  1. to discover or verify the clinical, pharmacological or other pharmacodynamic effects of the medicinal product,
  2. to identify any adverse reactions to such a product, or
  3. to study absorption, distribution, metabolism, and excretion of such a product, with the object of ascertaining the safety or efficacy of the product
- A clinical trial refers to a study conducted to evaluate the efficacy and safety of a medicinal product and is commonly referred to in practice as a CTIMP.
- It is an investigation conducted in human subjects; non-interventional trials are excluded.

Non-interventional trial

- Defined in the Medicines for Human Use (Clinical Trials) Regulations 2004
- Authorized medicinal products are used in the usual manner.
- The assignment of any patient involved in the study to a particular therapeutic strategy is not decided by a protocol but falls within current practice.
- The decision to prescribe a medicinal product is clearly separated from the decision to include the patient in the study.
- No diagnostic or monitoring procedures are applied; only those used in normal clinical practice are permitted.
- Epidemiological methods are to be used for the analysis of the collected data.

3. Classification for determining applicable regulations

When conducting interventional clinical trials or clinical research of medicinal products in the UK, several classifications may be considered in order to determine the applicable regulations and guidance.

3-1. Regulations applicable to clinical trials fall under CTIMPs

In the UK, research is not primarily distinguished by whether it is intended for marketing authorisation. Instead, the “presence or absence of intervention” determines whether the research falls under CTIMPs or non-CTIMPs, which in turn determines the applicable regulatory framework. If the research falls under a CTIMP, the Medicines for Human Use (Clinical Trials) Regulations 2004 and their amendments apply. These regulations impose comprehensive requirements covering trial authorisation, ethical review, trial conduct, safety reporting, and compliance with GCP.

For CTIMPs, CTA authorisation by MHRA and ethical review by a REC are mandatory. The review processes of MHRA and the REC have been aligned and streamlined, and a combined review submitted through IRAS is required. This integrated process covers authorisation, modifications, and end-of-trial notification. In conducting the trial, compliance with GCP is a legal requirement. The regulations set out requirements relating to the trial plan, monitoring, auditing, supply and management of the investigational medicinal product, notification of serious breaches, reporting of adverse events and suspected unexpected serious adverse reactions (SUSARs), and the maintenance and archiving of the trial master file. Non-compliance may result in strict regulatory

action, including orders to suspend or terminate the trial, administrative corrective measures, and criminal penalties in some cases.

3-1-1. Risk classification of CTIMPs

MHRA recommends a “risk-adapted approach,” whereby trial requirements and conduct are adjusted according to the level of risk, in order to ensure the safety of clinical trials and to improve the efficiency of trial conduct. For CTIMPs, the MHRA guidance, Risk-Adapted Approach to Clinical Trials and Risk Assessments, categorizes trials into Type A (no higher than the risk of standard medical care), Type B (somewhat higher than the risk of standard medical care), and Type C (markedly higher than the risk of standard medical care), and provides corresponding principles for risk management.

These type classifications are not fixed categories specified directly in legislation. Rather, they serve as a framework applied after assessing the additional risk of the trial compared with standard medical care. Accordingly, the classification is not determined mechanically using a fixed checklist. Instead, it is based on an overall risk assessment that takes into account factors such as the authorisation status of the investigational medicinal product (IMP), dosage and administration, the target population, known safety information, the trial design, and any additional procedures involved in the trial.

In general, trials classified as Type A involve relatively low additional risk, and simplified monitoring or procedures may therefore be acceptable in some cases. In contrast, trials classified as Type C involve relatively higher additional risk, and more stringent safety measures, monitoring plans, and documentation are required to ensure subject protection and safety.

Before the trial begins, it is important to clearly identify the risks specific to the trial and the corresponding mitigation measures and to organize them into an appropriate risk management plan. In the application process (e.g., submissions through IRAS), information on the risk assessment and risk mitigation measures may be required to be provided.

In addition, complex and innovative trial designs, such as adaptive trials (designs that allow planned changes to the sample size, allocation ratio, dose, or addition/suspension of arms based on data obtained in interim analyses and according to predefined decision rules), platform trials (designs that allow the simultaneous and continuous evaluation of multiple intervention arms using a common control arm under a single master protocol, with the addition or removal of intervention arms over time), and basket trials (designs that evaluate the same treatment across different “baskets” defined by common biomarkers rather than by organ site across different diseases or populations), require careful consideration beyond the standard CTIMP requirements. From the protocol design stage, elements such as pre-planned adaptation rules, change control, transparency of statistical methods, and staged safety evaluation are essential. Such applications may fall within the category of “Applications that need expert advice” under MHRA guidance, and prior consultation with specialists (MHRA Scientific Advice Service) is recommended.

3-2. Regulations applicable to clinical trials that do not fall under CTIMPs (non-CTIMPs)

Research that does not involve an intervention is treated as a non-CTIMP. For example, observational research in which an authorized medicinal product is used within the authorized conditions of use and no tests imposing an additional burden on patients are conducted for research purposes fall into this category. In such a case, the research is expected to follow the

"UK Policy Framework for Health and Social Care Research" issued by HRA. The regulatory focus is primarily on ethical requirements, including prior review by a REC, submission for ethical review through IRAS, informed consent from participants, management of conflicts of interest, and transparency of research information. Compliance with data protection legislation is also required, including the UK GDPR, the Data Protection Act 2018, and the Data (Use and Access) Act 2025. Although CTA authorisation and SUSAR reporting requirements do not apply to non-CTIMPs, it is expected to follow the guidance issued by HRA and UK Research and Innovation (UKRI) to ensure ethical and scientific validity.

3-3. Advanced therapy medicinal product (ATMP) trials

An overview of ATMPs, as defined in the Human Medicines Regulations 2012, and the products that fall within this category is provided below.

Advanced therapy medicinal product (ATMP)
This is a collective term for medicinal products that fall into one of the following categories: gene therapy medicinal products, somatic cell therapy medicinal products, or tissue engineered products. The concept also includes "combination ATMP (combined ATMP)," in which a medicinal product is integrated with a medical device.

Gene therapy medicinal product
This refers to a medicinal product designed to achieve therapeutic, preventive, or diagnostic effects by administering recombinant nucleic acid to humans or introducing it into human cells (*in vivo* or *ex vivo*) in order to regulate, repair, replace, add, or delete genetic sequences. Gene transfer using viral or non-viral vectors is included, but conventional vaccines against infectious diseases are not included in this definition.

Somatic cell therapy medicinal product
This refers to a product prepared using autologous, allogeneic, or xenogeneic cells or tissues related to its intended clinical use that have undergone "substantial manipulation," or that are used for "non-homologous use," meaning they are not used for the same essential function in the donor and the recipient, and that is intended for the treatment, prevention, or diagnosis of disease through pharmacological, immunological, or metabolic action.

Tissue engineered product
This refers to a product that contains or consists of "engineered" cells or tissues that have undergone substantial manipulation or are intended for non-homologous use, and that is used to regenerate, repair, or replace human tissue. The cells or tissues are typically viable and may be combined, where appropriate, with scaffold materials, biomaterials, matrices, or other supporting structures. When integrated with a medical device, the product is treated as a combination ATMP.

For the conduct of ATMP trials, MHRA has issued guidance on ATMPs (Advanced therapy medicinal products: regulation and licensing in UK). ATMP trials fall within the CTIMP framework but are expected to be applied according to the guidance, with the use of a classification opinion or scientific advice where appropriate. Given the specific characteristics of ATMPs, key regulatory considerations include GMP certification of manufacturing facilities, long-term follow-up plans,

safety assessments, and the maintenance of manufacturing records.
When cells or tissues of human origin are handled in an ATMP trial, it is necessary to confirm whether the material constitutes relevant material under the Human Tissue Act 2004. Under Section 53 of the Human Tissue Act 2004, relevant material is defined as “material, other than gametes (sperm or eggs), that consists of or includes human cells.” Where the material falls within this definition, requirements under the Human Tissue Act 2004 may apply depending on the purpose and method of its collection, storage, and use. Under the Act, a licence from the Human Tissue Authority (HTA) may be required when relevant material is stored for certain purposes. However, in clinical research that has undergone appropriate ethical review, such as conventional CTIMPs, an HTA licence is generally not required.

