Points to Consider for Operation and Management to Ensure the Reliability of Registry Data for Use in Application Dossiers of Pharmaceuticals and Medical Devices

[March 31, 2022 Ver1.0]

AMED Research on Regulatory Science of Pharmaceuticals and Medical Devices

Title of Research Project: Regulatory science research to achieve efficiency of clinical research and development with the utilization of a patient registry

［Grant Number: JP21mk0101154］

Subproject Title: Review of the quality management system and points to consider

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（Note）This document was prepared by the research team by compiling the research results from fiscal years 2019 to 2021.

1. Introduction

Pharmaceutical regulatory schemes concerning real-world medical data and evidence（hereinafter referred to as "medical RWD/RWE"), and derived from their analysis, have been undergoing remarkable changes considering both the development and post-marketing phases of drugs, medical devices, and regenerative medicine products（hereinafter referred to as "drugs, etc."）.[1)]

For the clinical development of drugs, etc., the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use（ICH）has proposed the "GCP Renovation,"[2)] which includes the modernization of the E8 Guideline and subsequent revision of the E6 Guideline. According to the Concept Papers and Business Plans issued in November 2019, the revised E6 Guideline covers clinical studies incorporating pragmatic clinical trials and decentralized clinical trials in Annex 2. In the US,"The 21st Century Cures Act" [3)] refers to the proposal of speeding up the approval review by making clinical trials more efficient. Moreover, in some cases medical RWD/RWE was used in the approval review for the expansion of applications. Also, in Japan, the Clinical Innovation Network（CIN）plan[4)] was proposed by the Japan Revitalization Strategy（Cabinet Decision dated June 30, 2015）; furthermore, utilizing the natural history data of patient registries as the control group in clinical trials for an approval review is now under consideration.

With regards to post-marketing surveillance, the implementation of a conditional accelerated approval system for pharmaceuticals[5)] positioned medical RWD/RWE, such as the medical information database network（MID-NET）project[6)] and patient registries, as surveys that require implementation for marketing approval. Moreover, the Ministry of Health, Labour, and Welfare（MHLW）ordinance related to standards for conducting post-marketing surveys and studies on drugs"[7)] provided a new post-marketing database study, which was conducted using medical databases like MID-NET, and by utilization of medical RWD/RWE for post-marketing pharmacovigilance.

Additionally, concerning the utilization of registry data for regulatory purposes, basic principles on the utilization of the registry for applications"[8)] and points to be considered for ensuring the reliability in the utilization of registry data for applications"[9)] were investigated by the Pharmaceuticals and Medical Devices Agency（PMDA）and issued by the MHLW on March 23, 2021.

This document aims to propose specific measures to ensure the reliability of regulatory purpose utilization of especially"patient registry"data from medical RWD/RWE that were discussed by AMED/Shibata Group（CIN）.

2. Objectives and background of this proposal

The challenges in the utilization of patient registry data for regulatory purposes seem to be barriers between the Pharmaceutical and Medical Device Act（ICH）and ethical principles concerning life science and medical research. These could be barriers on the regulatory side as well as on the side of researchers. Similarly, there could be a difference in understanding among interested parties concerning "drugs" and "medical devices."

To overcome such barriers and promote the utilization of patient registry data for regulatory purposes, this proposal aimed to demonstrate the conduct of primary studies related to registry establishment, which could contribute to assuring the reliability of registry data, strategies of operation and management, and specific examples of registry data utilization.

The "Handbook on the establishment and operation of registries ver. 1.0"（hereinafter referred to as "Kokudo Group's Handbook"）[10)] was created by AMED Kokudo Group（CIN）, considering that it would be utilized for an academia-based general patient registry, and not for regulatory purposes. The Shibata Group investigates the utilization of registry data for regulatory purposes, which has not been referred to in Kokudo Group's Handbook.

3. Scope

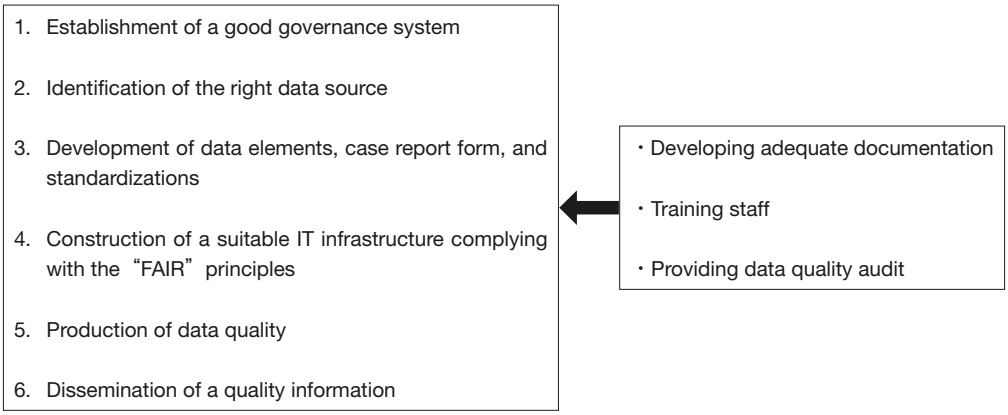
This proposal is applicable not only to medical RWD from patient registries（e.g., disease and product registries）, but also to the other medical RWD considering the data source of patient registries such as electronic medical records and electronic patient-reported outcomes（ePROs）. The target diseases include rare diseases（rare cancers, rare intractable neurologic diseases, pediatric diseases, etc.）, wherein conducting conventional randomized controlled trials（RCTs）is challenging; or diseases wherein conducting placebo-controlled studies are ethically challenging. Registry data could be used for regulatory purposes: 1）as an external control of clinical studies for efficacy and/or safety evaluation in applications; 2）to complement or substitute clinical studies for efficacy and/or safety evaluation in applications; and 3）in the evaluation of drugs and medical devices with conditional approval and of regenerative medicine products with conditional and time-limited approval. However, the abovementioned scope should be flexibly revised based on various technological innovations and the development of regulatory science in the future.

4. Objectives and background of patient registry establishment and operation（academic viewpoint）

As in Kokudo Group's Handbook,"registry" is a term widely used in the fields of medicine and healthcare, but it has no consistent definition. Kokudo Group's Handbook cites the following definitions presented by the US Agency for Healthcare Research and Quality（AHRQ）:"A patient registry is an organized system that uses observational study methods to collect uniform data（clinical and other）to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes."[11] Also citing other several definitions, Kokudo Group's Handbook defines a patient registry as"a system that collects medical information or health information on particular disease, disease group, health condition or exposure, or a database established by it." Although not specified in this definition, registries generally use observational study approaches, as defined by the AHRQ. Obtaining some outcome requires continuous data collection, and therefore, prospective cohort or retrospective cohort approaches are likely to be applied as a study design. The PMDA has investigated two guidelines, in which a registry is defined as "a systematic system to collect standardized data to evaluate specific outcomes related to the following matters: the specific disease, the use of drugs, medical devices and regenerative medicine products, etc. or the populations defined by specific conditions（e.g., age, pregnant women, and specific characteristics of patients）. Registry data may be prospectively obtained or retrospectively used". Most Use-results surveys conducted for drugs and medical devices based on the Pharmaceutical and Medical Device Act are, although often not clearly recognized, have a design that can be regarded as prospective cohort or retrospective cohort, substantially similar to registries.

The characteristics, purposes, etc. of registries have already been detailed in Kokudo Group's Handbook. The handbook describes various purposes of registry, including description of natural history of disease, assessment of clinical practice, and evaluation of clinical usefulness and cost-effectiveness. To achieve these purposes different from those in interventional studies, registries are often different from interventional studies in terms of research protocol and operation: for example, registries for patients with particular diseases or patients receiving a particular medical technology are designed to enroll as many patients as possible comprehensively without stringent exclusion criteria; test data, which is unlikely to be obtained from all patients but is valuable even in a small number of cases, is also included in the data collection item; and management is performed for a long time with few funds. Due to these characteristics, there may be which are generally regarded as weaknesses in data quality control: for example, it is difficult to collect all data without exception; occasionally, the primary outcome cannot be collected, and high-quality and high-cost systems as recommended by interventional studies cannot be used due to a low operating budget. In addition, even if patient registries are comprehensive, the collected data may contain systematic bias for various reasons, including participating sites, budget, medical insurance covering of target diseases, and method to provide incentives for registration.

Therefore, it is true that registries are more likely to have characteristics that could be viewed as defects in quality control compared with interventional studies conducted under strict regulations, such as the Pharmaceutical and Medical Device Act. However, registries have been regarded as an effective method of evidence accumulation in clinical practice where interventional studies are virtually impossible to be conducted. Even now, registries are an important research approach, especially in the surgical field, including emergency medicine and medical transplantation, and in the field where the number of patients is extremely small, such as intractable diseases and rare diseases; they are also used for formulating clinical practice guidelines. Recently, measures for the establishment and operation of a reliable and good-quality registry have been considered. The AHRQ has published"Registries for Evaluating Patient Outcomes: A User's Guide" in 2007. The 1st and subsequent editions refer to registry "Quality," and the 3rd edition states "As a general rule, quality should be evaluated by elements that directly impact the ability of the registry to achieve its main objectives. In other words, a registry must be fit for its purpose" and presents "essential elements of good practice" at each stage of research designing and implementation. In 2018, a European group also released recommendations for improving the quality of disease registries,[12] providing a total of 17 recommendations in terms of 11 elements, including the registry definition, classification, governance, data source, case report form, data standardization, IT infrastructure, and data quality（**Figure 1**）. Presumably, in the discussion of registry"quality"based on these, it is preferable to aim for the academic "fit-for-purpose" quality control that each registry originally aims at, rather than applying the "one-size-fits-all" rule, and it is necessary to consider the balance of various elements associated with individual registries. Discussions that contribute to the improvement of the registry quality as a whole while keeping an eye on the recent activities of research-



Note）"FAIR": a set of four principles（Findable, Accessible, Interoperable, and Reusable）for humans and computers proposed by FORCE11 to describe how open data should be made public.

Figure 1 A framework for the quality management of rare disease registries (modified from Reference 12)

ers aiming to improve the quality of registries are expected to help further improve medical standards in areas where interventional studies are difficult.

5. Environment considering the use of patient registry data as application data for the marketing approval of drugs, etc.

