Proposal on Assuring the Reliability of Patient Registry Data for Use in Application Dossiers of Pharmaceuticals and Medical Devices.

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AMED Research on the Regulatory Science of Pharmaceuticals and Medical Devices
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Introduction

For rare diseases and in other cases where traditional and/or orthodox randomized controlled clinical trials are difficult to conduct, efforts have been made in recent years to explore the use of the data from existing patient registries for marketing approval applications of pharmaceuticals, medical devices and regenerative, cellular therapy and gene therapy products（hereinafter referred to as "drugs, etc."）; or for re-examination applications（including use-results survey of medical devices）（hereinafter referred to as "approval applications, etc."）; or for evaluation of drugs, etc. as "real-world data."

Patient registries are designed/operated by diverse parties, including governments, healthcare institutions and academic societies, for various medical and scientific purposes. Data of relevant patients, such as those related to medical practice, are accumulated in databases in an integrated manner according to those purposes. There are different ways to use patient registries for the development of drugs, etc. The 5 usages presented below are the main ones assuming they are used for individual drugs, etc.

（1）Market research/Investigation of feasibility of clinical trials
（2）Preparation of protocols of clinical trials/postmarketing clinical trials
（3）Recruitment of candidate patients for participation in clinical trials/postmarketing clinical trials
（4）External controls（including historical controls）in clinical trials/investigator-initiated clinical trials（hereinafter referred to as "clinical trials, etc."）in the field of rare diseases or other fields or on medical devices or other products, for which it is difficult to implement the development by randomized controlled trials at the significance level/statistical power that is commonly used in confirmatory trials, under the following conditions:
- randomized controlled trials at a less strict significance level/with a lower statistical power are difficult to conduct
- a control group is not necessary in the same

（Note）This document was prepared by the research team by compiling the research results from fiscal years 2016 to 2018.

study but information on an external control is useful as supporting data for evaluation of drugs, etc.

(5) Postmarketing surveillance

For the purpose of approval applications, etc., patient registry data are expected to be used in an application dossier for (4) and in a re-examination application dossier for (5) above. In particular, the use for (4) is roughly divided into (i) use as an alternative to the data from randomized controlled clinical trials that serve as evidence for efficacy; (ii) use as a supplement, in terms of safety and other information, for the clinical data package; and (iii) use as a source of data on actual medical practice when these data are difficult to obtain in clinical trials, etc.

For each patient registry, whether or not its data can be used for approval applications, etc. depends on the purpose and status of its design/operation. Because there are extremely diverse ways to use patient registries depending on the therapeutic areas or purposes, and the registries are not usually designed/operated for approval applications, etc., the quality of the accumulated data varies. As required in "Ethical Guidelines for Medical and Health Research Involving Human Subjects (28 MEXT/RPB Notification No. 406, MHLW/MS/HSD Notification No. 0228-1, and MHLW/HPB Notification No. 0228-1 dated February 28, 2017, issued by the Director General of Research Promotion Bureau, the Ministry of Education, Culture, Sports, Science and Technology, the Director of the Health Sciences Division, Minister's Secretariat, the Ministry of Health, Labour and Welfare, and the Director General of Health Policy Bureau, the Ministry of Health, Labour and Welfare)", researchers should ensure the reliability of data-they have to make sure that the information used in their research and the records related to the information concerned are accurate. However, there will be different opinions regarding the degree and the method of this assurance, depending on the situation. In light of these circumstances, the concept of data reliability assurance in the use of patient registries for approval applications, etc., needs to be carefully discussed. Decisions on the level of data reliability required for patient registries and the method for ensuring this reliability should be made according to the purposes of the use of the registries. Therefore, it is difficult and inappropriate to define uniform reliability criteria for all purposes. When using patient registry data for approval applications, etc., the reliability of the data needs to be ensured at a level considered sufficient in light of the purpose of the use. However, it is also not necessarily adequate to define the same level of requirements as those for clinical trials, etc. in the use of patient registries for approval applications, etc. Instead, it is desirable to clarify the level specific to patient registries. Nevertheless, patient registries vary in their characteristics and so do the methods for using them; it is therefore unclear how the reliability of the data should be ensured, which may inhibit the utilization of otherwise potentially useful data.

Focusing on the use of patient registry data for a new drug application dossier or a re-examination application dossier (hereinafter referred to as "application dossier, etc."), we will present in this document (hereinafter referred to as "this proposal") the basic ideas for the requirements for the design and operation of patient registries that should be met in the use of these registries for the purpose of approval applications, etc. of drugs, etc., as well as possible requirements that applicant companies should meet in the use of patient registries for approval applications, etc. of drugs, etc.: the former requirements are presented for parties that design/operate patient registries (hereinafter referred to as "patient registry holders") and the latter requirements are presented for users of these patient registries for approval applications, etc. of drugs, etc. We hope that, with the help of this proposal, use of patient registries for approval applications, etc. will be considered more often and there will be more chance of actual use.

1. Objectives

In this proposal, we list the points that patient registry holders and the users of patient registries for approval applications, etc. of drugs, etc. need to consider in order to appropriately ensure the reliability of the data being used or expected to be used for such purposes. In doing so, we divided the points into i) those related to the design/operation of patient registries and ii) those related to confirming that the reliability of the information presented in an application dossier, etc. was ensured at a level considered sufficient in light of the purpose of use.