3-4. Regulations for clinical trials involving combination products

In the UK, when drug–device combination products are used in clinical trials, the applicable regulations differ depending on whether the product is treated as a medicinal product or as a medical device. In practice, however, the combined review conducted in parallel by MHRA and HRA serves as the central review process. Where the combination product is regulated primarily as a medicinal product, CTA authorisation by MHRA is required before the trial can begin, together with ethical review by a REC. In such cases, the application is submitted through the HRA combined review using IRAS, allowing a single application and a single decision, and the requirements related to medicinal products and medical devices are reviewed in parallel.

3-5. Phase I accreditation scheme trials

Trial sites conducting phase I and first-in-human (FIH) trials are encouraged (on a voluntary basis) to participate in MHRA phase I accreditation scheme. Applications for participation require the establishment of rigorous internal procedures, including emergency and resuscitation capabilities, arrangements for emergency collaboration for patient transfer, continuous availability and regular training of qualified personnel, detailed risk assessment and management plans, sentinel dosing, stepwise dose escalation and stopping criteria, and measures to prevent excessive volunteer participation (e.g., the Over-Volunteering Prevention System, TOPS).
There is no separate regulatory application procedure specific to phase I or FIH trials; the basic framework—CTA authorisation and REC review—is the same as for other CTIMPs. However, MHRA expects study plans to follow the 2017 EMA guidance on FIH risk mitigation and MHRA’s own guidance (Applications that need expert advice). Accordingly, risk-mitigation measures, such as selection of the starting dose, sentinel dosing, staggered dosing, and stopping criteria, should be clearly defined. Where appropriate, it is recommended to seek expert input from the Commission on Human Medicines (CHM) or to obtain pre-submission advice through MHRA Scientific Advice Service. From an ethical standpoint, the appropriateness of remuneration and consent based on the HRA/REC guidance is reviewed, and when radioactive medicinal products, etc. are involved, the requirements of the Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) and the Administration of Radioactive Substances Advisory Committee (ARSAC) apply. Although these guidance documents are not standalone legislation, they are widely referenced in practice as a safety-focused operational approach specific to phase I and FIH trials.

3-6. Trials involving orphan drugs

Clinical trials of medicinal products intended for rare diseases are generally conducted under the same CTIMP regulations as other medicinal product trials, based on the Medicines for Human Use (Clinical Trials) Regulations 2004. Such trials are carried out following authorisation by MHRA and ethical review by HRA/REC.

3-7. Pediatric CTIMPs

When conducting CTIMPs involving pediatric participants in the UK, pediatric-specific requirements are set out in guidance issued by MHRA and HRA/REC apply. These include the submission of a Paediatric Investigation Plan (PIP), child consent and assent procedures, the legality of proxy consent (e.g., consent provided by a legal representative for participants under 16 years of age), pharmacokinetics and dose-finding, and special considerations for safety monitoring. Documentation and reporting are expected to be aligned with ICH E11/E6. MHRA also provides checklists and guidance specifically for pediatric CTIMPs, and such trials are subject to more careful review.

3-8. Regulations for clinical trials conducted in emergency settings

Emergency research refers to research conducted in urgent clinical situations, such as cardiac arrest, severe stroke, or impaired consciousness, where immediate treatment is required and the participant lacks the capacity to provide consent, making prior informed consent practically impossible to obtain. In the UK, the regulatory approach to such research is outlined in the HRA guidance “Research in emergency settings.”

According to this guidance, in clinical trials (particularly CTIMPs) where treatment must be administered urgently and obtaining prior informed consent would delay necessary medical intervention, and where the participant lacks decision-making capacity and it is not reasonably practicable to obtain consent from an appropriate legal representative, enrolment without prior consent may be exceptionally permitted under procedures approved in advance by an NHS research ethics committee. When the research has been proceeded under this exception, formal consent must be obtained as soon as possible once the participant regains capacity or a legal representative becomes available.

3-9. Regulations for clinical trials involving controlled narcotic drugs

Controlled drugs, such as narcotic and psychotropic drugs, are strictly regulated under the Misuse of Drugs Act and the Misuse of Drugs Regulations and are subject to additional legal requirements when used in clinical research.

In particular, for studies involving Schedule 1 substances (which may be used only for research purposes: hallucinogens, MDMA, psilocybin, etc.), each site that stores, supplies, or administers the substance in the study must obtain a Schedule 1 research licence from the Home Office in advance, in addition to the standard CTIMP procedures. Possession, storage, supply, and administration of the substance must then be conducted in accordance with the conditions of that licence. If the substance is sourced from overseas, a separate import licence is required. In addition, for the production or compounding of the substance, a production licence must also be obtained from the Home Office.

Chapter 2: Detailed requirements for clinical trials of medicinal products in the UK

The requirements applicable to the following elements that constitute a clinical trial are summarized below.

1. Authorisation of the conduct of clinical trials by the UK regulatory authority

For the conduct of CTIMPs, CTA authorisation is required as noted above. The CTA framework is established under the Medicines for Human Use (Clinical Trials) Regulations 2004, and applications must be submitted in accordance with the procedures and requirements specified by MHRA. Even for phase I trials (e.g., those involving healthy volunteers), CTA authorisation is required as long as the trial qualifies as a CTIMP. In recent years, regulatory simplification has progressed, including the introduction of approaches such as low-intervention trials and notification-based frameworks. Accordingly, it is important to confirm the applicable requirements and procedures based on the latest information provided by MHRA.
For non-CTIMPs, CTA authorisation by MHRA is generally not required.

2. Approval by an ethics committee for the conduct of clinical trials

For the conduct of CTIMPs, ethical review by a REC is required, and a favourable opinion must generally be obtained before the trial can proceed. Applications for REC review are submitted under the HRA framework, typically through IRAS. In addition, where a CTIMP is conducted within the NHS setting, HRA approval may also be involved in addition to ethical review, and the applicable procedures should therefore be confirmed depending on the study setting.
For non-CTIMPs (e.g., observational research or medical data research), REC review is often required depending on the nature of the research and from the perspective of subject protection. In particular, when research is conducted within the NHS environment, both REC review and HRA approval are likely to be required. In contrast, for research conducted outside the NHS setting, HRA approval may not be required, although obtaining an opinion from a REC may still be necessary.

3. Conflict of interest (COI) in clinical trials

For CTIMPs, the management of COI is carried out within the framework of sponsor responsibilities under the Medicines for Human Use (Clinical Trials) Regulations 2004 and compliance with GCP. Sponsors are required to establish appropriate management systems for COI, identify research funding sources and relationships between investigators and companies (e.g., employment, shareholdings, honoraria), and disclose relevant information in subject information documents or other materials, where necessary. During REC review, these interests are assessed to determine whether they are appropriately managed from an ethical perspective, including whether there are any undue inducement or concerns regarding subject protection.
For non-CTIMPs, COI management should be conducted by the research organization in accordance with research governance frameworks such as the UK Policy Framework for Health and Social Care Research. In particular, for research conducted within the NHS setting, REC review often requires the disclosure and clarification of research funding sources and investigators' COI. In commercial research, ensuring transparency in financial relationships is

particularly important. In non-commercial research, various interests, such as secondary employment, joint research, or endowments and sponsored academic positions, tend to be points of discussion.

4. Explanation to subjects, informed consent, and multilingualization

Providing information to subjects and obtaining informed consent are core requirements in REC review regardless of the type of research. Participants must be able to understand the content and make a voluntary decision about participation. This principle applies equally to both CTIMPs and non-CTIMPs.

However, the regulatory framework and the level of operational requirements differ depending on whether the research is a CTIMP. In non-CTIMP research, the primary focus is generally on subject protection. In contrast, CTIMPs are required to be conducted within the framework of clinical trial regulations and GCP, which impose more comprehensive regulatory requirements, including the management of the IMP, safety monitoring, documentation, and quality management. Accordingly, with respect to informed consent, CTIMPs typically require more detailed and structured explanations regarding the risks and benefits associated with the trial intervention or the use of the medicinal product, available alternative treatments, and possible adverse events and their management.