5.1 Circumstances in Japan

5.1.1 Clinical Innovation Network（CIN）

The Clinical Innovation Network（CIN）is a scheme that aims to improve the clinical development environment to facilitate efficient implementation of clinical trials/studies by using the information on various diseases registered in disease registration systems (patient registries), etc., with the collaboration of relevant organizations. The CIN was selected as one of the 2020 Japan Challenge Projects and as a specific scheme for the "Japan Revitalization Strategy Revised in 2015 and 2016" and "Future Investment Strategy 2017 and 2018." In the development of new drugs and post-marketing pharmacovigilance activities, new approaches for clinical development and safety evaluation using patient registries have been garnering global attention. Hence, there is a compelling need to establish a network of relevant organizations and clinical trials consortium of industries and academic institutions to efficiently use patient registries for clinical trials/studies as well as for conducting regulatory science studies concerning clinical evaluation methods using patient registry data.

5.1.2 Guidelines studied by the PMDA

The PMDA, an agency in charge of reviews for approval, re-examination, and the evaluation of the usage results of drugs, etc., has established "Basic principles on utilization of registry for applications" and "Points to consider for ensuring the reliability in utilization of registry data for applications," primarily for companies that could be applicants for the marketing authorization of drugs, etc. These notifications were issued by the MHLW on March 23, 2021.

5.2 Circumstances outside Japan

5.2.1 Foreign regulatory authorities

In the field of medical devices, domestic as well as international cooperation has been promoted in terms of utilization of data other than clinical trial data.

In the regulatory approval systems in the field of medical devices, wide differences exist among Japan, US, and European countries. The regional difference is particularly significant in Europe, where CE marking by an authorized third party is essential; therefore, conducting clinical trials is not always necessary for obtaining marketing approval. Under such circumstances, the Global Harmonization Task Force（GHTF）was founded in 1992 with the participation of Japan, US, EU, Canada, and Australia to promote international coordination. The deliverables of GHTF are available on the PMDA website. After the dissolution of the GHTF in 2012, the International Medical Device Regulators Forum（IMDRF）was established to discuss various issues taken over from the GHTF. The deliverables of the IMDRF are also available on the PMDA website. Notably, the Registry Working Group, one of the working groups of the IMDRF, focused on medical device related registries, which were initially diverse in nature, and summarized discussions on the definitions, analysis methodologies, and qualities of registries used by regulatory authorities.

During the working period of the IMDRF, an article

titled "Real-world evidence—what is it and what can it tell us?" was published in the *New England Journal of Medicine* mainly by persons affiliated with the U. S. Food and Drug Administration（FDA）at year-end 2016, which immediately aroused public interest in the concepts of "real-world evidence（RWE）" and "real-world data（RWD）." In 2018, the medical device division as well as the FDA, as a whole, published the "Real-world evidence program," providing definitions of relevant terms and a summary of basic concepts. In 2020, the European Medicines Agency（EMA）published a draft guideline on registry-based studies providing a definition of a registry-based study and that of a patient registry separately to clarify requirements for registry-based studies.

5.2.2　Medical device field

In this section, we wish to highlight the achievements of the IMDRF Registry Working Group, which worked ahead of other groups for the international harmonization of registries. The IMDRF published three documents presenting a definitions of terms（N33）, methodologies（N42）, and assessment tools（N46）, respectively.

In the N33 document, on the basis of international harmonization, a medical device registry is defined as "an organized system that primarily aims to increase the knowledge on medical devices contributing to the improvement of the quality of patient care." The document evaluates existing registries after establishing the following indicators to evaluate the effects, value, and sustainability of each registry:（1）device identification data,（2）quality enhancement system,（3）stakeholder identification,（4）efficiency,（5）timely action,（6）transparency,（7）linkability, and（8）consideration for product lifecycle.

The N42 document summarizes the methodologies of the international harmonization of registries. With respect to medical devices, in particular, the same product is used in different countries, and could therefore be applied being aligned with regional registries. The document provides points to consider as well as the advantages and disadvantages considering the above situation. Note that the N42 document discusses registries with a focus on the total product lifecycle（TPLC）of medical devices, which is expected to contribute to the enhancement of the availability of information that could be significant evidence for decision-making, such as long-term evaluation, evaluation of outcomes of diseases with a markedly low incidence, and comparative studies of effectiveness.

For cases described in the N33 or N42 document, see Sase et al.（2017）[13], wherein the cases are presented.

In the N46 document, seven cases were assumed to represent categories to be used by medical device regulatory authorities. The document defines a list of requirements for each category and provides recommendation levels for the discussion/handling of such factors when relevant regulatory authorities use registry data（**Table 1**；modified from IMDRF N46[14]）. The seven categories correspond to registries having various natures in terms of robustness of the registry process. Based on the TPLC, highly reliable, robust, and appropriate analysis methods should be used for cases involved in highly sophisticated decision-making, such as initial marketing approval. Meanwhile, there are some other cases for which decision-making can be undertaken with fewer requirements depending on the purpose of use, such as finding safety signals. Although the document defines requirements for initial marketing approval and additional indications, this does not mean that the IMDRF Registry Working Group recommends the use of registries in such activities while preparing the relevant dossier. Attention should be paid to the fact that the IMDRF Registry Working Group considers the above for limited cases, such as use of a medical device for a rare disease, or as a simultaneous control in a clinical study for initial marketing approval, and cases wherein an agreement is reached with relevant regulatory authority for additional indications, taking account of local circumstances.

For the respective factors, the definition of the medical device registry established in the N33 document could serve as a useful reference.

5.2.3　Pharmaceutical field

In the third ICH conference held in Osaka in November 2016, the FDA proposed the renovation of GCP（i.e., modernization of ICH E8 and continuation of revision of ICH E6）. In 2017, the ICH headquarters issued a reflection paper on the GCP renovation on January 12 and conducted a public consultation until March 11.

According to a concept paper issued on November 17, 2019, the revised E6 guidelines（ICH E6［R3］）comprises three parts, viz.,"overarching principles"describing common principles of any type of clinical studies; and two annexes prepared depending on the type of clinical studies. Study designs such as those of clinical studies incorporating pragmatic or decentralized clinical trials are included in Annex 2, which provides points to consider while conducting clinical studies to enhance generalizability, or while using computerized data sources. The scope of application of ICH E6（R3）involves interventional clinical studies in principle; furthermore, primary studies related to registry establishment, which generally use observational study methods, are outside the scope. However, it is necessary to understand GCP renovation to ensure data reliability when using patient registry data as application data for the marketing approval of drugs, etc.

Table 1 A list of requirements（modified from IMDRF N46[14]）

ELEMENTS	Legend（XX：Highly Recommended/X：Recommended/□：Optional/NR：Not Recommended）						
	Initial Approval	Broadening Indication	Post market study	Postmarket Surveillance	Development of OPC/PG	Device Tracking	Field Safety Corrective
Governance							
Governance structure and process	XX	XX	XX	X	XX	X	X
Quality Management System							
Legal requirements for data collection/handling	XX	XX	XX	X	XX	X	X
Information on Patient Data Protection（e.g. if Exempt from consent, Opt-out, Opt-in）	XX	XX	XX	X	XX	X	X
Policy on access to data	XX	XX	XX	XX	XX	X	X
Essential information available for verification by relevant authority（e.g. competent authority, notified body）	XX	XX	XX	XX	XX	XX	XX
Data Gathering							
Relevant Variables	XX	XX	XX	XX	X	X	X
Unambiguous Device Identification（preferably internationally recognized UDI system）	XX	XX	XX	X	X	X	X
Linkability（Registry with other data source）:							
Deterministic	XX	X	X	X	X	X	X
Probabilistic	NR	X	X	X	X	X	X
Use of Controlled Vocabularies	XX	XX	XX	X	X	X	X
Use of nationally/internationally harmonized minimum data model	X	X	X	X	X	X	X
Data Storage							
Security Protection against hacking, altering, deleting or stealing data	XX	XX	XX	XX	XX	XX	XX
Methodologies Leading to Actionable Data							
Conduct of analyses across different types of analysis frameworks	XX	XX	XX	XX	XX	X	X
Data Interpretation	XX	XX	XX	XX	XX	X	X
Transparency/Display/Distribution							
Report; Key elements and frequency of reports	X	X	X	X	X		
Website and web-reporting	X	X	X	X	X	X	

Note）"With intervention（post-marketing clinical study）" indicates a post-marketing clinical study defined by the Pharmaceutical and Medical Device Act of Japan or a specific clinical study, etc., conducted within the approved dose and regimen based on the Clinical Trials Act of Japan."Without intervention（post-marketing survey）" indicates a use-results survey defined by the GPSP Ordinance in Japan.

6. Operation/management helping to ensure data reliability in the utilization of patient registry data as application data for marketing approval of drugs, etc.

6.1 Items concerning patient registry design/operation（relationship between medical institutions and patient registry holders）

6.1.1 Purposes of primary studies related to registry establishment

As stated in Section 4, there are various types of registries in terms of characteristics and purposes. When planning to start a primary study related to registry establishment, it is important to define the purpose of the study, identify stakeholders, and clarify their requirements. Aside from the registry holder, stakeholders may include regulatory authority, applicant, patients, and research institutions engaging in data entry.

Even if the purpose of the primary study related to registry establishment is defined, it should be considered that some registries are established, taking into account the following types of registry use covered by this proposal, whereas some other registries are established without taking them into account:"use of registry data as external control, etc., in a clinical study to be used for efficacy and/or safety evaluation in application for marketing approval, etc.," "use of registry data as supplement or substitution for clinical studies for efficacy and/or safety evaluation in application for marketing approval, etc.," and "use of registry data for evaluation of drugs or medical devices approved with conditions or regenerative medicine products approved with conditions and time-limit."

Just as a registry is newly established for application for marketing approval, it is important to take into account the use of a registry for approval application from the stage of its designing and, if the purpose of use of the registry is clearly defined, to have consultations with the applicant from the early stage of its development based on the purpose of use by reference to "Basic principles on utilization of registry for applications" and "Points to consider for ensuring the reliability in utilization of registry data for applications" in terms of informed consent obtainment method, requirements for ensuring data reliability, patient population for the registry, endpoints, etc.