Ethical issues associated with the use of patient registries for approval applications, etc., are important and need to be handled appropriately. However, the details of

these issues will not be handled in this proposal. Moreover, use for approval applications, etc. may raise issues that are difficult to handle in accordance with the current Japanese GCP ordinance. We therefore consider that it is necessary to separately discuss how the regulatory system should respond to such use. This discussion is also outside the scope of tasks conducted by our research team and is therefore not included in this proposal.

2. Parties to which this proposal is applicable

This proposal is applicable to ⅰ）the patient registry holders who provide or are considering providing the patient registry data concerned to the parties that plan to file marketing approval applications, etc. of drugs, etc.（hereinafter referred to as "applicants"）for the use in application dossiers, etc. that are classified into the categories（4）or（5）, mentioned above in "Introduction" and ⅱ）the parties（applicants）that use or are considering using the concerned patient registry data for application dossiers, etc., in a manner classified into the categories（4）or（5）mentioned above. This proposal is not applicable to patient registry holders or parties that use patient registries that do not meet the above conditions.

This proposal is also not applicable to cases including（1）,（2）, and（3）above, clinical research where the use is not for the purpose of application dossiers, etc., or cases where the patient registry concerned is originally designed to fulfill the approval conditions and is subject to other regulations including the GPSP（Good Post-marketing Study Practice）ordinance. From the perspective of regulatory sciences, patient registry data may be used, for example, to evaluate the adequacy of alternative endpoints for individual diseases, not assuming development or regulatory approval applications, etc. of specific drugs, etc. Such use is not dealt with this proposal.

3. Concept of data reliability

3.1 Standards of reliability of application dossiers, etc. in general and process of confirmation

The Pharmaceuticals and Medical Devices Agency（PMDA）confirms the reliability of application data from clinical trials, etc. attached to the approval application using roughly 2 processes: ⅰ）confirmation in accordance with the standards of reliability（Article 43 of Enforcement Regulations for Law on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics［hereinafter referred to as "Enforcement Regulations"］for drugs, Article 114-22 of Enforcement Regulations for medical devices, Article 137-25 for regenerative, cellular therapy and gene therapy products and, during re-examination, Article 61 of Enforcement Regulations for drugs, Article 114-42 for medical devices and Article 137-42 for regenerative, cellular therapy and gene therapy products）and ⅱ）confirmation in accordance with GCP（Good Clinical Practice）（**Figure 1**）.

In the confirmation in accordance with the standards of reliability, the accuracy, integrity/completeness, and preservation of the data（specifically, the data that serve as evidence）attached to the approval application are confirmed. Main evidence data include the materials or other forms of data that clinical trial sponsors should retain. An example is evidence data related to quality assurance of the data, including those in the data management plan/report and the statistical analysis plan/report. Case report forms and monitoring records at all healthcare facilities are also considered to be main evidence data. Among these evidence data, some, including the data from case report forms at healthcare facilities, need to be checked in terms of the compliance with GCP. This compliance is checked in on-site inspections at a certain number of selected healthcare facilities. Specifically, evidence data that should be retained at healthcare facilities, including medical records, laboratory test slips, and patient diaries, are checked. Overall, there are 2 purposes of this inspection: one is to ensure the scientific quality of clinical trials and the reliability of the results; the other is to protect the human rights and safety of the subjects. From the latter perspective, the process involved and other aspects of the acquisition of consent from subjects are also confirmed.

3.2 Standards of reliability and confirmation process for use of patient registries in application dossiers, etc.

When confirming the reliability of patient registry data, it is unrealistic to apply all the requirements related to on-site inspection for GCP compliance（although their necessity cannot be denied）, because studies using patient registries are planned and conducted differently than clinical trials, which are intervention studies. Never-