In addition, with regard to the provision of multilingual information sheets and informed consent forms, it is important that information is provided in a form that is understandable to participants and that consent is appropriately obtained, rather than that UK legislation uniformly stipulates the “provision of information in a specific language.” Accordingly, when language barriers are anticipated within the target population, appropriate measures are required to ensure participant comprehension, including support such as the preparation of translated documents and arrangements for interpreter services. In CTIMPs in particular, because greater emphasis is placed on the importance of the information provided and on safety-related communication systems, the quality assurance of translations and the appropriateness of the operational framework are more likely to become points of focus during review.

In light of the above, although the fundamental requirements relating to the provision of information, the obtaining of informed consent, and multilingual support are common to both CTIMPs and non-CTIMPs, it should be noted that, for CTIMPs, the scope of regulatory requirements applicable to clinical trials is broader, and consequently a higher level of expectation applies to both the content of the information provided and the operational framework.

5. Compensation for subjects

For CTIMPs, it is important that the sponsor establishes an appropriate framework for compensation and indemnity in the event that a subject suffers harm arising from the trial. In the UK, particularly for sponsor-initiated clinical trials, it is common practice to follow the Compensation Guidelines of the Association of the British Pharmaceutical Industry (ABPI), which incorporate the concept of no-fault compensation. Accordingly, prior to the initiation of the trial, it is expected that the compensation arrangements are appropriate and that the approach to compensation is clearly described in the subject information sheet and related documents.

For non-CTIMPs, where participation in the study may involve risks, appropriate arrangements for compensation and liability should also be organized. In particular, for research conducted within NHS settings, matters are typically addressed based on the responsibility structure of the

implementing body (NHS, university, etc.) and existing compensation schemes. However, depending on the nature of the research, additional insurance coverage may be required. Therefore, from a research governance perspective, it is important that such arrangements are appropriately defined and clearly documented.

6. Reporting of safety information to the regulatory authority

For CTIMPs, in order to ensure the safety of subjects, safety information relating to serious adverse events must be appropriately evaluated and reported to MHRA in accordance with the specified procedures. In practice, the sponsor is required to establish a safety reporting system that includes expedited reporting of SUSARs and periodic safety reporting such as the Development Safety Update Report (DSUR), and to ensure continuous safety monitoring throughout the conduct of the trial.
For non-CTIMPs, MHRA safety reporting framework (e.g., SUSAR and DSUR) does not generally apply. However, depending on the nature of the research, appropriate safety management may still be required. In research involving interventions, procedures should be established for the identification and management of adverse events, and, where appropriate, REC review should be obtained, and reporting and information sharing should be undertaken in accordance with the rules of the study sites to ensure the safety of study subjects.

7. Protection of subject information (protection of personal data and personal health information)

For CTIMPs, as personal data and health information of subjects (special category data) are processed, appropriate data protection measures are required in accordance with the UK GDPR, the Data Protection Act 2018, and the Data (Use and Access) Act 2025. Sponsors and trial sites are expected to establish appropriate data governance arrangements, including the lawful basis for data processing, purpose limitation, data minimization, access control, data retention periods, and safeguards for international data transfers, and to ensure transparency to subjects (e.g., the provision of relevant information in information sheets).

For non-CTIMPs, the handling of personal data and health information is often a primary consideration in medical data research and observational research, and data protection obligations under the UK GDPR and related legislation apply. In particular, when NHS medical information is used, ensuring the confidentiality of the data and clearly explaining the appropriateness of the intended use are important. It is therefore necessary to demonstrate through the research plan and ethics review process that appropriate data management measures are in place.

8. Disclosure of clinical trial data (registration and results disclosure)

For CTIMPs, in order to ensure transparency in clinical trials, it is required that the trial be registered in an official database (e.g., ISRCTN) and that the requirements for results disclosure be fulfilled. In the UK, HRA places particular emphasis on clinical trial registration as an ethical requirement, and registration may be required as a condition for obtaining a favorable ethical opinion. In addition, based on relevant guidance from MHRA, it is important to register the trial

prior to trial initiation and disclose the results after trial completion in a planned manner.
For non-CTIMPs, research registration and results disclosure are also important elements for ensuring research transparency. In particular, for studies that fall within the scope of clinical trials, HRA may require registration in a public registry. From the perspectives of ethical review and research governance as well, it is desirable that policies regarding registration and disclosure be clarified in advance. Depending on the nature of the research, appropriate public registries and methods for the publication of results should be selected.

9. Regulatory framework for digitalization of data

As a key UK official document directly related to digitalization, MHRA provides guidance on electronic health records (EHRs). Based on the Guidance on EHRs and the ICH E6 (GCP), electronically maintained medical records must have sufficient completeness and integrity to allow the course of a clinical trial to be faithfully reconstructed at a later stage. This requirement is essential for ensuring the credibility of trial results. If records are inadequate and the trial cannot be reconstructed, the trial may be considered non-compliant with GCP. MHRA considers the inability to reconstruct a clinical trial to be a significant regulatory risk that may constitute a regulatory breach and undermine the reliability of clinical trial data. In addition, electronic record systems themselves must be appropriately designed and validated and must comply with GCP. Furthermore, appropriate security and access control measures must be in place when third parties who have access to electronic records, such as monitors or auditors, view the records.
Electronic signatures may generally be used in clinical trials, and properly designed electronic signatures are considered “valid signatures.” However, not all forms of electronic signatures are acceptable. According to joint guidance issued by MHRA and HRA, specific requirements are set out to ensure reliability through identity, integrity, and timestamp.

Appendix: List of laws, regulations, and guidance cited in this summary (in order of appearance)

1. Medicines and Medical Devices Act 2021
   https://www.legislation.gov.uk/ukpga/2021/3/contents

2. The Human Medicines Regulations 2012
   https://www.legislation.gov.uk/uksi/2012/1916/contents

3. The Medicines for Human Use (Clinical Trials) Regulations 2004
   https://www.legislation.gov.uk/uksi/2004/1031/contents

4. The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019
   https://www.legislation.gov.uk/uksi/2019/775/contents

5. The Human Medicines (Amendment) (Modular Manufacture and Point of Care) Regulations 2025
   https://www.legislation.gov.uk/uksi/2025/87/contents/made

6. The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025
   https://www.legislation.gov.uk/uksi/2025/538/contents

7. HRA Guidance: UK Policy Framework for Health and Social Care Research
   https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

8. Guidance: Risk-Adapted Approach to clinical trials and Risk Assessments
   https://www.gov.uk/government/publications/risk-adapted-approach-to-clinical-trials-and-risk-assessments/risk-adapted-approach-to-clinical-trials-and-risk-assessments

9. Data Protection Act 2018
   https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted

10. UK General Data Protection Regulation
    Abbreviation: UK GDPR
    https://ico.org.uk/about-the-ico/what-we-do/legislation-we-cover/general-data-protection-regulation/

11. Data (Use and Access) Act 2025
    https://www.legislation.gov.uk/ukpga/2025/18/contents

12. Guidance: Advanced therapy medicinal products: regulation and licensing in UK
    https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing

13. Human Tissue Act 2004
    https://www.legislation.gov.uk/ukpga/2004/30/contents

14. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products(2017)
Term used in this summary: EMA guidance on FIH risk mitigation
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-and-mitigate-risks-first-human-and-early-clinical-trials-investigational-medicinal-products-revision-1_en.pdf

15. Ionising Radiation (Medical Exposure) Regulations 2017(IR(ME)R)
https://www.legislation.gov.uk/uksi/2017/1322/contents/made

16. Administration of Radioactive Substances Advisory Committee(ARSAC)
https://www.gov.uk/government/organisations/administration-of-radioactive-substances-advisory-committee

17. Guidance: Clinical trials for medicines: expert advice
Term used in this summary: MHRA's own guidance
https://www.gov.uk/guidance/clinical-trials-for-medicines-expert-advice

18. HRA Guidance: Research involving children
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-involving-children/

19. Guidance: Completed paediatric studies: submission, processing, and assessment
https://www.gov.uk/guidance/completed-paediatric-studies-submission-processing-and-assessment