If a registry is established taking into account its use for approval application without defining the purpose of its use, consent should be obtained concerning the possibilities of secondary use of the registry data by a sponsoring company and third parties'[Note 2)] access to medical records. It is also needed to store history data concerning data generation and data deletion/correction with its reasons and the names of persons engaging in such deletion/correction (audit trail), manage passwords and persons in charge of the data entry, and provide training to persons in charge of the data entry（registry user management）. These activities can minimize the risk of data fabrication/falsification and visualize the absence of fabrication, etc., and thereby enhance data reliability. Backup recovery procedures should be established to prevent overwriting with old data or deletion of data during data backup. Furthermore, given that a registry study often requires a long period of time, it is also necessary to consider the issue of study expenses（e.g., how to cope with the costs of the study after the period of study funding obtained at the start of the study is expired）and the issue of operation（e.g., breaking tasks into smaller parts and assigning them to respective doctors in a medical institution）. The above methods are considered to have been taken for usual studies. Procedure manuals and records should be retained so that whether a company applying for marketing approval is suitable for the purpose of use of a registry can be judged.

If the use of a registry for approval application is not considered at the establishment of the registry, the registry holder should provide the applicant with information of the purpose of the registry at the time of its establishment, definition of data reliability, ethical considerations, etc. In such a case, procedure manuals and records can play important roles.

Note 2): Third parties indicate monitors, auditors, and regulatory authorities etc. See "Points to consider for ensuring the reliability in utilization of registry data for applications" issued by the MHLW.

6.1.2 Quality control of data

This section does not propose additional activities for registry studies but aims to deepen understanding by clearly describing what has often been performed in many registry studies.

Monitoring conducted for quality control is classified into several types, including on-site monitoring conducted by monitors visiting medical institutions from which data are collected and checking the consistency between source documents and data, off-site monitoring conducted *via* telephone or FAX without visiting sites, and central monitoring conducted using completed registry data by checking systematic errors. Monitoring may be performed by combining some of these monitoring types, and procedures are specified depending on the purposes and risks. It should be noted that monitors' direct access to medical records, etc., requires prior consent from relevant subjects.

Regarding the quality control of computer systems, the necessity of computer system validation（CSV）is presented in "Points to consider for ensuring the reliability

in utilization of registry data for applications" issued by the MHLW. With CSV required for systems used in academia-initiated clinical studies in mind, the details of CSV should be devised based on the potential risks. A clinical trial takes about 1 to 3 years to complete, whereas a registry study can take a much longer time. Even if CSV is conducted at the start of a registry study, the status of the computer system may not be maintained throughout the study. Therefore, in addition to CSV at the start of the study, some sort of quality control should be performed for the computer system. It is recommended to discuss specific quality control methods and their appropriateness during consultations with PMDA（e.g., registry use consultation, registry reliability survey consultation）.

Concerning computer system, the following tasks should be performed: preparation of system design specification suitable for the study purpose, conduct of acceptance tests before delivery, and checking whether the system can run in accordance with the design specification. In addition, the following 3 requirements for electronic data should be met: 1）accurate and reliable data free from fabrication or falsification（authenticity）, 2）readable data（legibility）, and 3）storage of data for a necessary period（storability）. As stated in Section 6.1.1, it is important to establish the outline of audit trail and procedures for backup recovery and to specify methods of operation and persons in charge for data storage. Care should be taken not to create a situation where the person responsible for data control is lost due to transfer of the principal investigator, etc.

6.1.3 Quality assurance of registries

For the quality assurance of registries, registry holders should check the implementation structure and whether the registry operation, data collection, and handling of data collected are implemented in accordance with the pre-specified procedures depending on the purpose of registry establishment and quality of data obtained; they should also record the results of the check, including corrective measures taken as needed. In Japan, the term "quality assurance" tends to be associated with audit, and the term "audit" tends to be associated with "audit performed by auditors in a clinical trial." In the field of clinical studies, however, there are no internationally accepted definitions of audit, which is interpreted in various ways depending on countries, industries, or organizations.[15] As mentioned earlier, registry studies often take a long period of time to complete, whereas study funding is limited in many cases. The balance of quality and costs should be taken into consideration when devising the methods of quality assurance.

6.1.4 Rules and operating procedures for primary studies related to registry establishment

In "Items related to registry design/operation" prepared based on investigation by the CIN-Hayashi Group, a proposal was made by reference to "Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Drugs,"[16] a notification related to the use of medical information database in post-marketing pharmacovigilance activities. However, since these proposal and notification were prepared with companies' medical RWD management structures in mind, their strict application to the use of patient registry data for regulatory approval, etc., could be too idealistic to be feasible.[17] Nevertheless, items that should be pre-specified in conducting primary studies related to registry establishment are well summarized in the above proposal. These rules are not necessarily proposed on the assumption that standard operating procedures（SOPs）should be prepared and are considered to be replaceable with rules, etc., related to organizations and operation/management of registry holders（operating rules, etc.）or protocols, monitoring procedures/plans, and data management procedures/plans（DMPs）, etc., for primary studies related to registry establishment.

Therefore, in the present proposal, a comparison table with a summary of items to be presented required in "Items related to registry design/operation"（e.g., procedure manuals that should be prepared by registry holders）proposed by the Hayashi Group, and example alternative rules, etc., such as SOPs is provided as an attachment.

In the attachment, documents of primary studies related to registry establishment and those of studies using registry data are presented separately. The goal of the study is not to prepare procedure manuals but to specify relevant items and follow the procedures for each of these items. In other words, it is important to establish and maintain an appropriate quality management system（QMS）and act in accordance with the QMS and thereby ensure the reliability of registry data.

6.1.5 Considerations for personal information protection in primary studies related to registry establishment

Legal regulations/guidelines to be observed in conducting primary studies related to registry establishment vary depending on the purposes, etc., of studies. According to the "Ethical Guidelines for Medical and Biological Research Involving Human Subjects,"[18] individual participant/patient data（IPD）are allowed to be provided to third parties by opt-out policies when obtainment of consent from study participants is difficult. However, compliance with the Act on the Protection of Personal Information is

required in cases where the company's commercial use is expected, such as in regulatory approval application. Therefore, in order to provide the IPD of study subjects to companies, it is necessary to inform study subjects in advance of the provision of their data to companies in and outside Japan and secondary use of data by these companies by presenting such information in the patient information document and consent form for primary studies related to registry establishment as well as to obtain written consent from these subjects or their legal representatives（i.e., opt-in）.

However, it is considered acceptable to provide summary statistics, not IPD, to companies by opt-out policies for the addition of companies' regulatory use to the purposes of use of registry data.

Even if the intended use of a registry is not clear at the establishment stage of the registry, it is desirable to obtain consent from subjects in terms of the possibilities of the commercial use, provision to third parties, and provision to foreign entities of IPD on the assumption that IPD may be used for approval application, etc.

Concerning ethical considerations when using IPD as approval application data while consent of subjects has not been obtained for the commercial use or provision to third parties of IPD,"Basic Concept of Ethical Norms Related to Commercial Use of Patient Registry Data"[19] can be consulted for reference.

6.1.6 Costs of primary studies related to registry establishment and burden of expenses

Public funds can often be used for planning and short-term operation/management of primary studies related to registry establishment; however, given that most registries are held for a long period of time, the burden of expenses for operation/management can be a significant issue. If funding from a company who uses registry data is desired, it is necessary to understand registered data and quality level required by the company and take measures accordingly from the early stage of registry establishment. The relationship between quality and costs for operation/management is of trade-off. Care should be taken to set an optimal quality level taking into account the goal of the primary study related to registry establishment and an estimated period of time to maintain the registry. If funding from a company is expected, funding-related policies should be specified and published in advance to ensure the transparency of registry management."Study of Burden of Expenses for Use of Disease Registration System"[20] can also be consulted for reference.

6.2 Matters required to determine that the reliability of information presented in application data/documents is ensured at a sufficient level in light of its intended use（relationship between the patient registry holder and the applicant）

6.2.1 Protocols of studies using registry data, consent, and opt-out

Studies using registry data are database studies based on secondary use of existing registry data in principle.

The pharmaceutical regulations applicable to these studies using registry data, similarly to primary studies related to registry establishment, are the "Ethical Guidelines for Medical and Biological Research Involving Human Subjects." Because, these guidelines are administrative, not legal regulations, the studies are within the scope of the Act on the Protection of Personal Information.

From the ethical point of view, in order to provide companies with IPD, it is ideal to clarify the possibilities of provision of patient data to companies in and outside Japan, secondary use of data by these companies, and provision of data to third parties in study protocols and patient information documents/consent forms for primary studies related to registry establishment as well as to obtain written consent from study subjects or their legal representatives in advance(i.e., opt-in). It is also desirable to prepare new protocols and information disclosure documents of studies using registry data, apply to the ethical review board for prior review/approval, and provide an opportunity of agreement/refusal of information disclosure（i.e., opt-out）before using data.

In cases where a study is performed as a collaborative study by researchers belonging to an academic society and a company and summary statistics are only used as analysis results for the regulatory purpose, the use of data is considered to be acceptable without consent for the company's secondary use or provision to third parties with opt-in policies.

Concerning ethical considerations and personal information protection related to database studies using existing samples/information, a separate study is currently underway. The results of that study will be referred.

6.2.2 Data management procedures/plans for studies using registry data

In studies using registry data, registry data-related procedures, such as data cleaning, coding of previous/concurrent diseases, adverse events, and prior/concomitant drugs and preparation of datasets for analyses, are generated at the time of secondary use of existing registry data. These activities are specified in data management

procedures and data management plans prepared in studies using registry data.

6.2.3 Procedures/plans for ensuring data reliability of studies using registry data (e.g., monitoring procedures/plans)

In studies using registry data, the measures to ensure reliability of registry data include determination of data items to collect and unification of methods to collect data as well as on-site and central monitoring based on potential risks.

Meanwhile, also in studies using registry data, activities such as preparation of protocols and informed consent-related documents（including opt-out cases with written re-consent and guarantee of provision of an opportunity of agreeing or refusing information disclosure), activities to ensure the reliability of registry data including data management and monitoring, statistical analyses, and preparation of study reports are conducted. With the objective check and the assurance for the appropriate conduct of these activities by third parties, the conduct of audits may be considered according to the purposes of use of the registry data. The following 2 types of audits are likely to be conducted: 1）system audits to check the organization structures of registry holders and various procedures and the status of compliance with protocols and various procedures for primary studies related to registry establishment; 2）audits of individual research institutions to check the study implementation statuses and data reliability at research institutions serving as information sources of registry data in the context of the organizational structures and management statuses of registry holders. The details are specified in audit procedures/plans of studies using registry data and primary studies related to registry establishment.