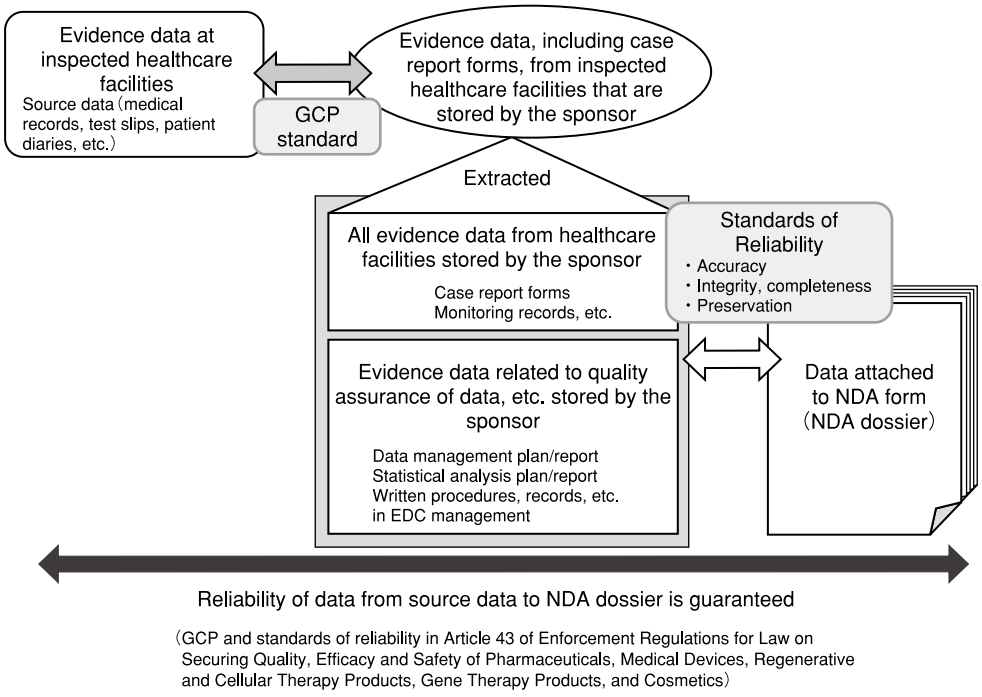

Figure 1　Overview of data reliability assurance in clinical trials of drugs ——GCP standard and standards of reliability

theless, as patient registries are intended for medical/scientific purposes, they need to be designed/operated in a manner in which data reliability is sufficiently ensured in light of the actual status of consultation and follow-up of patients in each therapeutic area, as well as the purposes regarding the use of patient registries. In this sense, it is considered rational to confirm data reliability by referring to the standards of reliability.

For this reason, we do not list in this proposal the possible requirements of compliance review in accordance with GCP and with the standards of reliability. Instead, regarding the items for which inspection or compliance review is carried out, we maintain the structural relationships between patient registries and clinical trials when discussing the following 2 aspects: ⅰ）matters related to the design/operation of patient registries（relationship between healthcare facilities and patient registry holders, **Figure 2**,(a)), and ⅱ）matters necessary for determining that the reliability of the information presented in application dossiers, etc. is ensured at a level considered sufficient in light of the purpose of its use（relationship between patient registry holders and applicants and relationship between applicants and application dossiers, etc., **Figure 2**,(b) and (c)). For the criteria for postmarketing surveillance, the GPSP ordinance is applied, while for the criteria for postmarketing clinical trials, the GPSP and GCP ordinances are applied.

It should be noted that unlike clinical trials, many patient registries are not planned/operated by pharmaceutical companies, and thus the relationship between the clinical trial sponsor（pharmaceutical company）and the contract research organization assumed in Article 12 of the GCP ordinance is hardly applicable to the relationship between the applicant（pharmaceutical company）and the patient registry holder. Even if the contract signed by the applicant（pharmaceutical company）and the patient registry holder in the above relationship corresponds to Article 12 of the GCP ordinance, the actual contract depends on the usage of data and the relationship between the parties involved in the contract, and may be similar to the contract for data provision or other matters between a pharmaceutical company and a sponsor-investigator in cases of utilization of the data from an investigator-initiated clinical trial, or the contract between a pharmaceutical company and a business operator handling medical information database（a DB business）based on the GPSP ordinance（**Figure 3**). The relationship between a healthcare facility and a patient registry holder generally varies

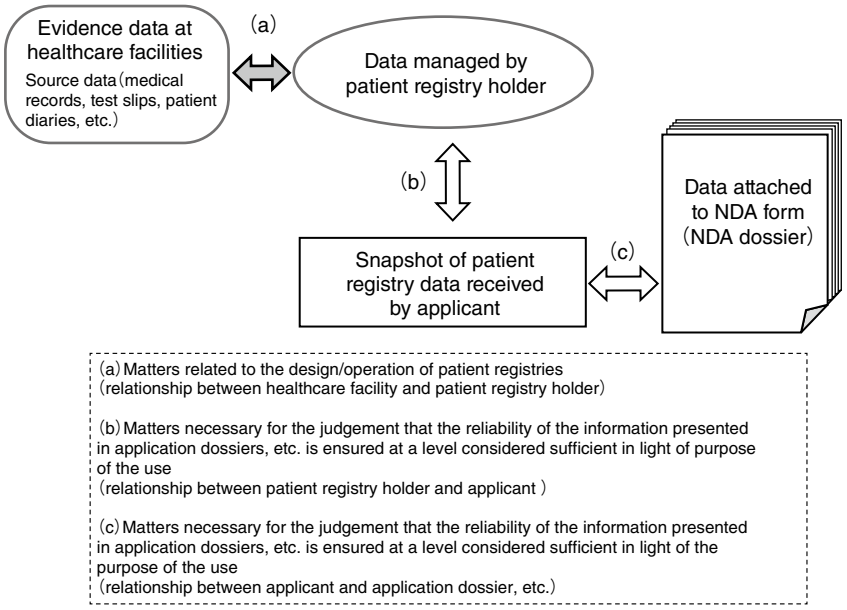

Figure 2　Points of reliability assurance between parties involved in patient registries