20. HRA Guidance: Research in emergency settings
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-emergency-settings/

21. Misuse of Drugs Act 1971
https://www.legislation.gov.uk/ukpga/1971/38/contents

22. The Misuse of Drugs Regulations 2001
https://www.legislation.gov.uk/uksi/2001/3998/contents

23. ABPI — Clinical trial compensation guidelines
Term used in this summary: Compensation Guidelines of ABPI
https://www.abpi.org.uk/media/wz1k4sww/compensation_guidelines_2014.pdf

24. Guidance: Access to Electronic Health Records by Sponsor representatives in clinical trials
Term used in this summary: Guidance on EHRs
https://www.gov.uk/guidance/on-site-access-to-electronic-health-records-by-sponsor-representatives-in-clinical-trials

Regulatory Framework for Clinical Investigations of Medical Devices in the UK

Date of preparation: February 20, 2026

Chapter 1: Regulations governing clinical investigations of medical devices in the UK

1. Regulatory hierarchy

1-1. Legal system

In the UK, the legal framework governing clinical investigations of medical devices, similar to that for medicinal products, is structured hierarchically, with Acts of Parliament at the highest level. These establish the fundamental framework for the safety and marketing of medical devices. A key example is the “Medicines and Medical Devices Act 2021,” which forms the basis of medical device regulations.

The next level consists of statutory instruments (SI), which provide detailed provisions under delegated legislative authority. For medical devices, the key regulation is the “UK Medical Devices Regulations 2002 (UK MDR 2002).” This regulation provides the framework for scientifically assessing the safety and performance of medical devices and for ensuring the protection of patients. Within this regulatory hierarchy, Acts of Parliament form the highest tier, followed by the UK MDR 2002 as secondary legislation (SI). These are supplemented by guidance and notices issued by the Medicines and Healthcare products Regulatory Agency (MHRA), as well as review requirements imposed by research ethics committees (RECs). It should also be noted that in Northern Ireland (NI), the Regulation (EU) 2017/745 on medical devices (EU MDR) applies; therefore, regulatory requirements may differ depending on the region. In this summary, the “UK” refers to the United Kingdom; GB refers to Great Britain (England, Scotland, and Wales), while NI refers to Northern Ireland. The discussion below focuses primarily on the regulatory framework under the UK MDR 2002.

1-2. Main related legislation

- Medicines and Medical Devices Act 2021 (2021 c.3)
- The Medical Devices Regulations 2002 (SI 2002/618)
- The Medical Devices (Amendment etc.) (EU Exit) Regulations 2019 (SI 2019/791)
- The Medical Devices (Amendment) (Great Britain) Regulations 2023 (SI 2023/627)
- The Medical Devices (In Vitro Diagnostic Devices) (Amendment) Regulations 2024 (SI 2024/221)
- Data Protection Act 2018 (2018 c.12)

1-3. Main regulatory authorities

The main regulatory authorities and review bodies involved in clinical investigations of medical devices in the UK are outlined below.

- Medicines and Healthcare products Regulatory Agency (MHRA)
Under the oversight of the Department of Health and Social Care, MHRA acts as the competent authority for medical device regulation. It is responsible for receiving and reviewing notifications or applications for clinical investigations of medical devices, issuing decisions (e.g., “no objection” or “objection” in GB, and “authorisation” or “refusal” in NI), presenting requirements for safety reporting and amendment procedures, and maintaining relevant guidance.

- Health Research Authority (HRA)
HRA is established as a non-departmental public body. It operates the Research Ethics Service (RES), providing the framework for ethical review of research conducted mainly within the National Health Service (NHS) and is responsible for research governance and compliance review (part of the UK research approval process) and developing policies and guidance for research transparency.

- Research Ethics Committee (REC)
RECs review the ethical aspects of research plans, including subject protection, informed consent procedures, and the appropriateness of risks and burdens. In the UK, multiple RECs are operated, and allocation (booking) based on the research characteristics and review by “flagged RECs” capable of handling specific areas may be conducted (in NI, the Health and Social Care (HSC) REC A/B correspond to such RECs).

1-4. Regional differences in regulation

In the UK, different regulatory systems apply to medical devices depending on the region. This is based on arrangements introduced after UK’s withdrawal from the EU, including the “Northern Ireland Protocol” and the subsequent “Windsor Framework.”
In GB, the UK MDR 2002 applies, and approvals and clinical investigations of medical devices are conducted under this domestic law. In the GB market, conformity assessment is mainly based on the UKCA (United Kingdom Conformity Assessed) marking. As a transitional measure following the UK’s withdrawal from the EU, CE marking may still be accepted for placing on the market for a limited period; therefore, the applicable period and conditions should be confirmed based on relevant guidance. Notifications or authorisations for clinical investigations are also overseen by MHRA under the UK MDR 2002.
In contrast, in NI, the EU MDR and the Regulation (EU) 2017/746 *In Vitro* Diagnostic Medical Device Regulation (EU IVDR) continue to apply under arrangements with the EU. Therefore, devices placed on the NI market must obtain CE marking, and clinical investigations must be conducted in accordance with the requirements of the EU MDR. In addition, products intended for NI may need to bear the UKNI marking alongside the CE marking in certain cases.
This difference also impacts the requirements of clinical investigations. In GB, MHRA notification and ethical review are required prior to the start of an investigation under the UK MDR 2002. In NI, in accordance with the EU MDR provisions, EU-standard requirements for safety and performance evaluation and reporting obligations apply. Therefore, when conducting investigations in both GB and NI, procedures and documentation must comply with each legal framework. As the submission destination and authorisation processes differ, coordination at the planning stage is essential.

2. Classification for determining applicable regulations

When conducting clinical investigations of medical devices in the UK, several classifications may be considered in order to determine the applicable regulations and guidance.

2-1. Regulations applicable to clinical investigations with or without marketing authorisation intent

In GB, clinical research involving medical devices is governed by the UK MDR 2002 as the legal basis, with practical implementation supported by guidance published by MHRA and HRA. Regardless of whether the research is intended to support a marketing authorisation application, the research involving medical devices may fall under the definition of a clinical investigation (CI) under the UK MDR 2002. Therefore, the practical starting point is to determine whether the planned research constitutes a CI that requires procedures with MHRA (notification or application). The determination of CI applicability should be made based on the GB flowchart and accompanying guidance published by MHRA. This involves reviewing decision points according to the characteristics and objectives of the research, such as whether it involves human subjects, the regulatory status of the device, whether the use falls within the marketed indication, and whether the purpose is to evaluate safety or performance. Based on this assessment, the need for an application should be determined, and the regulatory classification of the planned research will be clarified.
In particular in GB, it should be noted that post-market studies conducted under certain conditions may not require a CI application. In addition, even retrospective or non-interventional research may be classified as a CI depending on the study design.
When conducting a CI, the main procedures required prior to initiation are as follows: (i) prior procedures with MHRA (notification or application), and (ii) ethical review by a REC. In conducting clinical investigations, in addition to the framework of the UK MDR 2002, BS EN ISO 14155:2020 is expected to be followed as best practice rather than as a regulatory requirement. Therefore, its principles should be reflected in the planning, conduct, recording, and reporting of the investigation to ensure subject protection and data reliability.

Note: The regulatory framework in NI differs from that in GB as the EU MDR/IVDR apply. Therefore, procedures and determinations regarding clinical investigations should be assessed based on NI-specific guidance (e.g., flowcharts).