Furthermore, there may be some cases where on-site inspection by the registry holder or on-site monitoring of the research institution *via* the registry holder are required. On-site monitoring *via* the registry holder is specified in the monitoring procedures and monitoring plans of studies using registry data.

6.2.4 Statistical analysis procedures/plans of studies using registry data

In studies using registry data, statistical analysis activities such as specification of statistical analysis items and analysis methods, designing of analysis programs, and finalization of analysis datasets are performed. These activities are specified in the statistical analysis procedures and statistical analysis plans of studies using registry data.

6.2.5 Study reports of studies using registry data

In studies using registry data, study reports are prepared based on the results of the statistical analyses conducted on the basis of protocols and statistical analysis plans of such studies as well as registry data.

In cases where a study is performed as a collaborative study by researchers belonging to an academic society and a company and summary statistics are used as analysis results, the documents to be used for regulatory purposes such as documents for approval application and re-examination/use results assessments are prepared based on the report of this study.

6.3 Matters required to determine that the reliability of information presented in application data/documents is ensured at a sufficient level in light of its intended use（relationship of the applicant to the application data/documents)

6.3.1 Standards of reliability of application data

Article 14, paragraph（3）of the Pharmaceutical and Medical Device Act, specifies that application data submitted for manufacturing/marketing approval application for drugs, etc.,"must be collected and prepared according to the standards specified in the MHLW Ordinance," and paragraph（6）of the same article specifies that "a document-based or on-site investigation is to be provided in order to examine whether or not the document complies with the standards" as well as Article 43 in the Enforcement Regulations of the Pharmaceutical and Medical Device Act specified the standards of reliability. This section addresses points for discussion relating to the document-based investigation（document-based compliance assessment）and on-site investigation（on-site GCP inspection). The standards are defined as follows in the Article 43 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

> Article 43 Data provided in the second sentence of Article 14, paragraph（3）of the Act（including as applied mutatis mutandis pursuant to paragraph(9) of the same Article)must be collected and prepared *via* the following means beyond those specified by the Ministerial Order on Standards for Non-Clinical Studies Concerning Safety of Pharmaceuticals（Order of the Ministry of Health and Welfare No. 21 of 1997）and the Ministerial Order on Standards for Clinical Studies of Pharmaceuticals（Order of the Ministry of Health and Welfare No. 28 of 1997):
>
> (i) the data is correctly prepared based on results of the investigation or the test conducted for the purpose of preparing the data;

（ii）if results of the investigation or the test in the preceding item cast a doubt on whether pharmaceuticals and medical devices pertaining to an application have sufficient quality, efficacy, or safety for the application, results of the investigation and the test are reviewed and evaluated and the results are described in the data;

（iii）data on which the data is based is preserved until the date of disposition when the approval prescribed in the provisions of Article 14 of the Act is provided or not provided. provided, however, that this does not apply to the case where it is recognized that the nature of the data makes it extremely difficult to preserve;

In other words, generally, the reliability from source documents to application data is confirmed through document-based compliance assessment and on-site GCP inspection from the above viewpoints. Usually, document-based compliance assessment confirms whether application data（clinical study report）is appropriately prepared from records retained by the sponsor（case report forms, etc.）. In addition to that, on-site GCP inspection is conducted on the sponsor and study sites.

Checklists and management sheets have been provided for these actions, and changes in the R & D environment have been responded to by revision of notification and issuance of new notification. Especially, the concept of confirmation through“EDC management sheets”, and the concept of on-site GCP inspection such as“the status of management of the study site may be intensively investigated for persons requesting or conducting a clinical trial, and based on the results, the necessity of visit investigation to the study site may be determined”[21] can be a starting point when considering methods for ensuring reliability for utilizing patient registries and RWD to be considered in the future, as described later, although it is difficult to utilize them as they are without modification.. In the near future, it appears to be beneficial to utilize materials such as EDC management sheets originally prepared for clinical trials, ultimately reaching a consensus among registry holders, regulatory authorities, and applicants.

For the utilization of patient registries and other RWD sources, unlike with clinical trials, on-site inspection of the medical institution generating data is not easy or, in some cases, impossible. In light of the actual situation of utilizing such data source other than clinical trials, the adoption of a framework of document-based compliance assessment, and on-site GCP inspection that PMDA conducts for usual clinical trials, i.e.“the status of management of the study site may be intensively investigated for persons requesting or conducting a clinical trial,” may be beneficial. Regarding such approach, by presenting specific examples of“the status of management of the study site”and categorizing criteria for requiring the implementation of intensive investigation, it may also be necessary to organize points to consider for adopting these suitably for the situation to utilize patient registries and other RWD sources. Actually, the notification“Points to consider for ensuring the reliability in utilization of registry data for applications”does not state that it is essential for a third party to view source documents but only states“If there is a possibility［...］will access source documents, etc.”Conditional approach also used in clinical trials as described above is likely to be applied. However, whether or not this principle is adopted is officially uncertain at present, and therefore, it is necessary to confirm the rationale for methods which ensure reliability by the approach as described above in advance in consultation with the PMDA.

“Points to consider for ensuring the reliability in utilization of registry data for applications”presents the compliance matters for applicants utilizing registry data, points to consider for the registry utilized as application data/documents for marketing approval, etc. An applicant will consider whether or not each of these matters can be addressed. However, as mentioned in the notification, an applicant is not required to ensure all the matters in a unified manner. In addition, when the registry holder's actions for the matters covered are confirmed, it is not necessary to prepare SOPs and documents for each matter. The essential requirement is considered that it can be confirmed, by the third party, that the registry is operated and managed transparently which allows confirmation of these items. Therefore, as presented in the attachment of this document, if the situation can be confirmed based on the description in the registry holder's organizational regulations, research protocol, etc., there is not much need to additionally require the creation of just formally prepared SOPs and related documents.

Regarding the confirmation for situation of registries, registry holders are not always familiar with the procedures for regulatory approval applications, and due to the variety of forms, registries are not always standardized in terms of matters that are relatively standardized in clinical trials, including the structure of related documents, procedures, and terms. Registries have many parts that are not suitable for standardization in nature. Therefore, it may be difficult to grasp the actual situation of registries just by formally asking the applicability of each item listed in the

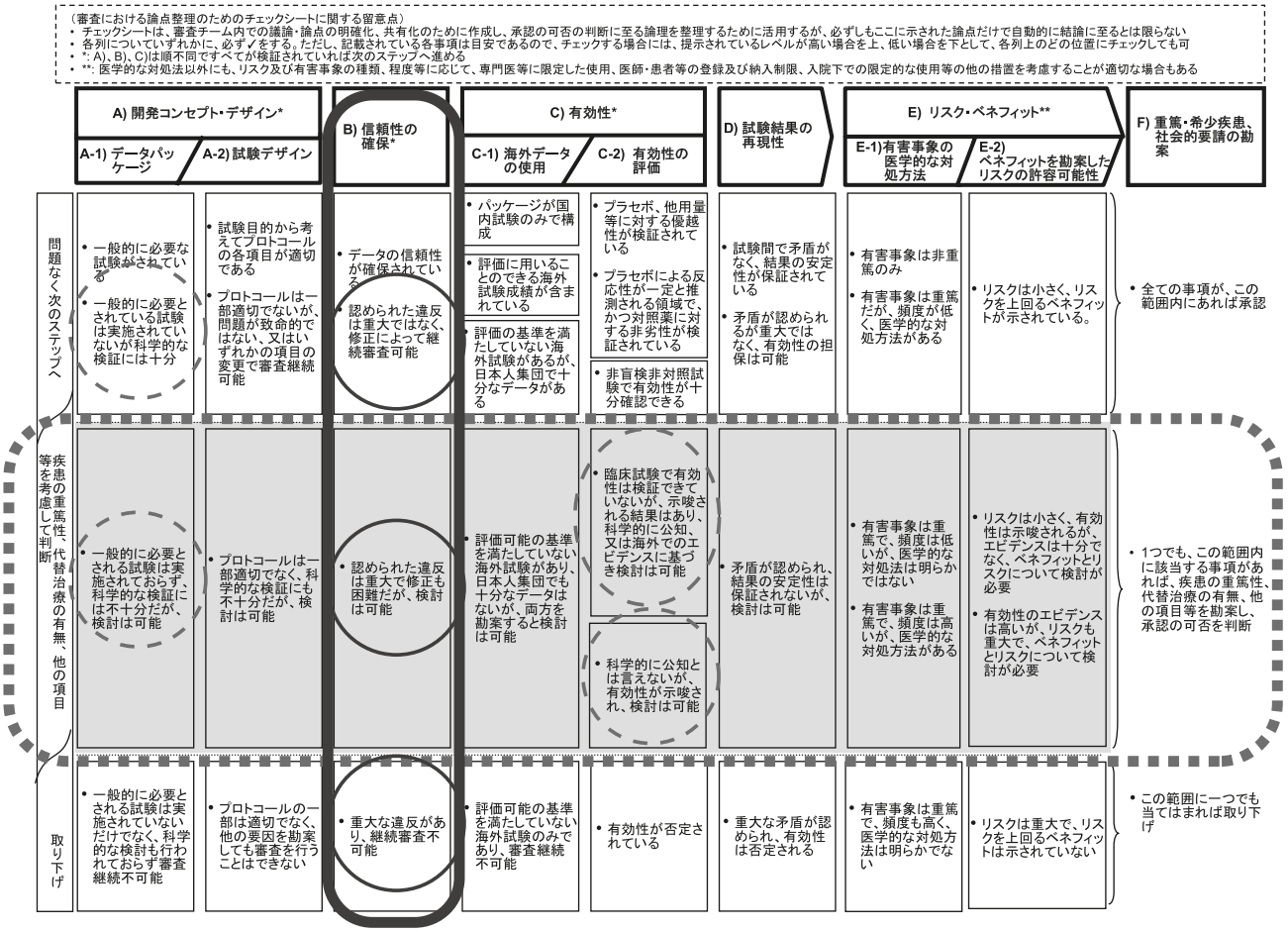


Figure 2 Points to be considered for the review staff involved in the evaluation process of new drug
(Derived from "Points to be considered for the review staff involved in the evaluation process of new drug", PMDA, 2008)

PMDA points to consider document. For example, if there is a fact that the data registered in the registry is periodically aggregated and reviewed among the parties concerned, it is one of the actions for "data quality control" in the PMDA points to consider document depending on the purpose of utilization. That is, there may be room for utilization even of registries that seem superficially impossible to utilize for regulatory purposes by obtaining information on operation and management of the registry and organizing the correspondence between the matters listed in the PMDA points to consider document and the actual situation. The attachment of this document will be useful for that consideration. This also leads to the expansion of the target of potentially available registries. Of course, concerning this point, when the registry holder also considers the utilization for regulatory purposes of their data, mutual communication is beneficial. That is because cooperation with the pharmaceutical company can be smooth by considering in advance whether the actual situation of various operation and management is consistent with the matters listed in the PMDA points to consider document.