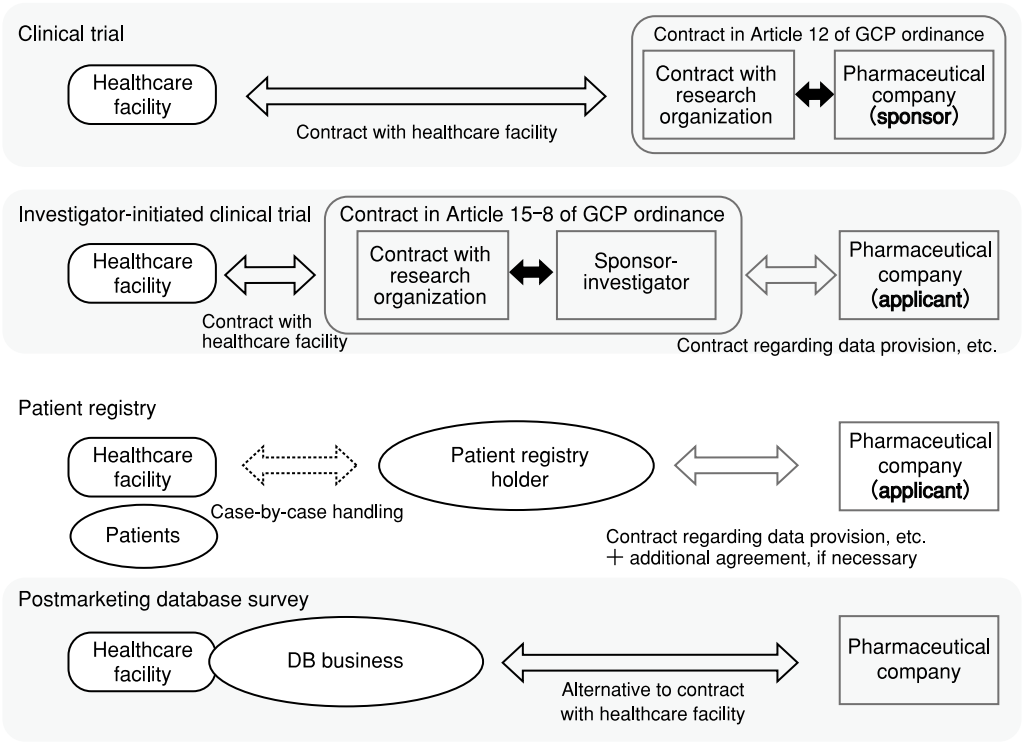

Figure 3　Diagram of contractual relationship

according to the presence or absence of a contract. For some patient registries, the holder has a direct relationship not with a healthcare facility, but with patients. That is to say, because of the diversity in how patient registries are planned/operated, their relationships with pharmaceutical companies may range from those similar to the ones in investigator-initiated clinical trials shown in **Figure 3** to those similar to the ones in postmarketing database surveys. However, one point of view is that in use cases of approval applications, etc. that are beyond the scope dis-

Table 1　Responses of involved parties categorized by purpose/usage

Purpose	Usage	(a) Between healthcare facility and patient registry holder	(b) Between patient registry holder and applicant (or health care company, etc.)	(c) Between applicant and application dossier, etc.
Other than approval applications, etc.	(1) Market research/Investigation of feasibility of clinical trials	Confirmation of achievement of the standard specified jointly by the healthcare facility and the patient registry holder	Confirmation of the absence of a gap between the quality of information the patient registry can provide and the quality of information requested by the company, etc.	−
	(2) Preparation of protocols for clinical trials/postmarketing clinical trials			−
	(3) Recruitment of candidate patients for participation in clinical trials/postmarketing clinical trials			−
Approval applications, etc.	(4) External controls (including historical controls) in clinical trials, etc. (including postmarketing clinical trials) in the field of rare diseases and other fields in which development by regular clinical trials, etc. is difficult	Confirmation of consistency between the source data at healthcare facilities and the patient registry data which are based on GCP (for example, confirmation of consistency with the source data under a certain condition; if confirmation is difficult, the reason should be explained)	Direct confirmation by the applicant of the status of operation and other aspects of the patient registry	Compliance review
	(5) Postmarketing surveillance	Confirmation that the patient registry is designed and operated in a way that the source data at the healthcare facility are appropriately registered in the registry (if confirmation is difficult, the reason should be explained)	Direct confirmation by the applicant of the status of operation and other aspects of the patient registry	Compliance review

(a) Matters related to the design and operation of patient registries
(b) Matters necessary for the judgement that the reliability of the information presented in application dossiers, etc. is ensured at a level sufficient in light of the purpose of the use
(c) Matters necessary for the judgement that the reliability of the information presented in application dossiers, etc. is ensured at a level sufficient in light of the purpose of the use

cussed in this proposal, the formatting of contracts, handling of data, and other aspects should be performed in the same way as in clinical trials, complying with the GCP ordinance. In other words, it is crucial whether or not the use case is within the scope discussed in this proposal. To resolve this difference in opinions, case-by-case discussions of specific situations are necessary. It is important for the applicant and/or patient registry holder to proactively consult PMDA regarding these specific situations.

3.3 Relationship between usage of patient registries and reliability confirmation process

For the usage of patient registries in (1) to (3) in "Introduction," it should not be problematic in **Figure 2** (a) if appropriate measures are taken between the healthcare facility and the patient registry holder, and no problems related to (c) should arise. For (4) and (5), certain responses need to be taken for (a) (see **Table 1**). However, the standard required for (4) and (5) is not the same as the standard assuming the requirements corresponding to those in GCP or GPSP. In principle, under the qual-

ity management system created according to the therapeutic area or the characteristics of the patient registry at the time the registry is established, reliability needs to be assured from the perspective of(a), through the operation of the registry and other related tasks in accordance with various written procedures listed as examples in "4. Matters related to design/operation of patient registries: examples of written procedures and other materials of patient registry holders（for reference)".