[UK MDR]
1) Flowchart (PDF)
Studies under UK MDR 2002 (CI determination flowchart)
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1072413/flowchart_CIs_-_Studies_under_UKMDR2002_v1_A4.pdf

2) Accompanying Guidance to the Flowchart
GB Flow Chart Accompanying Guidancehttps://assets.publishing.service.gov.uk/media/69247ba05f7777c304ba7ee4/GB_Flow_Chart_Accompanying_Guidance_v3.pdf

[EU MDR] (NI)
1) Flowchart
Flow Chart – Clinical Investigations in Northern Ireland

https://assets.publishing.service.gov.uk/media/67619df526a2d1ff182534a1/Flow_Chart_-_Clinical_Investigations_in_Northern_Ireland.png

2) Accompanying Guidance to the Flowchart
NI Flow Chart – Accompanying Guidance
https://assets.publishing.service.gov.uk/media/67619e4126a2d1ff182534a2/NI_Flow_Chart_-_Accompanying_Guidance_v1.0.pdf

2-2. Classification of medical devices requiring clinical investigations

2-2-1. Class classification and approval process (GB: UK MDR 2002)

Class	Overview	Example of Devices	Need for Clinical Investigation
Class I	Low risk	Syringes without needles, standard adhesive bandages, examination lamps	Generally not required if the device is already marked and used within its intended purpose. Additional data may be required if there are special uses or performance modifications.
Class Is / Im	Class I devices that are sterile (Is) or have a measuring function (Im)	(Case-by-case depending on the device)	Evaluation related to sterility (Is) or measurement (Im) is required, but a clinical investigation is generally not required when used within the intended purpose.
Class IIa	Medium risk	Short-term corrective contact lenses, suture needles, standard hearing aids	Conformity assessment is required. A CI may be required if a clinical evaluation is not sufficient to support compliance with the applicable requirements. If gaps arise due to novelty (e.g., new materials or new indications) or specific conditions of use, a CI should be considered.
Class IIb	Medium to high risk	Apnea monitors, ventilators, surgical lasers, diagnostic X-ray sources	Due to higher risk, gaps in the clinical evaluation are more likely, and a CI is therefore more frequently required. A CI may be required if existing data cannot sufficiently demonstrate safety and performance.
Class III	High risk	Pacemakers, hip replacement systems, breast implants, contraceptive IUDs	A clinical investigation is highly likely to be required, and detailed verification is essential.

A UK approved body (conformity assessment body) is designated by MHRA. Under the UK MDR 2002, it assesses whether manufacturers and medical devices meet the applicable requirements and issues the necessary certification (certificate) as the result of conformity assessment. Based on this certification, the manufacturer affixes the UKCA marking, allowing it to be placed on the market of GB. It corresponds to a notified body (third-party conformity assessment of CE marking) in the EU, and in Japan, it plays a similar role as a registered certification body under the third-party certification system.

The criteria for determining whether a clinical investigation is required are as follows. The manufacturer first prepares a clinical evaluation report (CER) and assesses whether existing clinical data adequately demonstrate safety and performance. If the device is used within its intended purpose and sufficient literature and pre-market data are available, a clinical investigation is generally considered unnecessary. However, if data are insufficient due to factors such as new materials, AI technology, or use outside the intended purpose, a clinical investigation is required, and notification to MHRA at least 60 days in advance is required.
Whether a clinical investigation is required depends on the certification status of the device and its intended use. For example, a clinical investigation is required in the following cases:

- A new medical device that has not obtained UKCA marking
- Use of an approved device for a purpose outside its certified intended purpose
- Cases where safety and performance cannot be sufficiently demonstrated based on existing data or literature alone (e.g., highly advanced technological products or devices incorporating AI)

On the other hand, when an approved device is used within its certified intended purpose, or when sufficient existing data are available in the context of post-market clinical follow-up (PMCF), a clinical investigation is generally not required. Determinations are made using the official guidance and checklists provided by MHRA.

3. *In vitro* diagnostic medical devices (IVD)

3-1. Handling of *in vitro* diagnostic medical devices in the GB

In vitro diagnostic medical devices (IVDs) in GB are regulated under the legal framework centered on the UK MDR 2002. Following its withdrawal from the EU, the UK has continued to operate the regulatory system in GB based on the UK MDR 2002, with provisions being updated through EU Exit-related amendments (e.g., SI 2019/791) and subsequent amending SIs (e.g., SI 2023/627 and SI 2024/221).
Furthermore, the UK MDR 2002 constitutes a framework that implemented the former EU directives into UK domestic law. With respect to IVDs, it was established to implement several directives, including the Directive 98/79/EC (IVDD). (Note that the EU IVDR does not apply in GB.)
A key feature of the legal positioning of IVDs is that they are defined as a category of “medical device.” According to GB-specific guidance published by MHRA and based on Regulation 2 of the UK MDR 2002, an IVD is defined as a “medical device which is a reagent, kit, instrument, apparatus, equipment, or system intended by the manufacturer to be used *in vitro* for the examination of specimens derived from the human body for the purpose of providing information (i) concerning a physiological or pathological state, (ii) concerning a congenital abnormality, (iii) to determine the safety and compatibility of donations, including blood and tissues, or (iv) to

monitor therapeutic measures." Accessories are also addressed. Although they do not provide diagnostic information on their own, they may be treated as IVDs under the UK MDR 2002 when they are intended to be used together with a specific IVD. For this reason, elements directly applied to the human body, such as invasive specimen collection devices, are generally addressed under Part II (general medical devices). In addition, IVDs that are intended to evaluate the performance of a product prior to market placement (under development) are defined as devices for performance evaluation. While such devices are outside the scope of the standard conformity assessment route, the preparation of a prescribed statement of conformity and registration with MHRA are required.

3-1-1. Classification

The regulatory classification of IVDs in GB differs from the Class A–D system under the EU IVDR and is instead organized into four categories based on Part IV of the UK MDR 2002. MHRA's GB-specific guidance on IVDs presents four categories in accordance with increasing levels of regulatory control (perceived risk): (a) general IVDs, (b) IVDs for self-testing, (c) IVDs coming within List B of Annex II to Part IV, and (d) IVDs coming within List A of Annex II to Part IV, and clarifies that these categories constitute the basic framework for classification in GB.

Category UK MDR 2002 Part IV	Overview (Regulatory Position: Summary)	Examples	Conformity Assessment (Overview)
General IVDs	Relatively lower regulatory category among the four categories (IVDs that, in principle, do not fall under self-testing, List A, or List B)	Biochemistry, hormone tests, etc.	Conformity assessment is generally carried out primarily through self-declaration (declaration of conformity). Details should follow the MHRA IVD guidance.
Self-test IVDs	Category subject to stronger regulatory control than general IVDs. IVDs intended for use by lay persons.	Self-pregnancy tests, self-blood glucose tests, etc.	Self-declaration alone is not sufficient, and involvement of a third-party certification body (e.g., a UK approved body) may be required, particularly for the assessment of design aspects. Determination of applicability should follow the MHRA IVD guidance.
IVDs coming within List B of Annex II	Relatively higher regulatory category (lower than List A but subject to stronger regulatory control than general IVDs and self-test IVDs).	Rubella, toxoplasmosis, phenylketonuria (PKU), etc.	Conformity assessment is generally required with the involvement of a third-party certification body (e.g., a UK approved body). The conformity assessment route should follow the UK MDR 2002 Part IV and MHRA IVD guidance.

Category UK MDR 2002 Part IV	Overview (Regulatory Position: Summary)	Examples	Conformity Assessment (Overview)
IVDs coming within List A of Annex II	The most highly regulated category among the four categories	HIV, HBV/HCV, ABO/anti-Kell, etc. (including blood donation and transplantation-related testing)	Conformity assessment is generally required with the involvement of a third-party certification body (e.g., a UK approved body). The conformity assessment route should follow the UK MDR 2002 Part IV and MHRA IVD guidance.

3-1-2. Conformity assessment and launch (marking/registration)

For market placement, regardless of the category, IVDs are required to comply with the essential requirements set out in Part IV Annex I. Based on the category, the appropriate conformity assessment route must then be selected. For general IVDs, the process is generally carried out through the manufacturer's declaration of conformity within the prescribed scope (self-declaration based on Annex III). In contrast, for self-test IVDs, confirmation of design aspects intended for use by lay persons is required, and the involvement of a UK approved body may be required for design examination or similar assessments. Furthermore, for IVDs falling under Annex II (List A or List B), conformity assessment involving a UK approved body is generally required.