6.3.2 Regulatory grade

Regarding the utilization of patient registries for regulatory approval application, the diseases targeted for discussion in this document were limited to rare diseases (rare cancers, rare intractable neurologic diseases, pediatric diseases, etc.), in which conventional RCTs (randomized controlled trials) are difficult to be conducted. Therefore, we start the discussion of the concepts such as "fit-for-purpose" and "regulatory grade" by looking back at the discussion of a general application package structure without patient registries in the field of these diseases.

"Points to be considered by the review staff involved in the evaluation process of new drug" (**Figure 2**), which was issued by PMDA in 2008 as part of disclosure of the Good Review Practice, states that perfection is not necessarily required in terms of reliability assurance. For example, it has been clarified that even if the application material meets the condition "Recognized violations are crucial and difficult to amend," if it is "considerations are possi-

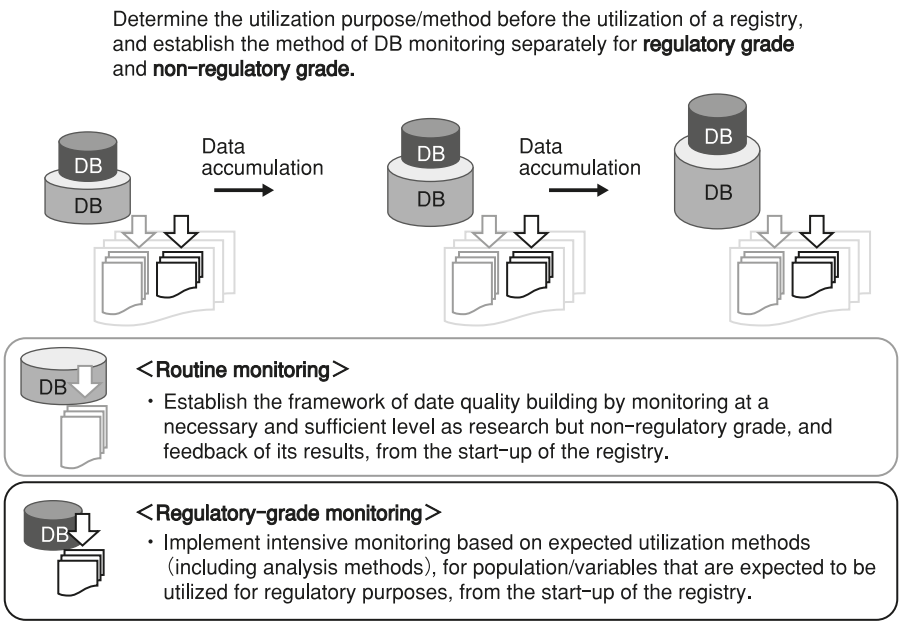


Figure 3　Pre-determined monitoring

ble" for some reason, it will be regarded as "approval or non-approval should be judged considering with the seriousness of the disease, availability of alternative therapy, and other points," and the judgment can be made flexibly.

Of course, when utilizing patient registries, it is outrageous claim that the utilization of data should be promoted unconditionally even for the data reliability is not ensured. However, in a situation where it is clearly stated that even GCP violations in some part of the dataset that are difficult to amend may be acceptable in some cases, it is unreasonable to determine that the registry is ineligible for regulatory use just because the data quality control status/registry quality assurance status is not equivalent in those in clinical trials. Actually, the PMDA points to consider document does not require the registries, etc., to be equivalent to that in clinical trials.

On the other hand, if complete data without any drawbacks are not assumed, confusion may occur as to what the basis is for determining that quality is sufficient. In the utilization of patient registries and RWD, the expression of regulatory grade is used, but it is really not defined specifically even if these above are not perfect.

We would like to mention two points as a proposal to discuss what regulatory grade is:(1) The details of data quality control, quality assurance for registry, etc., can be confirmed from the outside or third party, and (2) it can be inferred with some probability that the conclusion of regulatory approval decision is within the range that does not distort significantly even if these above are not perfect.

The former can be interpreted as what lies behind the requirements throughout the PMDA points to consider document. In other words, the checking of procedures and records can be interpreted as not asking for the existence of procedures and records themselves but asking for the situation to be recognizable from the outside or the third party through them. The latter is a point for discussion that can be inferred from the PMDA points to consider document for reviewers described above.

One of the issues to be considered in (1) is how to implement monitoring. Predetermined monitoring method (**Figure 3**), which is implemented in some of the registries established as part of the CIN Project, can be considered as one of the standard methods, assuming the utilization of registries for regulatory purposes in Japan. On the other hand, as mentioned even in the PMDA points to consider document related to reliability, the registries supposed to be utilized are not always those that can be predetermined. An alternative in such cases can be an adaptable monitoring approach (the idea of performing add-on monitoring separately in addition to routine monitoring when a plan of utilization for regulatory purposes is proposed), in which monitoring is added at the start of the utilization project. If such frameworks may be acceptable, it is expected that the possibility of utilization of patient registries, RWD, etc., for which the purpose of utilization is not determined in advance, may increase. This supports the development of treatment in the field of rare diseases for which conventional development of drugs, etc., is difficult (i.e., diseases targeted in this document). In terms of

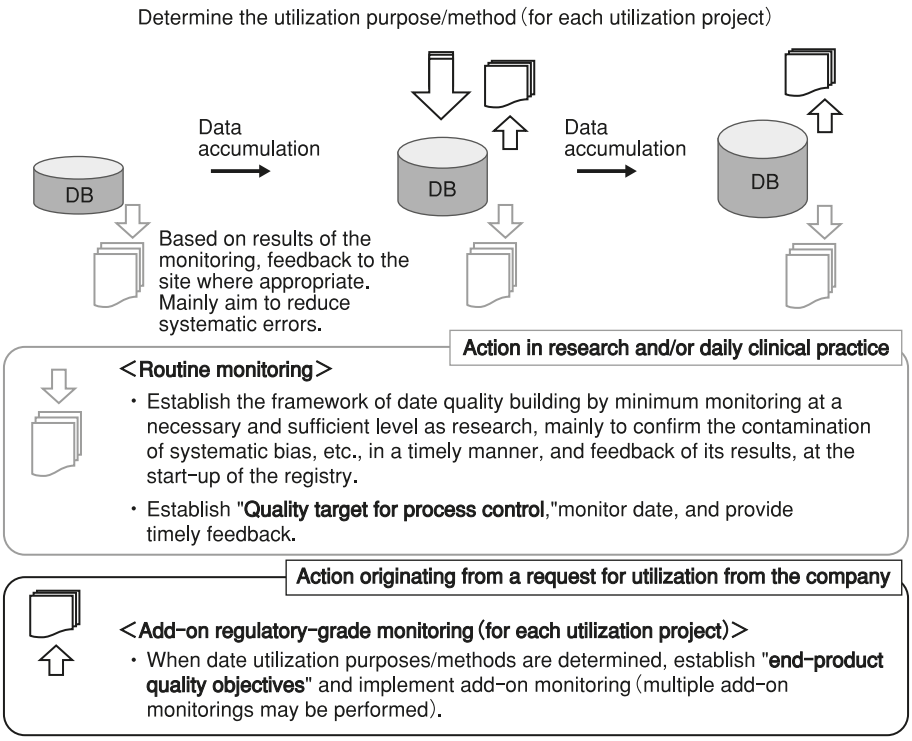


Figure 4 Adaptable monitoring

funding, the cost burden after the possibility of utilization arises makes it easy to maintain the beneficiary pays principle and can be one of the means for establishing the ecosystem of a multipurpose registry.

Regarding adaptable monitoring（**Figure 4**）, there are some cases where the PMDA's view presented no objection at the drugs registry utilization consultation. However, requirements for add-on monitoring may change depending on the intended use, and therefore, it is required to consider specific methods that can ensure the quality of data. The PMDA also added a comment that at the start of monitoring using this method, the applicant should discuss the methodology with the PMDA again by presenting the specific method of add-on monitoring.

If add-on monitoring is implemented after the analysis result for the purpose of utilization is obtained, some doubt would be thrown on the validity of the final analysis result obtained after that. It should be noted that add-on monitoring is assumed to be implemented before the analysis of the primary endpoint related to the purpose of utilization.

Even when monitoring is performed, its method and points to be focused must be different from those in clinical trials. Possible alternative approaches include omitting some methods of data quality management in clinical trials or increasing the weight of central monitoring. For patient registries or RWD derived from various data sources to be considered in the future, in light of the actual status that the data collection method is different from that used in clinical trials, there may be room to consider the methods of data quality management from a perspective different from that for the methods of data quality management used in clinical trials.

One possibility is to consider adopting a methodology of focusing on performance/characteristic evaluation of persons who enter the data or perform the data entry/capture process（e.g., algorithm-based e-phenotyping）rather than focusing on confirming the consistency of data on the DB with source documents. For example, one possible method may be evaluation of the degree of coincidence when a person who enters the data enters the same data multiple times and the degree of coincidence when multiple persons who enter the data enter the same data, by using some data or based on work log, etc.(Some cases of such an approach have been reported as efforts by overseas companies).

What is evaluated above is different from the degree of coincidence of data on the DB with source documents. However, unlike clinical trials, in patient registries and other RWD, when entering data on the DB, it is unlikely that the same information is recorded in charts, etc., assuming SDV to be implemented later, and therefore, it is not uncommon to have to change the SDV principle itself. Given this, the "accuracy" measure of the data should be

reconsidered. This is expected to be a point for discussion that may become an issue in the process of considering how PMDA will specifically confirm the source documents in the future. At this time, no specific procedure that may be justified has been established, but if the PMDA's case studies is published externally with categorization of examples, there may be room for industry and academia to consider methods of data quality management accordingly, and therefore, active information disclosure is expected.