3.4 Concept of reliability in use as "control group, etc. in clinical trials, etc. in the field of rare diseases and other fields in which development by regular clinical trials, etc. is difficult"

（ｉ）Circumstances in the development of drugs, etc. for rare diseases and other diseases in which drug development by regular clinical trials, etc. is difficult

In this proposal, it is assumed that the main circumstances in which patient registries are used are: ｉ）"the field of rare diseases or other fields in which randomized controlled trials at the significance level/statistical power commonly used in confirmatory trials and other clinical trials designed/planned acceptable by regulatory authorities are difficult to conduct," in other words, circumstances in which regular development is difficult, and ii）"the circumstances/fields in which controlled trials used to be difficult, but it is considered appropriate to conduct controlled trials with concurrent control formed using patient registries."

The main purpose of this proposal is to clarify the currently obscure conditions and points of discussion for data usage in situations where it is difficult to collect sufficient data under a common development policy. Therefore, this proposal does not discuss the use of patient registries for straightforward data collection in situations where sufficient data collection is possible.

If the same level of reliability as in clinical trials, etc. is required in the above situation where sufficient data collection is difficult, this requirement defeats the purpose of using patient registries; the need to rely on patient registries is assumed in this discussion. In addition, this requirement would make it difficult to use the registries. Nevertheless, as long as registries are used for approval applications, etc., data reliability needs to be ensured. Therefore, patient registry holders must maintain the reliability of data or other information they provide to applicants when they prepare the data sets at the time of data lock or data cutoff, when they prepare the data sets for analysis, and, if analysis results are provided to outside parties, when they compile the analysis results（including output sheets, tables, figures, and other forms）and prepare the analysis reports. Applicants or regulatory authorities may request that patient registry holders provide documents confirming the above reliability assurance.

（ii）Method for assuring the reliability of patient registry data on individual patients

Unlike the case in which summary statistics are cited from published papers or other sources for use as an external control, the use of data on individual patients provides researchers with the advantage of being able to perform detailed/precise statistical analysis of patient background factors, clinical information and other data, instead of having only the information regarding endpoints. To make this possible, the reliability of data in patient registries has to be ensured at a level considered sufficient in light of purpose of their use. For this reason, when usage（4）is intended, certain methods for data reliability assurance, for example, Source Document Verification（SDV), are supposed to be performed by the patient registry holder; that is, sampling and checking of the accuracy of the source documents, including medical records and the data registered in the patient registry. If data are obtained not by manual input but through a computer system that retrieves the data from electronic charts or other records, confirmation that the system is working as designed can be one method of reliability assurance.

Depending on the therapeutic area and the form of patient registry, SDV or other methods may be difficult to perform. This is because the data concerned may not be recorded in the source document, or because confirming the record in the source document may not be possible for reasons including the following:

- The system for patient follow-up in daily medical practice varies by disease.
- Medical records are not intended to include information that is necessary for potential future analyses, but rather information that is necessary in daily medical practice, and therefore these records may not be considered to be source data.
- When a patient registry is established without assuming the use of its data for approval applications, etc.,

patient consent may not have been obtained for viewing of medical records and other information by the applicant or other parties. If this consent was not obtained, SDV, which is considered as one option to directly confirm the status of the operation and other aspects of the patient registry by the applicant, is difficult to perform.

- The patients concerned are not necessarily treated at the same facilities throughout their clinical course, and there are limitations regarding the collection of information from other facilities.

In the above cases, the reason it is difficult to assure data reliability using the patient registry holder's SDV or other methods needs to be clarified by the applicant, as does the adequacy of the use of the relevant patient registry for approval applications, etc. Alternatively, a rule can be set specifying that certain information registered in the patient registry is handled as source data.

However, even when the source document is specified, it is not acceptable to perform SDV in a formal manner only. Because of the characteristics of patient registries, the following issues would arise.

- Unlike in clinical trials, etc., endpoints, observation schedules, analysis methods, and other details are not specified in advance; therefore the definition of the source document that provides the source data for patient registries may be ambivalent, as may the information itself.
- Unlike in clinical trials, etc., it is difficult to determine what cost is acceptable for reliability assurance when it is uncertain if the data are going to be used; even if they are used, the purpose of the use or requirements for the use, including the level of accuracy/precision of the registries, are uncertain.

Therefore, it may be necessary to check, in light of the purpose of data usage, if there are any problems with the analysis plan and evaluation of the analysis results.

Moreover, patient registry holders should, if they assume there will be a future use for an application dossier, etc., establish or review the design/operation system of the registries. For example, holders can introduce a mechanism to retain the records that serves as the source data for the patient registry data, in forms including the source document and alternative documents. They can also attempt to obtain the consent of patients for possible use of their data. In addition, depending on the usage, consent needs to be obtained for the collection/utilization of data and for the confirmation of the source document by involved parties.

（iii）Different levels of rigor required for data reliability assurance

Assuming that SDV or other methods are necessary, the level of rigor required needs to be discussed not only considering the regulatory systemic aspects and feasibility mentioned above, but also in relation to the level of precision required for the specific usage and the strength of unavoidable bias.