Finally, at the stage of placing the product on the market following conformity assessment, administrative procedures such as affixing a marking to show conformity (e.g., UKCA) and registration with MHRA become practical requirements. One important exception should be noted: devices for performance evaluation are excluded from the normal conformity assessment procedures. However, this does not mean that regulatory requirements do not apply. For such devices, the manufacturer is required to prepare a statement of conformity (Part IV Annex VIII) and complete registration with MHRA. Therefore, it is important to recognize that the applicable requirements differ depending on the intended purpose of the device (market placement or performance evaluation).

3-2. Clinical investigations / performance evaluation studies for IVDs

3-2-1. Studies to be performed

When conducting a performance evaluation study for an IVD in GB, the IVD is treated as a "device for performance evaluation" under Part IV of the UK MDR 2002. According to the MHRA GB-specific guidance on IVDs, devices for performance evaluation are described as IVDs intended by the manufacturer to be the subject of one or more performance evaluation studies, and performance evaluation must be conducted in accordance with this framework.

In a performance evaluation study of an IVD itself, the performance of the device is assessed using the IVD under evaluation, and the results are accumulated as technical documentation and data. In such cases, the process must proceed in the following order: "first ensuring that the requirements applicable to devices for performance evaluation (preparation of a statement of conformity and registration with MHRA) are met, and then conducting the performance evaluation."

Accordingly, at the beginning of the study planning stage, it is necessary to proceed on the premise that the IVD will be handled as a device for performance evaluation, and to prepare the required documentation and complete the registration in advance. This constitutes a key practical point in the implementation process.

The legal checkpoints when planning a performance evaluation study of an IVD itself are threefold: (i) confirming that the IVD can be classified as a device for performance evaluation, (ii) preparing a statement of conformity in accordance with Part IV Annex VIII, and (iii) completing registration with MHRA. Designing and conducting the performance evaluation study after satisfying these requirements constitutes an approach that is consistent with the GB regulatory framework.

3-2-2. Reporting of adverse events

In GB, adverse event reporting (safety reporting) for IVDs is organized not under Article 76 of the EU IVDR, but under the GB medical device vigilance system based on the post-market surveillance requirements (Part 4A) newly introduced into the UK MDR 2002. Manufacturers (including the UK responsible person, if applicable) are required to report serious incidents, adverse trends, and field safety corrective actions (FSCAs) related to the IVD to MHRA, in accordance with the specified requirements and timelines. Reporting timelines are classified according to the level of seriousness. A serious public health threat must be reported no later than 2 days, death or an unanticipated serious deterioration in a person's state of health no later than 10 days, and other serious incidents no later than 15 days, after the manufacturer becomes aware of the incident. Reports are submitted through the online reporting environment designated by MHRA, the Manufacturer's Online Reporting Environment (MORE). Where necessary, an initial report may be submitted with incomplete information, followed by supplementary and final reports. For performance studies conducted in NI, safety reporting is organized in accordance with the framework of the EU IVDR. Where the European Database on Medical Devices (EUDAMED) is not yet fully operational, reporting is, in practice, carried out using alternative procedures in accordance with the Medical Device Coordination Group (MDCG) guidance.

3-3. Handling of *in vitro* diagnostic medical devices (IVDs) in NI (differences from GB)

In NI, a regulatory framework different from that of GB applies under the Windsor Framework. Specifically, IVDs in NI are regulated based on the EU IVDR, and therefore the applicable legislation differs from the UK MDR 2002 (Part IV), which forms the core regulatory framework in GB. Accordingly, instead of being organized according to the IVDD-based four categories used in GB (general IVDs, self-test IVDs, Annex II List B, and Annex II List A), IVDs in NI must be assessed and brought into conformity in accordance with the classification system of the EU IVDR (risk Classes A to D) and the related requirements.

This difference also affects practical aspects of market placement and investigations. IVDs placed on the market in NI are, in principle, organized on the basis of CE marking in conformity with the EU IVDR, and, where necessary, NI-specific marking requirements (such as the UKNI marking) must also be considered. In addition, where a performance evaluation study for an IVD is conducted in NI, the study must be planned, conducted, documented, and reported in accordance with the provisions on performance studies under the EU IVDR, rather than under the framework of Part IV of the UK MDR 2002 used in GB.

Furthermore, to ensure the implementation and enforcement of the EU IVDR in NI, the domestic legal framework has been supplemented by the Medical Devices (*In Vitro* Diagnostic Devices etc.) (Amendment) Regulations 2024 (SI 2024/221). Accordingly, for projects conducted in NI, it is necessary first (1) to identify the applicable requirements on the basis of the EU IVDR, and then (2) to confirm consistency with the relevant domestic law governing implementation and enforcement in NI (including SI 2024/221).

Chapter 2: Detailed requirements for clinical investigations

1. Regulatory framework for the authorisation of clinical investigations by the UK regulatory authority

In GB, companies planning to conduct clinical investigations that require prior notification to the regulatory authority (e.g., investigations involving devices without marking or off-label use) are required to notify MHRA at least 60 days before the start of the investigation. The application is submitted through IRAS together with the required documentation. The submission package includes the clinical investigation plan (protocol), technical specifications and risk assessment, the investigator's brochure where applicable, patient information sheets and participant consent forms, as well as documentation demonstrating insurance coverage and indemnity arrangements. Following submission, MHRA reviews the application and notifies the applicant by letter of either no objection or objection within 60 days. During this period, ethical review by a REC is conducted in parallel. Where the investigation combines a clinical trial of an investigational medicinal product (CTIMP) and a medical device investigation, the review by MHRA and REC may be conducted together under the combined review process.

[Note: Regulatory framework in NI]
In NI, unlike in GB, a regulatory framework aligned with the EU medical device regulations (MDR and IVDR) applies. Accordingly, for clinical investigations that include study sites in NI, the submission is made to MHRA as in GB; however, the application requirements and the basis for review must be organized in accordance with the NI regulatory framework. In addition, in NI, the outcome of the regulatory review is expressed as "authorisation or refusal" by the authority, rather than the "no objection or objection" approach used in GB. Consequently, a clinical investigation may not be conducted without prior authorisation from the authority. Furthermore, in NI, the standard timeframe for the preliminary procedure (authority's review) is 45 days. Where the involvement of external experts is required, this period may be extended by a further 20 days. In addition, applications involving healthcare institutions in NI may be handled together with those involving institutions in GB for the same investigation. Therefore, the regulatory assessment and procedures may not necessarily follow the same approach as for investigations conducted solely in GB. In particular, even in cases where notification to the authority may not be required in GB (e.g., studies corresponding to post-market use within the intended purpose), the regulatory requirements and procedural considerations in NI may differ. Accordingly, when planning investigations that include NI, it is important to clearly describe the NI-specific requirements and operational differences in addition to the explanation of the GB framework.

2. Compliance with ISO 14155

In GB, ISO 14155 (BS EN ISO 14155:2020) is not positioned as a direct obligation (i.e., a designated standard) under the applicable legislation for conducting clinical investigations of medical devices. However, regulatory authority guidance indicates that compliance with ISO 14155 is expected as best practice. In its official guidance on the notification and review of clinical investigations, the regulatory authority, MHRA specifies the documentation required for submission, such as the clinical investigation plan, investigator's brochure, and patient information sheet/informed consent form (PIS/ICF), as well as the key review considerations, including ethics, safety, and the validity of the procedures. These are implicitly expected to be

aligned with the GCP principles (design, conduct, recording, and reporting) set out in ISO 14155. The MHRA guidance further supplements these requirements at the operational level and specifies detailed expectations for safety monitoring during the clinical investigation, procedures for modifications, reporting in the event of early termination, and the evaluation of human factors. In particular, serious adverse events and clinical investigation deviations must be reported to MHRA without delay, and appropriate corrective actions must be implemented where necessary.

[Note: Relationship with ISO 14155 (BS EN ISO 14155:2020) in NI]
In NI, clinical investigations are conducted under a framework aligned with the EU MDR/IVDR. Accordingly, ISO 14155 is regarded as a GCP standard representing best practice for operationally meeting EU clinical investigation requirements and should be reflected in the planning, conduct, recording, and reporting of clinical investigations. Therefore, where NI is included, documentation and operational processes should also be prepared on the basis of alignment with ISO 14155, with particular emphasis on subject protection and data reliability.