One of the issues to be considered in（2）is how to evaluate that the conclusion of regulatory approval decision is not significantly distorted. PMDA's view regarding this is expected to be presented, but as one assumption, it can be one of the considerations that the type Ⅰ error does not significantly increase. If the data quality is so low that systematic errors cannot be overlooked, using such data as an external control for a single-arm clinical trial will induce the bias of the therapeutic effect of the drug; as a result, an ineffective drug may be mistakenly determined to be effective. Of note, this may also be caused by the difference in the definition of endpoint. For example, in the case of progression-free survival（a time-to-event endpoint, where an event is defined as disease progression or death）, which is commonly used in the oncology field, within the framework of clinical trials, disease progressions are cases where only radiographic progression by CT, etc., is an event as well as cases where radiographic progression or clinical progression is an event. If the definition is different between a single-group clinical trial and a registry, there may be cases where the therapeutic effect cannot be estimated appropriately.

However, even if there is a systematic error, when it is uniformly included in the data in the same registry, the effect of bias may be small in comparison between groups in the same registry, which is one of the utilization methods mentioned in the PMDA's document on registry utilization.

In other words, the "characteristics" of data, which is a non-negligible issue related to quality in one utilization case, may be negligible "characteristics" in another utilization case. This point differs from the cases of clinical trials in that the purpose or analysis methods are predetermined, and this is one of the reasons for the difficulty in predetermining monitoring, etc., for ensuring the data quality at the stage when the use purpose, method, and proposed statistical methods are not determined in advance in the registry used for secondary purposes. However, this issue may be addressed using the adaptable monitoring described above.

After thoroughly examining these issues, the final quality management system will be appropriately constructed, and quality acceptance limits will be appropriately established. However, regarding the issues including the concept of quality management system that was explicitly introduced in ICH E6（R2）, and quality acceptance limits, discussion is still far from a clear policy and established consensus even in the area of clinical trials. Based on such situation in clinical trials, it is currently difficult to hold similar discussion assuming the utilization of patient registry. As mentioned above, the reliability assurance of utilization of a registry for regulatory purposes was discussed, although limited to the main issues.

While the above discussion may give the impression of denying the quality management system that has been built up in clinical trials, this document does not argue that quality assurance is not required. As a major basis of discussion, if data is utilized for regulatory purposes, it goes without saying that it is necessary to assure a certain level of quality considering the magnitude of the impact. However, proportionality is important in such action as discussed in the ICH GCP renovation. In addition, a solution is being considered based on the fact that the problem originally arises due to the difficulty of development based on usual multiple full-package clinical trials and clinical trials that fully meet the external design requirements, at least in terms of utilization for the purposes of this document. In this situation, it cannot be concluded that the same response as the clinical trial is required. Regarding this point, although the reason is not specified, there are some statements in MHLW "Points to consider for ensuring the reliability in utilization of registry data for applications" that it does not necessarily require that monitoring be carried out in the same way as in clinical trials. For example, taking into account conditional expressions such as "when monitoring is carried out by the registry holder," suggesting that the regulatory authority shows a certain understanding the difference between clinical trials conducted by the company.

Therefore, as a conclusion at this point, it is possible to judge that the recognition that "the same process/same（resulting）data quality as the clinical trial should be sought" is not appropriate, even if data such as patient registry is included in the evaluation data as a control group for clinical trials in the new drug application.

On the other hand, regarding what level is required, industry-government-academia discussion has not reached a conclusion yet. Previous cases of utilization may need to be categorized, including examination of exception cases and others（including cases of utilizing data not called RWD）in terms of the following points:

・Patient registry data（including those in the previous

cases, not specified as patient registry, etc., but utilizing data other than clinical trials), clinical study report containing evidence derived from those data.
- Whether or not there are cases in which the clinical trial is being receiving a document-based compliance assessment as a pivotal study in application data.
- Whether or not there are cases in which patients derived from a patient registry included in the clinical study report of the clinical trial are under investigation.

With future progress of utilization of patient registries, accumulating and categorizing information, and transmitting information from the PMDA, the predictability at the early stage of research and development is expected to be improved in the future, although patient registry aspects and utilization purposes/methods are varied.

6.3.3 Significance of PMDA consultation system related to registries

The PMDA or MHLW presented the basic principles required for the utilization of patient registry, greatly advancing improvement in environment for the utilization of patient registries in Japan. However, there are still not many cases. The utilization of patient registries for the development of drugs etc., especially the utilization of those containing data and/or evidence in application data, may not be actively addressed due to a notion that the development risk is high.

Although the basic principles were presented, it is inevitable to make judgments based on individuality due to the great variety of registries. Therefore, it is currently important both for industry and academia to utilize the consultation system related to registries provided by the PMDA. On the other hand, the hurdles are high especially for academia, and if the possibility of utilization of the registry cannot be estimated at an early stage of planning of the company's development strategy, it may be difficult to start the project, and therefore, it is desirable to operate the system so that consultations can be received more flexibly. However, regarding this point, the PMDA has proposed an operation to lower the hurdle of preparatory consultation, and it is considered that starting discussions under such a framework is a possible option at this time. In the future, in addition to that, as one countermeasure, it is expected that while considering the confidentiality of individual cases, cases in the PMDA's review and reliability investigation will be categorized and presented as external examples. In particular, for cases that have not been approved, industry and academia cannot analyze such cases, and therefore, it is strongly required for the PMDA to categorize the cases and present issues in a way that avoids the identification of a company and in a way that protects corporate secrets. In light of the fact that, in Europe, the review details when the conclusion is not approvable are published with the drug name and that, also in the US, similar cases, which are discussed in the advisory committee, are published with the drug name, there may be room for exploring categorization and information disclosure in a form in which individual cases cannot be specified.

If the issues assumed at registry consultation are categorized, it is more likely that the registry holder or the applicant can utilize the consultation for registry with the PMDA more rationally and effectively. It also facilitates to consider the quality control method of data and the quality assurance method of the registry in advance. It is expected that discussions at consultation can be more intensive, leading to efficient clinical development and facilitating the development of drugs, etc. In addition to the above, we would like to point out that there are some cases where the actions taken by the academia to achieve the research purpose meet the PMDA requirements, but it is not noticed. For example, if reports, etc., summarizing the data registration status are published regularly, it may play a role in data quality control. Therefore, if it is possible to coordinate views for determining whether or not there is an action that substantially meets the PMDA requirements by interviewing the operation and management status of the registry, rather than formally inquiring from the applicant whether or not to comply with the PMDA requirements, patient registries that were recognized as unavailable could be utilized. On the contrary, for registry holders, there is room to appeal to companies that they can utilize registry for regulatory purposes by carefully reviewing the operation and management status from the perspective of regulatory purposes, not adding a new approach, or not creating new SOPs, etc. In addition, a company's efforts to reduce investigation costs may promote the development projects, etc., for drugs, etc., required in clinical practice in the long run.

Methods for ensuring the reliability of the data in clinical trials/studies have been sophisticated since the enactment of ICH-GCP. Accordingly, the division of work based on standardization and specialization has progressed, and the concepts of "risk-based monitoring" and "quality by design" have become widely recognized, leading to improved quality and making project progress management relatively easy. However, with the exception of company-sponsored registries supposing utilization for particular regulatory purposes, in most cases, it is not easy to introduce the concept of quality by design from the time the registry is launched in order to utilize the patient

registry and RWD. In addition, because of the difficulty of standardization due to the diversity of purposes, each project will require coordination of recognition of the current situation and value standard for judgment between experts/between industry–government–academia stakeholders. While this can be a factor that hinders the utilization of patient registries, it can also be a factor that supports development projects for drugs, etc., that were once difficult if coordinating views leads to the possibility of utilization of patient registries, etc., that have not been considered to formally meet the requirements. The cost of coordination is currently high, but in the future, efforts will be made to generalize the experience of the PMDA, and the cost required for coordination should be reduced by accumulating cases of industry, government, and academia.

The PMDA's consultation system and categorization of points for discussion and information transmission can be a catalyst for such industry–academia activities, and more activities are expected from the perspective of regulatory science in the future.

6.4 Other points to consider

6.4.1 Securing the transparency of research funds and management of conflict of interest

It is widely known that the Clinical Trials Act[22] was enforced on April 1, 2018 as a consequence of misconduct by certain companies.

The significance of the management of conflict of interest（COI）has been notified to relevant organizations and institutions via "Management of conflict of interest in clinical trials under the clinical trials act"[23] to ensure that any COI is managed based on this notification.

In the annex of the above notification, i.e.,"Guidance for conflict of interest management under the Clinical Trials Act"（partially revised on November 30, 2018）, COI is defined as "any circumstance where a third party could have concerns about a risk that fair and appropriate judgment in a study could be affected by the involvement of a company or a financially profitable relationship between a company involved in the study and the researchers." According to the guidance, such concerns are not about the involvement of the company or the presence of a financially profitable relationship but about a possibility that the presence of such potential benefits could negatively influence the reliability of the study, and that the study subjects could have inadequate protection. Securing a certain amount of funds is necessary to appropriately conduct a clinical study; moreover, researchers can receive financial support from a company. According to the guidance, a COI does not indicate the "fact" that a study is actually under undue influence arising out of personal interests but the "appearance" that the study appears to outsiders to be under undue influence. In other words, the primary aim of COI management is for researchers to appropriately manage a potential COI and achieve social accountability, and thereby earn the trust of subjects and the public for clinical studies.

In activities related to the use of registry data under the pharmaceutical regulatory system, it is essential to ensure collaboration between academia and industry, secure transparency of research funds including expenses for the operation/management of primary studies related to registry establishment and use of registry data, and manage COI appropriately.

6.4.2 Coordination of consortium activities and stakeholder management

For registry holders, long–term maintenance or continuation of patient registries is challenging. To address this, the following schemes are considered: 1）A consortium is formed by multiple companies, which contribute to research funding for the operation/management of primary studies related to registry establishment; and 2）A company that actively works on the research and development of therapeutic drugs for rare diseases（e.g., rare cancers, rare intractable neurologic diseases, pediatric diseases）proposes and solely contributes to research funding for the operation/management of primary studies related to registry establishment.

Meanwhile, for providing new treatments to patients and their families, opportunities to use registry data under the pharmaceutical regulatory system should also be guaranteed for companies not participating in consortiums, etc., or not contributing to research funding for the establishment, operation, and management of registries.