First, for both rare diseases and other diseases, when errors and their proportions and other characteristics in the data concerned are identified by SDV or other methods, it is easy to determine whether or not the data in the relevant patient registry are sufficiently precise given the purpose of the data usage. For example, when the capture proportion of an outcome event is not 100%, but the uncertainty involved can be estimated, it is possible to make an inference in the statistical analysis that takes the uncertainty into account. If the precision for the final inference is sufficient even when the uncertainty in the event capture is taken into account, an event capture proportion below 100% would not in itself pose any problem in the sense that erroneous judgement can be avoided. In other words, what is important is not the absence of errors in data, but the fact that the quality and quantity of errors are maintained within a range that does not lead to erroneous judgements based on the data. In order to make such judgements possible, methods for reliability assurance and associated records are beneficial. This is similar to scientific experiments where the measurement error of each measurement device used in the experiments is not zero, but there is no problem if the measurement error can be identified and the level of overall error resulting from the accumulation of individual errors still allows for conclusions to be drawn at a sufficient level of precision.

Additionally, regarding patient registries for which the timing of data collection is not specified in advance, unlike interventional studies, attention should be paid to the impact of bias associated with data collection. Patient registry data include 1）the data related to patient background before the start of the treatment with the drugs, etc. that are to be evaluated, and 2）the data related to the outcome measured after the start of the treatment. For the

latter, whether or not data are collected is likely to be associated with each patient's condition, that is to say, with the outcome of treatment with the drug, etc. Unlike interventional studies in which the timing of tests is specified in advance and the tests are performed regardless of patient condition, in cases of patient registries physicians decide whether or not to perform certain tests according to patient condition. Therefore, analyzing the obtained data as they are may give rise to bias in the evaluation of treatment results. Moreover, patients' conditions may sometimes affect whether or not information from certain patients is registered into patient registries. In such cases, there may be a concern regarding the appropriateness of registered patients as comparators. Even when complete consistency between source documents and data in a patient registry is confirmed by SDV or other methods, the data might not be usable because of the bias mentioned above, depending on how the data will be used.

Thus, the level of rigor required for data reliability assurance depends on how the patient registry data are used in approval applications, etc.(how they are characterized compared with other data in clinical data package, importance placed on them in PMDA review, etc.), disease, status of existing therapeutic methods, characteristics of drugs, etc., statistical characteristics of the used data, including the level of precision required for discussion, and other factors. In addition, patient registries differ in their design/operation, which makes it difficult to ensure the reliability of data using a uniform standard. For this reason, the level of data quality should be objectively defined by the quality management system in each patient registry, and, in discussion/consultation with PMDA and other parties, the following matters should be addressed: 1）matters for which applicants should present their opinions in discussion, 2）matters for which PMDA should present its opinions, and 3）matters for which patient registry holders should present their opinions, as necessary.

If consultation experience accumulates to a certain extent in the future and consultation cases are classified into certain types and the result is disclosed by PMDA, the issues that should be addressed in consultation are clarified/specified for both applicants/pharmaceutical companies and patient registry holders. Discussion should take place about the feasibility of clarifying the issues to be addressed in consultation with PMDA and about related systemic improvement. In this section, we discussed how to scientifically conceptualize and respond to the limits of data reliability assurance that necessarily arise despite maximum measures taken in light of the data usage.

（iv）Data storage

In addition to the above, appropriate storage of data is important. In "Ethical Guidelines for Medical and Health Research Involving Human Subjects," storage of information is mentioned in relation to research reliability assurance. Some research institutions have a specific system for storing the data sets and other information that serve as evidence in research papers and other materials. Patient registry holders need to specify the data storage site and the person responsible for the storage to ensure the appropriate storage of the data concerned, even when the data are used for approval applications, etc.

4. Matters related to design/operation of registries: examples of written procedures and other materials that patient registry holders should prepare (for reference)

The written standard operating procedures and other materials that patient registry holders should prepare when data are used for postmarketing surveys are listed in the attachment to "Points to Note regarding Reliability Assurance in Postmarketing Database Surveys for Drugs" (MHLW/PSEHB/PED Notification No. 0221-1 dated February 21, 2018, issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, the Ministry of Health, Labour and Welfare). Patient registry holders should refer to this list when preparing and following the written procedures and other materials.

However, the written procedures and other materials necessary for the conduct of clinical trials, etc. that utilize patient registries should be discussed further.

The items with * are not included in the above notification.

1）Rules regarding establishment/management

○ Organizational structure: Responsible person, manager, locus of responsibility for facilities, education/training and other matters at patient registry holders.

○ Management of outsourcees: The procedures or plans

to confirm the appropriate management of outsourcees by patient registry holders in cases where patient registry holders outsource some of their tasks.

2）*Standards/procedures for entering data into patient registries

○ Roles of the department in charge and persons in charge: Responsibilities of patient registry holders and persons involved in the tasks, including the healthcare facilities and other parties that provide the data, are specified in written procedures.

○ Receipt, entry/import of data: Methods for provision and receipt of data（via network, media, etc.）, procedures for input/import, handling of entered data and other details are specified in written procedures. For data entry, in particular, the preparation of detailed procedures regarding handling of entered data and other tasks leads to data quality assurance.