3. REC/ IRB approval process and regulatory framework

In GB, clinical investigations of medical devices are structured as a dual process requiring both regulatory review by MHRA and ethical review by REC, as described above. In terms of application timing, it is standard practice to prepare the full set of application documents via IRAS and to proceed with MHRA procedure and REC review (and, where applicable, governance approvals depending on the research region and site classification) in parallel. Therefore, rather than “one preceding the other,” both an MHRA decision (e.g., no objection) and a favourable opinion from a REC are required as conditions for initiation.
For submission, documents such as the clinical investigation plan (protocol), investigator’s brochure, patient information sheet (PIS)/participant consent form, and technical documentation (including risk assessment and relevant data) are generally prepared and submitted via IRAS. The reviews are generally conducted in parallel: MHRA focuses primarily on safety, performance, and the validity of the investigation design, while the REC evaluates ethical aspects, such as subject protection, the appropriateness of the consent process, and the acceptability of risks and burdens.
Regarding the establishment and operation of REC, multiple RECs are organized and operated nationally in accordance with the Governance Arrangements for Research Ethics Committees (GAfREC) based on standardized operating procedures. Each clinical investigation is assigned to an appropriate REC according to the nature of the research through an online allocation system (booking mechanism). Depending on the characteristics of the research, review by RECs capable of handling specific areas (flagged RECs) may be required; however, unlike systems such as that of the Netherlands, where a “limited number of central RECs accepted by the country review almost all medical device clinical investigations,” the UK adopts a decentralized review system involving multiple RECs.

[Note: Ethical review by RECs in NI]
In NI, review is conducted by two RECs within the Health and Social Care (HSC), namely HSC REC A and HSC REC B. These RECs are supported by the Office for Research Ethics Committees Northern Ireland (ORECNI) and conduct reviews within a framework aligned with the UK-wide system (including GAfREC and standardized procedures). Applications follow the same IRAS-based submission and booking process as in GB.

4. Regulatory framework for conflicts of interest (transparency-related)

In clinical trials of medical devices in GB, the management of conflict of interest (COI) is regarded as an important element related to the trust of research and the fairness of review. At a minimum, transparency-related information and guidance on clinical investigations of medical devices published by HRA set out process requirements, including the management of interests on the part of ethics review bodies and those involved in the review, rather than exhaustively specifying the COI of individual investigators. With respect to applicants (sponsors), information related to COI is also reviewed as part of the application documents during ethical review.

A notable feature in GB is that COI management on the part of the regulatory authorities (such as MHRA) is clearly institutionalized. In particular, MHRA has established and published policies for managing COI among experts and reviewers in order to avoid decisions within the organization being influenced by other interests. These policies are intended to prevent situations in which decisions by those with review authority lack neutrality or appear to lack neutrality.

Furthermore, principles relating to transparency in GB are regarded as a fundamental basis supporting the neutrality of the research process and of evaluation and review, and it is clearly stated in the HRA transparency guidance that research should be conducted fairly and that its results should be appropriately made public, thereby contributing to the trust of research participants and society as a whole.

Overall, COI management in GB is structured to ensure neutrality not by “detailed specification of individual researchers’ COI,” but by multiple mechanisms, including review by ethics committees, internal COI management by the regulatory authorities, and the assurance of transparency across the research as a whole.

[Note: COI management in NI]

In clinical investigations of medical devices in NI, COI management is also regarded as an important element related to the trust of research and the fairness of review. Ethical review in NI is conducted by HSC RECs and supported by ORECNI; these operate within the framework of the UK-wide Research Ethics Service (RES) and are managed under common standards and procedures. The framework for COI management in NI is broadly consistent with that in GB.

5. Regulatory framework for information provision, informed consent, and multilingualization

In GB, with respect to the provision of information and the obtaining of consent in clinical investigations of medical devices, detailed procedures and review criteria for consent are implemented through a framework combining multiple regulations and systems, not solely in legislation.

In GB, in order to initiate a CI subject to the medical device regulations, ethical approval by REC is required, and in the course of this ethical review, the appropriateness of the information provided to participants and the methods for obtaining consent are subject to review. Through the ethical review process, investigators are required to demonstrate the appropriateness of documents and procedures related to informed consent. Clinical investigations of medical devices in GB are primarily governed under the framework of the UK MDR 2002.

Furthermore, MHRA clearly requires the submission of the “patient information sheet (PIS)” and the “participant consent form” as part of the documentation for CI applications. This requirement

is incorporated into official guidance as part of the application requirements for clinical investigations and serves to ensure that participants are provided with clear information on the purpose, risks, benefits, and impacts of participation in the investigation, and that consent is given voluntarily based on such understanding.
In the UK, there is no system in which multilingual requirements for clinical investigations of medical devices are stipulated on a provision-by-provision basis in legislation. However, it is an ethical and legal requirement that information provided to study participants be presented in a "form that is understandable," and in order to achieve such understandability, measures such as translation (multilingualization) and interpretation may be required depending on the content of the research and the target population. Rather than legislation explicitly prescribing an "obligation of translation" in provisions, the necessity for multilingual measures is assessed within the framework of HRA and REC review and operations.
While the general approach to the provision of information and the obtaining of consent is broadly the same in NI, it should be noted that the regulatory basis (applicable legislation) for clinical investigations of medical devices in NI differs from that in GB, and the EU MDR/IVDR apply in NI.

6. Regulatory framework for compensation for subjects

In clinical investigations of medical devices in GB, with respect to requirements relating to subject compensation, methods of compensation or amounts of indemnification are not set out in detail on a provision-by-provision basis in a single specific piece of legislation.
Under the UK MDR 2002, notification to MHRA and ethical review (REC approval) are required in order to conduct a clinical investigation. While this legislation does not specify the details of compensation on a provision-by-provision basis, it requires that subject safety be ensured and that appropriate risk management measures be in place for the conduct of clinical investigations. As part of such safety assurance, the adequacy of compensation and insurance is incorporated in practice.
In addition, MHRA clearly states in its official guidance "Clinical investigations for medical devices" that "evidence of insurance or indemnity" must be submitted as part of the application documentation for clinical investigations. This is required to demonstrate that the sponsor has the capacity to assume adequate compensation responsibility in the event that subjects suffer harm as a result of participation in the investigation, and constitutes a central practical requirement of the compensation framework.
Furthermore, REC reviews not only the appropriateness of the clinical investigation plan but also, from the perspective of subject protection, whether compensation and insurance systems are appropriately ensured. If the compensation system is insufficient, approval will not be granted.

In NI, although the applicable legislation is the EU MDR/IVDR, the fundamental approach of ensuring appropriate compensation (insurance and indemnity schemes) from the perspective of subject protection is broadly the same as in GB. It should be noted that in NI, the EU MDR explicitly requires the establishment of a system for compensation for damage (e.g., insurance or guarantees).

7. Regulatory framework for safety reporting to the regulatory authority

In clinical investigations of medical devices in GB, the reporting of safety information (such as adverse events and device deficiencies) is regarded as an essential element for ensuring the

protection of participants and the ethical conduct of the investigation and is implemented within a multi-layered structure combining a legal framework and detailed operational requirements set out in the MHRA guidance.
The UK MDR 2002 (and related regulatory frameworks) do not specify detailed classifications of adverse events or specific reporting formats on a provision-by-provision basis; however, these frameworks are structured on the premise that the sponsor, as the party conducting the clinical investigation, is responsible for accurately identifying safety-related information and reporting it to MHRA as necessary.
According to the MHRA official guidance, events identified during a clinical investigation that fall under serious adverse events (SAEs), serious adverse device effects (SADEs), or device deficiencies are required to be reported without delay and are treated as information directly relevant to decisions on the continuation of the investigation and the evaluation of participant safety. Furthermore, issues affecting the safety of the investigation and significant procedural deviations are also subject to reporting to MHRA without exception. These detailed reporting requirements form the basis for MHRA to appropriately monitor safety risks throughout the investigation and to take necessary supervisory measures, and constitute a core component of safety management in clinical investigations of medical devices in GB.
In addition, in GB, in order to enhance the accuracy of safety monitoring, reporting of SAEs and related information is required to be conducted through MORE, thereby ensuring the timeliness and systematic handling of reports. MORE is the official platform for centrally receiving all medical device-related incident reports, and the submitted information is analyzed by MHRA. Regulatory actions and risk mitigation measures are considered as necessary.