Given that the beneficiary–pays principle is applied to the use of registry data under the pharmaceutical regulatory system as a rule, there seems to be no significant problem if expenses for registry use are borne by the company. However, based on fairness and transparency, the registry holder should pay adequate attention to researchers providing data for the registry or the company contributing to research funding. Creating systems to minimize conflicts among stakeholders and to work on stakeholder management is also important. For example, exclusive rights to use registry data can be given for a certain period to researchers providing data for registry establishment or companies contributing to research funding; thereafter, data can be shared by restricted publication; or companies planning to newly use registry data under the pharmaceutical regulatory system are asked to pay an appropriate portion of research expenses needed

for registry operation/management.

7. Summary

This is a document for registry holders and investigators of primary studies related to registry establishment, primarily considering rare diseases（rare cancers, rare intractable neurologic diseases, pediatric diseases, etc.）, wherein conducting conventional RCTs is challenging. It describes the points to consider for the operation and management, so as to ensure data reliability while utilizing registry data under the Pharmaceutical Affairs system, especially the utilization of registry data: 1）as an external control of clinical studies for efficacy and/or safety evaluation in applications; 2）to complement or substitute clinical studies for efficacy and/or safety evaluation in applications; and 3）in the evaluation of drugs and medical devices with conditional approval and of regenerative medicine products with conditional and time-limited approval.

Assurance of data quality and reliability of patient registry, and considerations for the protection of personal information require a high level of consciousness and understanding of registry holders and principal investigators, investigators, sub-investigators, collaborators of primary studies related to registry establishment, health professionals such as physicians at medical institutions generating data; companies that undertake research/development and manufacturing/marketing of drugs, etc.; and patients and their family members. To promote further utilization of registry data under the Pharmaceutical Affairs system in the future, it is essential to make efforts, in Japan as a whole, and to gain experience and know-how in many examples.

There have been movements such as ICH's future promotion of GCP renovation and the PMDA's developmental reorganization of the CIN-working group and the RWD working group, as well as the utilization of registry data as well as medical RWD/RWE under the Pharmaceutical Affairs system, such as databases based on clinical information collected from electronic medical records, ePRO, and wearable devices. However, their basic principles and points to consider for ensuring reliability, etc., can be conducted based on a discussion of patient registries.

The clinical trials conducted in Japan are of high quality due to the uniformity of the evaluation criteria, and the existence of few violations of selection/exclusion criteria, regular visits of subjects, certainty of follow-up, and data accuracy. These are similar in primary studies related to registry establishment. Creating a mechanism to generate registry data by utilizing such strengths could trigger the practical use of new medical technologies such as drugs in Japan and suitable post-marketing pharmacovigilance, especially in the field of rare diseases wherein conventional RCTs cannot be conducted.

References

1) Oi H. and Nakamura H. The advance of utilizing real world data under pharmaceutical regulatory schemes regarding the approval review and post-marketing safety assessment. Japanese Journal of Pharmacoepidemiology 2019; 24（1）: 2-10. Doi: https://doi.org/10.3820/jjpe.24.2.
2) The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use（ICH）. ICH reflection on "GCP renovation": Modernization of ICH E8 and subsequent renovation of ICH E6, January 2017. URL: https://www.ich.org/products/gcp-renovation.html
3) U. S. Food and Drug Administration. 21st Century Cures Act. URL: https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothefdcact/21stcenturycuresact/default.htm
4) Nakamura H. and Takeda S. Clinical innovation network. The Journal of Orthopedics & Traumatology 2018; 61（4）: 419-24.
5) Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare. Implementation of conditional accelerated approval system for pharmaceuticals, PSEHB/PED Notification No. 1020-1. October 20, 2017.
6) Pharmaceuticals and Medical Devices Agency. Medical Information Database Network（MID-NET）. URL: https://www.pmda.go.jp/safety/mid-net/0001.html
7) Ministry of Health, Labour and Welfare. Ordinance related to standards for conducting post-marketing surveys and studies on drugs. MHLW Ordinance No. 116. October 26, 2017.
8) Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare; and Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare. Basic principles on utilization of registry for applications. PSEHB/PED Notification No. 0323-1/PSEHB/MDED Notification No. 0323-1. March 23, 2021.
9) Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare; and Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare. Points to consider for ensuring the reliability in utilization of registry data for applications. PSEHB/PED Notification No. 0323-2/PSEHB/MDED Notification No. 0323-2. March 23, 2021.
10) Establishment of registry information hub for the acceleration and promotion of CIN concept. Handbook on the establishment and operation of registries version 1.0. 2019. URL: https://cinc.ncgm.go.jp/?page_id=198
11) Agency for Healthcare Research and Quality. Registries for evaluating patient outcomes: A user's guide. Third edition. 2014.

URL: https://www.ncbi.nlm.nih.gov/books/NBK208616/
12）Kodra Y., Weinbach J., Posada-de-la-Paz M., Coi A., Lemonnier S. L., et al. Recommendations for improving the quality of rare disease registries. Int J Environ Res Public Health 2018; 15（8）: 1644. Doi: 10.3390/ijerph15081644.
13）Sase K. et al. Generating real-world evidence for innovative medical devices: Strategically coordinated registry network. Pharmaceutical and medical device regulatory science（PMDRS）2017; 48（8）: 533-41.
14）The International Medical Device Regulators forum Patient Registries Working Group, Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making, 27 March 2018.
URL: https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-180327-usability-tools-n46.pdf
15）Health, Labour and Welfare Sciences Research Grants（General Research Program for the Practical Application of Medical Technology）. Comparison of regulations and legal system of clinical trial between Western countries and Japan. General research report 2013 to 2014. Representative person in the research: Tetsu Isobe（Professor, Graduate School of Law, Keio University）
16）Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare. Points to consider for ensuring the reliability of post-marketing database study for drugs. PSEHB/PED Notification No. 0221-1. February 21, 2018.
17）Shibata T. Project title of AMED Research on Regulatory Science of Pharmaceuticals and Medical Devices: Utilization of real world evidence using patient registry data to support regulatory decision-making"Proposal on Assuring the Reliability of Patient Registry Data for Use in Application Dossiers of Pharmaceuticals and Medical Devices." Jpn Pharmacol Ther 2019; 47 suppl 1: s9-s22.
18）Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare/Ministry of Economy, Trade and Industry. Ethical guidelines for medical and biological research involving human subjects. MEXT/MHLW/METI Notice No. 1. March 23, 2021.
19）AMED clinical research/trial promotion project fiscal 2018 "Study on measures to promote the clinical innovation network project by effective utilization of disease registration systems." Study group of companies' utilization of disease registration systems in compliance with the Act on the protection of personal information. Basic concept of ethical norms related to commercial use of patient registry data.
20）AMED clinical research/trial promotion project fiscal 2018 "Study on measures to promote the clinical innovation network project by effective utilization of disease registration systems" and "Study on burden of expenses for utilization of disease registration systems."
21）Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare. Guidelines for document-based compliance assessment for new drug approval application data and on-site GPSP inspection. PSEHB/PED Notification No. 0831-4. August 31, 2020.
22）Ministry of Health, Labour and Welfare. Clinical Trials Act. Act No. 16 of 2017. April 14, 2017.
23）Director of the Research and Development Division, Health Policy Bureau, Ministry of Health, Labour and Welfare. Management of conflict of interest in clinical trials under the Clinical Trials Act. HPB Notification No. 0302-1. March 2, 2018.

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Acknowledgments

We would like to express our sincere appreciation to the members of the Japan Pharmaceutical Manufacturers Association, the Japan Federation of Medical Devices Associations, the Forum for Innovative Regenerative Medicine, and the members of Pharmaceuticals and Medical Devices Agency for their valuable comments and advice in the process of preparing this report.

（Attachment）

Comparison table summarizing items to be presented as required in "Items related to registry design/operation"（e.g., procedure manuals that should be prepared by registry holders）and examples of alternative rules, etc., such as SOPs

Prepared on March 29, 2021

Concerning post-marketing pharmacovigilance,"Points to consider for ensuring the reliability of post-marketing database study for drugs"（PSEHB/PED Notification No. 0221-1 issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated February 21, 2018）has been issued.

However, the standard operating procedures（SOPs）presented in this notification as documents to be established are shown considering the medical RWD management structure of the database companies. Therefore, strictly applying the above to the use of registry data under the pharmaceutical regulatory system could be significantly idealistic to be feasible. These rules, etc., have not necessarily been proposed with the assumption that SOPs should be prepared; furthermore, they are considered to be replaceable with rules, etc., related to organizations and operation/management of the registry holder（operating rules, etc.）or protocols, etc., of primary studies related to registry establishment.

Based on the above, we have prepared a comparison table with items related to registry design/operation（e.g., procedure manuals that should be prepared by registry holders）in the "Proposal on assuring the reliability of patient registry data for use in application dossiers of pharmaceuticals and medical devices"[1] and example alternative rules, etc., such as SOPs. Documents of primary studies related to registry establishment and those of studies using registry data are presented separately in the table.