○ Anonymization of data（anonymization with a decoding index retained at the facility as necessary）: The anonymization method used in the patient registry is described in written procedures. In anonymization of personal information, whether or not the decoding index should be retained at the facility depends on the purpose of the collection of patient registry data and the usage of the data.

○ Method of confirming that data entry/import is correct: Method of confirming the correctness of data entry/import is described in written procedures.

○ Management of outsourcees: Written standard operating procedures and plans for confirming the appropriate management of outsourcees by patient registry holders when patient registry data are used for approval applications, etc., in which patient registry holders outsource some of their tasks.

3）Standards/procedures for data cleaning

○ Roles of the department in charge and persons in charge: Departments and responsibilities of the person responsible for this task, manager of this task and person in charge of this task.

○ Standards/procedures of this task: Data items subject to cleaning and details specified for each step taken by patient registry holders to implement the cleaning（importing data collected from information sources, preparing data sets for analysis, etc.）.

○ Procedures for modifying the standards of this task: Procedures and process of modifying the standards of data cleaning.

○ Management of outsourcees: Procedures and plans for confirming the appropriate management of outsourcees by patient registry holders in cases where patient registry holders outsource some of their tasks.

4）Standards/procedures for coding

○ Roles of the department in charge and persons in charge: Departments and responsibilities of the person responsible for this task, manager of this task and person in charge of this task.

○ Standards/procedures of this task: Data to be coded and details specified for each step taken by patient registry holders to code the data（importing data collected from information sources, preparing data sets for analysis, etc.）.

○ Preparation of coding list and other materials（master）to be used for coding: Frequency and methods of updating the masters concerned.

○ Procedures for modification of the standards for this task: Procedures and process of modification of the standards for coding by patient registry holders.

○ Management of outsourcees: Procedures and plans for confirming the appropriate management of outsourcees by patient registry holders in cases where patient registry holders outsource some of their tasks.

5）Rules/procedures related to security

○ Roles of the department in charge and persons in charge: Departments and responsibilities of the person responsible for this task, manager of this task and person in charge of this task.

○ Rules for information security

（i）Rules for management of logging into and out of healthcare information databases: Rules for entry/exit are set at the level considered necessary in light of the healthcare data handled in the healthcare information databases, the structure of the system and the operation method to specify the preparation/use/storage of the log-in/log-out record.

（ii）Rules for management of users: Range of users and management methods, including user

account setup, are specified.
（iii）Rules for access control: Setup and control of authorization of user access in accordance with the importance of healthcare data are specified.
（iv）Rules for network security: Rules are set for network security.
○ Rules for other types of security: Rules related to the plans for continuation of business, etc. are set.

6）Rules/procedures related to data backup and recovery
○ Roles of the department in charge and persons in charge: Departments and responsibilities of the person responsible for this task, manager of this task and person in charge of this task.
○ Data to be backed up/frequency/generation management/destination: Rules including those regarding the back-up or update frequency of the whole healthcare information database, number of generations to be stored, media used for backup, storage location and storage period.
○ Plans and procedures for recovery: Plans for recovery, including specific details and procedures.
○ Recovery testing: Record of the results of recovery testing.

7）Rules regarding quality control of healthcare data collected from information sources
○ Roles of the department in charge and persons in charge: Persons in charge of this task and their responsibilities at the information sources and patient registry holders.
○ Provision and receipt, entry and import of healthcare data: Methods for provision and receipt of healthcare data（via network, media, etc.）, and procedures for entry（including standards for input［dictionaries, etc.］）and import.
○ Input to/output from healthcare information databases: Method for confirmation of correct entry/import of healthcare data.

8）*Plan/report for validation of computer systems
○ Person who performs validation, person responsible for validation: Record is prepared specifying the name of the person who performed validation and that of the person responsible for validation.
○ Systems to be validated, methods and procedures for validation: Systems to be validated and the interval, techniques and other details of validation are described in the plan.
○ Results of validation: Validation result report is prepared.

9）Rules for verifying the appropriate preparation of data sets for analysis or analysis results.
○ Roles of the department in charge and persons in charge: Departments and responsibilities of the person responsible for this task, manager of this task and person in charge of this task; preparation to be verified/methods/procedures of this task; interval, methods and other details of this task.
○ Report of results of this task.
○ Management of outsourcees: In cases where patient registry holders outsource some of their tasks, procedures and plans for confirming the appropriate management of outsourcees by patient registry holders.

10）Rules regarding plans related to quality control/report of confirmation results.
○ Roles of the department in charge and persons in charge: Departments and responsibilities of the person responsible for this task, manager of this task and person in charge of this task.
○ Rules regarding quality control plans（including rules regarding what is subject to quality control）and report（including confirmation results）.

11）Rules regarding quality assurance
○ Roles of the department in charge and persons in charge: Departments and responsibilities of the person responsible for this task, manager of this task and person in charge of this task.
○ Rules regarding quality assurance（including rules regarding how quality assurance is defined）.

12）Rules regarding storage of records related to preparation of application dossier for re-examination, etc.
○ Roles of the department in charge and persons in charge: Departments and responsibilities of the person responsible for this task, manager of this task and person in charge of this task.
○ Records to be stored: Rules regarding the preparation

of data sets for analysis or analysis results and the data or other materials prepared during the investigation.
○ Procedures for storage: Rules regarding location, procedures, period and other details of storage.
○ Procedures for transfer: In cases of transfer, rules regarding destination and procedures of transfer.
○ Procedures for disposal: Rules regarding procedures and other details of disposal.