[Note: Differences in NI]
In NI, as in GB, the reporting of safety information in clinical investigations of medical devices is an important element for ensuring the protection of participants and the ethical conduct of the investigation. However, as NI is subject to the EU MDR/IVDR under the Windsor Framework, it is necessary to note that the legal basis (applicable legislation) and the reference framework for terminology and procedures differ from those in GB.
The MHRA official guidance distinguishes between studies conducted in GB only, those conducted in GB and NI, and those conducted in NI only, in terms of applicability and explanatory content. For studies in NI, it is assumed that the recording and reporting of safety information are carried out in accordance with the requirements of the EU MDR/IVDR. Therefore, where sites in NI are included, it is important to ensure alignment of the clinical investigation plan (CIP) and procedures, taking into account that the scope and definitions of reportable events, as well as the basis for reporting formats and timelines, may differ from those in GB.
With regard to adverse incident reporting for medical devices, manufacturers (or those reporting on their behalf) are, in principle, required to submit reports to MHRA via MORE, regardless of whether the events occur in GB or NI. MORE is also positioned as the reporting route in NI.

8. Regulatory framework for protection of subject information (protection of personal data and healthcare information)

In the UK, the protection of personal data and healthcare information handled in clinical investigations of medical devices is not specified in detail by a single piece of legislation.
In the UK, even after withdrawal from the EU, the principles of data protection legislation (General Data Protection Regulation, GDPR) have been incorporated into domestic law as the UK GDPR,

and their detailed implementation is supplemented by the Data Protection Act 2018 (DPA 2018) and the Data (Use and Access) Act 2025 (DUAA).
These constitute the fundamental legal framework for the handling of personal data, in particular "data concerning health," which are highly sensitive in nature. HRA, as a public body, indicates that the application of the DPA 2018 and the UK GDPR is a prerequisite in the handling of research data and requires research institutions to appropriately determine "under what conditions the processing of personal data is permitted" and "what security measures are necessary."
The legal framework for personal data protection under the UK GDPR, the DPA 2018, and the DUAA is common to both GB and NI.

9. Regulatory framework for disclosure of clinical investigation data

In the clinical investigations of medical devices in the UK, ensuring the transparency of study content and results is positioned as an essential element for the protection of participants and the maintenance of public trust. However, there is no UK-specific registry or centralized database dedicated to medical devices comparable to EUDAMED in the EU or Japan Registry of Clinical Trials (jRCT) in Japan.
The HRA transparency guidance indicates the importance of registering research in publicly accessible databases and making results publicly available after completion. However, among these transparency obligations, those clearly established as new statutory requirements are limited to CTIMPs (under the amended regulations effective from April 28, 2026), and a comparable new legal framework has not been uniformly extended to clinical investigations of medical devices. On the other hand, HRA positions registration in publicly accessible registries as a condition for REC approval for "clinical trials," including clinical investigations of medical devices, and strongly recommends registration and results disclosure in public registries such as ClinicalTrials.gov and the International Standard Randomised Controlled Trial Number (ISRCTN) registry.
In NI, as the EU MDR/IVDR apply, EU regulatory frameworks such as EUDAMED are involved in medical device regulation. However, based on HRA research transparency requirements (registration in public registries and disclosure of results), ethical review requirements in NI (HSC REC A and HSC REC B) likewise require registration and results disclosure in public registries such as ClinicalTrials.gov and the ISRCTN registry, as in GB.

10. Regulatory framework for digitalization of data

As a key UK official document directly related to digitalization, MHRA provides guidance on electronic health records (EHRs).
First, electronically maintained medical records must have sufficient completeness and integrity to allow the course of a clinical trial to be faithfully reconstructed at a later stage. This requirement is essential for ensuring the credibility of trial results. If records are inadequate and the trial cannot be reconstructed, the trial may be considered non-compliant with fundamental principles such as ISO 14155. MHRA considers the inability to reconstruct a clinical trial to be a significant regulatory risk that may constitute a regulatory breach and undermine the reliability of clinical trial data. It is also required that such records comply with GCP requirements applicable to CTIMP, etc. Furthermore, appropriate security and access control measures must be in place when third parties who have access to electronic records, such as monitors or auditors, view the records.

In the UK, electronic signatures may generally be used in clinical trials, and properly designed electronic signatures are considered “valid signatures.” However, not all forms of electronic signatures are acceptable. According to joint guidance issued by MHRA and HRA, specific requirements are set out to ensure reliability through identity, integrity, and timestamp.

Appendix: List of laws, regulations, and guidance cited in this summary (in order of appearance)

1. Medicines and Medical Devices Act 2021
   https://www.legislation.gov.uk/ukpga/2021/3/contents

2. UK Medical Devices Regulations 2002
   Abbreviation: UK MDR 2002
   https://www.legislation.gov.uk/uksi/2002/618/contents
   - Part IV (In Vitro Diagnostic Medical Devices)
   - Part 4A (Post-market surveillance requirements)

3. Medical Devices (Amendment etc.) (EU Exit) Regulations 2019
   https://www.legislation.gov.uk/uksi/2019/791/contents

4. Medical Devices (Amendment) (Great Britain) Regulations 2023
   https://www.legislation.gov.uk/uksi/2023/627/contents/made

5. Medical Devices (In Vitro Diagnostic Devices etc.) (Amendment) Regulations 2024
   https://www.legislation.gov.uk/uksi/2024/221/contents/made

6. UK General Data Protection Regulation
   Abbreviation: UK GDPR
   https://ico.org.uk/about-the-ico/what-we-do/legislation-we-cover/general-data-protection-regulation/

7. Data Protection Act 2018
   Abbreviation: DPA 2018
   https://www.legislation.gov.uk/ukpga/2018/12/contents

8. Data (Use and Access) Act 2025
   Abbreviation: DUAA
   https://www.legislation.gov.uk/ukpga/2025/18/contents

9. Regulation (EU) 2017/745 on medical devices
   Abbreviation: MDR
   https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02017R0745-20250110

10. Regulation (EU) 2017/746 on in vitro diagnostic medical devices
    Abbreviation: IVDR
    https://eur-lex.europa.eu/eli/reg/2017/746/oj/eng

11. Directive 98/79/EC on *in vitro* diagnostic medical devices (no longer in force)
    Abbreviation: IVDD
    https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31998L0079

12. In vitro diagnostic medical devices: guidance on legislation

Term used in this summary: GB-specific guidance published by MHRA
https://www.gov.uk/government/publications/in-vitro-diagnostic-medical-devices-guidance-on-legislation

13. ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice
Abbreviation: ISO 14155

14. Governance Arrangements for Research Ethics Committees
Abbreviation: GAfREC
https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/GAfREC_Final_v2.1_July_2021_Final.pdf

15. Research transparency
Term used in this summary: HRA transparency guidance
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-transparency/#:~:text=If%20you%20work%20in%20research,research%20transparency%20in%20the%20UK.

16. Guidance on legislation: Clinical investigations of medical devices – compiling a submission to MHRA
https://assets.publishing.service.gov.uk/media/62f52991d3bf7f4c6a8677f8/Guidance_for_mfrs_-_compiling_a_submission_to_MHRA_-_May_2021.pdf

17. Guidance on legislation: Clinical investigations of medical devices – guidance for manufacturers
https://assets.publishing.service.gov.uk/media/68e3b0abef1c2f72bc1e4e17/Guidance_for_mfrs_on_clinical_investigations-October_2025.pdf

18. MHRA position statement and guidance: Electronic Health Records
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/470228/Electronic_Health_Records_MHRA_Position_Statement.pdf

19. Joint statement on seeking consent by electronic methods
Term used in this summary: Joint guidance issued by MHRA and HRA
https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/hra-mhra-econsent-statement-sept-18.pdf