No.	Items related to registry design/operation	Examples of alternative rules, etc., such as SOPs
1	Rules related to establishment/management Purpose/content (1) Establishment of operating/management structure Activities/procedures needed for registry holders to handle individual data appropriately and to continuously operate/manage registries should be specified, and an appropriate management/operating structure must be established. (2) Policies related to securing transparency Considering the collection/analysis of registry data as well as the influence on decision-making based on the results of the analysis, registry holders must specify and publish policies related to items needed to ensure transparency in terms of registry operation/management（conflict of interest, structure of registry operational entities, provision of funds for registries, purposes of registries, disclosure of data, etc.）. (3) Policies related to access to registry data As registries include sensitive health-related or treatment-related information of patients, registry holders must establish rules concerning registry data users' access to data（including data access by the regulatory authority）and the scope and rights of such access. Additionally, the application methods for access to registry data and criteria based on which registry holders assess the appropriateness of the application for registry data access must be specified as needed.	• Operating rules of registry holders（e.g., academic societies and research groups） • Protocols for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry establishment are affiliated
2	*Standards/procedures for data entry into patient registries Purpose/content For registries, data are collected using various methods, including paper-based case report forms（CRFs）and electronic case report forms（eCRFs）. Regardless of these methods, data must be gathered for pre-specified survey items and by using appropriate collection methods in accordance with the specified procedures. Examples of points to be checked • Procedures for data entry • Identification of persons in charge of data entry • Education/training of persons in charge of data entry	• Protocols and/or data management procedures/plans（DMPs）for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry establishment are affiliated
3	Standards/procedures related to data cleaning Purpose/content The data gathered must be handled in accordance with the procedures pre-specified by the registry holders. Data gathered from information sources and entered in databases must be locked and stored in accordance with the pre-specified procedures. Examples of points to be checked • Methods related to the anonymization of data before providing the data or data-access to registry users considering that sensitive information is included in the registries • Procedures for data cleaning（including procedures for checking information sources for doubtful points arising due to data cleaning） • Procedures for recording history of data correction • Procedures for data coding • Procedures for data lock	• Protocols and/or DMPs for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry establishment are affiliated • Protocols and/or DMPs for studies using registry data
4	Standards/procedures related to coding Purpose/content The gathered data are handled in accordance with the procedures pre-specified by the registry holders. The data gathered from information sources and entered in databases are locked and stored in accordance with the pre-specified procedures.	• Protocols and/or DMPs for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary

No.	Items related to registry design/operation	Examples of alternative rules, etc., such as SOPs
	Examples of points to be checked • Procedures for recording history of data correction • Procedures for data coding • Procedures for data lock	studies related to registry establishment are affiliated • Protocols and/or DMPs for studies using registry data
5	Rules/procedures related to security Purpose/content The overall security of computer systems used must be specified by registry holders and maintained in accordance with the pre-specified procedures. In particular, rules must be established for the following items: • Scope of access rights of computer system users according to the registry data content • Education/training of computer system users considering overall computer systems, security requirements, and registry-specific handling • Network security	• Operating rules of registry holders（e.g., academic societies and research groups） • Protocols and/or DMPs for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry establishment are affiliated
6	Rules/procedures related to data backup and recovery Purpose/content Registry data backup/recovery must be performed using methods specified by registry holders in accordance with the specified procedures.	• Operating rules of registry holders（e.g., academic societies and research groups） • Protocols and/or DMPs for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry establishment are affiliated
		• Definition of registry database(e.g., EDC) requirements
7	Rules related to the quality control of medical data gathered from information sources Purpose/content The gathered data are handled in accordance with the procedures pre-specified by the registry holders. The data gathered from information sources and entered in databases are periodically locked and stored. Examples of points to be checked • Methods related to the anonymization（pseudonymization）of data before providing the data or data-access to registry users considering that sensitive information is included in the registries • Procedures for data cleaning（including procedures for checking information sources for doubtful points arising due to data cleaning） • Procedures for recording history of data correction • Procedures for data coding • Procedures for data lock	• Operating rules of registry holders（e.g., academic societies and research groups） • Protocols, monitoring procedures/plans, and/or DMPs for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry establishment are affiliated • Definition of registry database(e.g., EDC) requirements
8	*Validation plans/reports related to computer systems Purpose/content Methods for computer system quality control can vary depending on the purposes, etc., of individual registries. Depending on the computer system configurations, the following activities must be performed by registry holders appropriately and efficiently: • Computer system validation based on risk assessments while introducing or renewing computer systems • Checking the operational status of the computer systems used • Establishment of the authenticity, legibility, and storability of electromagnetic records suitable for the specifications/operation methods of	• Operating rules of registry holders（e.g., academic societies and research groups） • Protocols and/or DMPs for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry estab-

No.	Items related to registry design/operation	Examples of alternative rules, etc., such as SOPs
	the computer systems used. The annex titled “Use of electromagnetic records and electronic signatures for application for marketing approval or licensing of drugs, etc. (ER/ES Guidelines)” (PFSB Notification No. 0401022, by the Director-General of Pharmaceutical and Food Safety Bureau, MHLW, dated April 1, 2005); and points to consider when handling data for approval application as electromagnetic data, can also be consulted for reference.	lishment are affiliated • Definition of registry database (e.g., EDC) requirements
9	Rules to validate whether the datasets for analysis have been appropriately prepared, or whether analysis results have been appropriately obtained Purpose/content During data extraction and preparation of datasets, the procedures for appropriately extracting information from locked data must be pre-specified by registry holders, and data must be extracted in accordance with the procedures. In cases where companies and applicants-to-be receive datasets, and where statistical analyses are performed, the companies should submit statistical analysis plans, etc., to registry holders before data extraction and agree with registry holders in terms of the range of dataset preparation. In cases where registry holders conduct statistical analyses, these analyses should be performed in accordance with the pre-specified procedures and plans specified in the statistical analysis plans, etc.	• Protocols and/or statistical analysis procedures/plans (SAPs) of primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry establishment are affiliated • Protocols and/or SAPs of studies using registry data
10	Rules related to the reporting of quality control related plans and results of investigation Purpose/content In cases where registry holders undertake monitoring, the procedures for monitoring must be specified in advance, while monitoring must be undertaken in accordance with the procedures. In terms of monitoring, registry holders must obtain the consent of patients who provide data for	• Protocols, monitoring procedures/plans, and/or DMPs for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking

No.	Items related to registry design/operation	Examples of alternative rules, etc., such as SOPs
	registries directly or via information sources. Companies and applicants-to-be could check records of monitoring undertaken in accordance with the specified procedures as needed. For the implementation procedures, “Basic principles on risk-based monitoring in clinical trials” (PSEHB/PED Notification No. 0705-7, by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated July 5, 2019), can also be consulted for reference.	primary studies related to registry establishment are affiliated • Definition of registry database (e.g., EDC) requirements • Protocols, monitoring procedures/plans, and/or DMPs for studies using registry data
11	Rules related to quality assurance Purpose/content The registry holders must confirm that the maintenance of organizational structures and data quality control have been performed depending on the purposes of registry establishment and quality of data obtained. Companies and applicants-to-be could check records of monitoring undertaken in accordance with the specified procedures as needed.	• Protocols and/or audit procedures/plans for primary studies related to registry establishment • Protocols and/or audit procedures/plans for studies using registry data
12	Rules related to the retention of records while preparing application documents for re-examination, etc. Purpose/content When application documents for marketing approval are prepared using registry data, the supporting data must be retained in accordance with the pre-specified procedures. Companies and applicants-to-be could check records of monitoring undertaken in accordance with the specified procedures as needed.	• Operating rules of registry holders (e.g., academic societies and research groups) • Protocols of primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry establishment are affiliated
13	Rules related to education/training of persons engaged in registry establishment/management	• Protocols, monitoring procedures/plans, and/or DMPs for

No.	Items related to registry design/operation	Examples of alternative rules, etc., such as SOPs
	Purpose/content Education/training must be provided to computer system users considering overall computer systems, security requirements, and registry-specific handling. Education/training must also be provided to persons in charge of data entry considering procedures to appropriately gather data on pre-specified survey items.	primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary studies related to registry establishment are affiliated
14	*Records on ethical considerations Purpose/content Protection of personal information must be considered regardless of the data quality control methods. When registry data are used for an application for marketing approval, it is necessary to pay adequate attention to the protection of personal information of patients, as the registry data are to be provided by the registry holder to the applicant. In accordance with the Act on the Protection of Personal Information and other applicable regulations, the requirements and procedures related to obtaining consent from patients providing data to registries must be specified. If consent is to be obtained from patients, a patient information	• Operating rules of registry holders (e.g., academic societies and research groups) • Protocols, monitoring procedures/plans, and/or DMPs for primary studies related to registry establishment • Rules of organizations/data centers to which the representative persons undertaking primary
	document presenting necessary information must be prepared. If it is possible for third parties (e.g., monitors, auditors, and regulatory authorities) to access source documents, etc., stored in information sources, this must be presented in the patient information document as needed.	studies related to registry establishment are affiliated • Definition of registry database (e.g., EDC) requirements • Protocols, monitoring procedures/plans, and/or DMPs for studies using registry data

Note: *Items that are not included in the Annex titled "Points to consider for ensuring the reliability of post-marketing database study for drugs" (PSEHB/PED Notification No. 0221-1 issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated February 21, 2018).

References

1) Shibata T. Project title of AMED Research on Regulatory Science of Pharmaceuticals and Medical Devices: Utilization of real world evidence using patient registry data to support regulatory decision-making"Proposal on Assuring the Reliability of Patient Registry Data for Use in Application Dossiers of Pharmaceuticals and Medical Devices." Jpn Pharmacol Ther 2019; 47 suppl 1: s9-s22.

<Example alternative rules, etc., such as SOPs>

Study title: A prospective clinical registry study of genetic profiling and targeted therapies in patients with rare cancers (MASTER KEY Project)

as of April 9, 2021

No.	Items related to registry design/operation	Organizational rules													Documents of individual studies												
		MASTER KEY Project collaborative study agreements	[Document No. omitted] EDC-based data management	[Document No. omitted] EDC system validation	[Document No. omitted] Registration/change of EDC system us	[Document No. omitted] Education of EDC system users	[Document No. omitted] Central monitoring	[Document No. omitted] Retention of records	[Document No. omitted] Information security measures	[Document No. omitted] Electronic records	[Document No. omitted] Computerized system validation	[Document No. omitted] Quality management system (QMS)	[Document No. omitted] Information security manual	Research protocol	Validation plan_version 1.0.0	Validation report	UAT plan	UAT report	WEB system manual	EDC operation manual	EDC entry manual	Electronic signature handling rule	Procedures provided by vendors	Central monitoring	Data management plan	Data cleaning plan	Monitoring procedure/plan	Audit procedure/plan
1	Rules related to establishment/management	●																									
2	*Standards/procedures for data entry into patient registries		●																●	●	●						
3	Standards/procedures related to data cleaning		●				●												●	●				●	●		
4	Standards/procedures related to coding		-Note	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	Rules/procedures related to security				●	●			●																		
6	Rules/procedures related to data backup and recovery							●		●												●					
7	Rules related to the quality control of medical data collected from information sources		●						●																●	●	
8	*Validation plans/reports related to computer systems			●						●	●				●	●	●										
9	Rules to validate whether the preparation of datasets for analysis or analysis results is performed appropriately													●													
10	Rules related to the reporting of quality control-related plans and results of investigation		●									●												●	●	●	
11	Rules related to quality assurance		●											●											●	●	
12	Rules related to the retention of records of the preparation of application documents for re-examination		●					●																			
13	Rules related to education/training of persons engaged in registry establishment/management		●			●																					
14	*Records of ethical considerations				●				●					●											●		

Note: Not applicable (coding is performed in accordance with the procedures for registry users but is not performed by registry holders.)