13）Rules regarding education and training of persons including those involved in establishment/management
○ Timing and total number of hours of education and training: Rules regarding timing and total number of hours of education and training.
○ People to be educated and trained: Rules regarding people to be educated and trained on each subject.
○ Persons in charge of education: Rules regarding the person in charge of each education and training session.
○ Content of education and training: Rules regarding the content of education and training sessions.
○ Evaluation of results of education and training: Rules regarding the record summarizing the results of education and training sessions.

14）*Record of ethical consideration

5. Points to note regarding data reliability assurance（matters applicants should address to ensure that the information presented in application dossiers, etc. are consistent with the objective）

The following points need to be examined when a decision is made to use the registry concerned for an application dossier.

1）System of operation and other aspects of the patient registry
○ Necessary arrangements for audit, access to data and other matters should be made with the applicant.
○ System/procedures that enable the applicant to confirm that the patient registry is properly and smoothly operated/managed should be prepared in advance.
○ From the perspective of personal information, appropriate management of data is necessary.

2）Management of patient registry
○ In approval applications, the computer system concerned is required to comply with the "Guideline on Use of Electromagnetic Records/Electronic Signatures in Applications, etc. for Approvals, Licenses, etc. of Drugs, etc."（MHLW/PMSB Notification No. 0401022 dated April 1, 2005, issued by the Director General of Pharmaceutical and Medical Safety Bureau, the Ministry of Health, Labour and Welfare）（however, the level of compliance differs according to the purpose of use）.
○ Regarding the above requirement, there is an opinion that the system should comply with the guideline in the same way as clinical trials. Therefore, it is desirable to consult PMDA in advance when the policy is determined in each situation.
○ In re-examination applications, compliance with the guideline is not required except in cases of postmarketing clinical trials. However, it is appropriate to establish the system by referring to this guideline.
○ In order to operate/manage patient registries in a manner that the source document, including medical records, can be retrospectively confirmed, decoding indices for each healthcare facility need to be prepared and appropriately stored.
  ● Because it is considered difficult to specify universal rules regarding who stores decoding indices and how to store them given the diversity of registry formats, operations and organizations, the tables should at least be utilized according to the "Ethical Guidelines for Medical and Health Research Involving Human Subjects."
  ● Moreover, when the use of the patient registry for an application dossier, etc. is planned, it is necessary to reach an agreement with the applicant regarding the possibility of confirming the source document and, if possible, details of the confirmation.

3）Quality assurance
○ The patient registry holder needs to ensure the quality of the data or other materials provided to the applicant in accordance with the rules regarding the quality assurance system that were specified in advance.
○ The patient registry holder needs to store related records.

○ The patient registry holder also needs to prepare materials regarding the quality of the patient registry so that these can be presented to the applicant.

4）Storage of records

○ It is assumed that records storage is implemented in accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects." However, as the data are used for application dossiers, etc., it is necessary to reach an agreement with the applicant regarding the storage method and duration for the records such that they will demonstrate appropriate data reliability assurance.

5）Contract with applicant

○ In cases where data are used for approval applications, a contract between the patient registry holder and the applicant based on GCP needs to be signed, depending on the situation.

○ In cases where data are used for re-examination applications, a contract between the patient registry holder and the applicant that complies with GPSP（Paragraph 2, Article 6 and, if necessary, Article 10）needs to be signed.

○ For both contracts, it is assumed that the patient registry holder and the healthcare facility/participating patients gave consent to the use of the data for approval applications or re-examination applications by the applicant, at an appropriate level.

○ The range of data that the patient registry holder provides to the applicant needs to be determined in advance.

○ In cases of the use of patient registries with investigator-initiated clinical trials, the question of whether or not the sponsor-investigator should play the same role as the applicant may arise in consideration of the fact that the result of investigator-initiated clinical trials may be used for regulatory approval applications, etc. in the future. However, as the sponsor-investigator cannot implement the approval applications, etc., this proposal does not assume that the sponsor-investigator plays the same role as the applicant.

○ Nevertheless, in cases of the use of patient registries with investigator-initiated clinical trials, it is desirable for the sponsor-investigator to examine related matters in advance so that the potential applicant or other parties can deal with the requirements listed in this proposal at the time of approval applications or other types of applications; or discuss contracts that will be necessary in the future and other related matters with parties, including the applicant, when the investigator-initiated clinical trial is being planned.

6. Definition of terms

Terms used in this proposal are defined as shown below.

Term	Definition
Patient registry	Database established for the purpose of collection of healthcare data, including those on a particular disease or disease group and their pharmacologic and nonpharmacologic treatment
Patient registry holder	Party that designs/operates a patient registry
Applicant	Party that files marketing approval applications, etc. of drugs, etc. using the data from a patient registry
Data cleaning	To improve a database by deleting/correcting the data
Coding	Replace data, including those on disease conditions, names/use of drugs, etc. and results/course of treatment with numbers and codes for efficient computer processing
Drugs, etc.	Pharmaceuticals, medical devices, regenerative, cellular therapy and gene therapy products
Approval applications, etc.	Marketing approval applications and re-examination applications（including use-results assessment of medical devices）

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