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Pharmaceutical Safety Division,
Pharmaceutical Safety and Environmental Health Bureau,
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Utilization of Medical Information Database in Pharmacovigilance and Its Examples

The basic principles for marketing authorization holders of drugs to use a medical information database in post-marketing pharmacovigilance have been shown in "Basic Principles on the Use of Medical Information Databases in Post-marketing Pharmacovigilance" (PSEHB/PED Notification 0609 No.8 and PSEHB/SD Notification 0609 No.4 dated June 9, 2017, Joint Notification by the Director of Pharmaceutical Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as MHLW)).

In the post-marketing pharmacovigilance, the utilization of the medical information database is not limited to post-marketing surveillance for re-examination and re-evaluation, and various methods of use are expected. To promote further utilization of the medical information database in post-marketing pharmacovigilance, the "Utilization of Medical Information Database in Pharmacovigilance and Its Examples" has been compiled as follows based on examples of utilization, etc. to date. Please understand the following information, and cooperate in disseminating it to the relevant organizations under your jurisdiction.

1. Background and objectives

In addition to post-marketing database studies specified in "Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171 of 2004; hereinafter referred to as "GPSP Ordinance")," which was revised according to "Ministerial Ordinance Partially Amending the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 116 of 2017)," medical information databases can be used to collect various information in pharmacovigilance (hereinafter collectively referred to as "examination").

In an examination using a medical information database, the medical information accumulated in daily clinical practice, etc. is utilized secondarily, and therefore it can be expected to be used for a drug evaluation that reflects the actual clinical settings in Japan. In addition, since past information may be available at the start of the examination, it may be used to compare the situation before and after the launch of drugs or before and after the implementation of safety measures. Furthermore, unlike drug use-results surveys using survey forms, etc., it is not necessary to collect information on an individual patient basis in each examination. If data necessary for examination have already been accumulated in the medical information database, etc., pharmacovigilance is expected to be implemented efficiently from the viewpoints of time, costs, human resources, etc. required for the examination.

There are medical information databases with different characteristics and limitations, in which various medical information has been accumulated such as reimbursement for medical fees and drug dispensing fees, electronic medical record data, Diagnosis Procedure Combination (DPC) data, and disease registry data. Therefore, it is necessary to accurately understand the characteristics and limitations of each medical information database, select a reliable medical information database according to the purpose of examination, and draw up an appropriate plan to conduct the examination.

Although examples of drug safety evaluation using a medical information database have been accumulated, the utilization of the medical information database in pharmacovigilance has not become widely adopted and established in Japan.

In order to promote further utilization of the medical information database in pharmacovigilance, this document describes the purpose of utilization of the medical information database and general points to consider when utilizing the medical information database based on the examples of utilization to date, with concrete example cases of utilization of the medical information database in pharmacovigilance summarized in the appendix.

2. Scope of application

This document applies not only to post-marketing database studies specified in the GPSP Ordinance but also to all examinations utilizing medical information databases in post-marketing pharmacovigilance, including examinations conducted voluntarily by pharmaceutical marketing authorization holders.

In this document, a medical information database refers to a "database systematically accumulating electronic medical information such as hospital information system data (electronic medical record data, Diagnosis Procedure Combination [DPC] data, etc.), claims data for medical fees and dispensing fees (e.g., receipt data of health insurance associations), and disease registry data."[1] This document does not deal with the utilization of information concerning reports to be made to the Minister of Health, Labour and Welfare pursuant to Article 68-10, Paragraphs 1 and 2 of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Act No. 145 of 1960) and Article 12, Paragraph 1 of the Immunization Act (Act No. 68 of 1948).

For examinations to be conducted following the contents of this document, the applicability to routine or additional pharmacovigilance activities specified in the "Risk Management Plan Guidance" (PFSB/SD Notification 0411 No.1 and PFSB/ELD Notification 0411 No. 2 dated April 11, 2012, Joint Notification by the Director of Safety Division and the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW) and the applicability to "Ministerial Ordinance on Standards for Post-marketing Safety Management for Drugs, Quasi-drugs, Cosmetics and Medical Devices (MHLW Ordinance No. 135 of 2004)" or the GPSP Ordinance are to be judged individually, and the basis of such a judgment is not covered by this document.

The purpose of use of the medical information database, points to consider, and examples of utilization compiled in this document are merely a summary of assumed methods of use of the medical information databases and examples for reference, and adherence to the items described in this document is not necessarily required.

3. Utilization of medical information databases in pharmacovigilance

1) Utilization of medical information databases for various purposes

The medical information database can be used in pharmacovigilance for various purposes including confirmation of the actual status of use and

[1] "Basic Principles on the Use of Medical Information Databases in Post-marketing Pharmacovigilance" (PSEHB/ELD Notification 0609 No.8 and PSEHB/SD Notification 0609 No.4 dated June 9, 2017, Joint Notification by the Director of Pharmaceutical Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

exploratory objectives to identify or clarify research questions, in addition to the confirmatory objectives to obtain conclusions on research questions[2]. Examinations using a medical information database can be, by objectives, classified into (1) examination of actual status of use, (2) examination of safety signals[3], and (3) examination of risk minimization activities. The characteristics of each examination are shown below. In these examinations, various methods (e.g., simple tabulation, cohort design, etc.) may be used in cases where multiple purposes are intended or depending on the purpose of the examination. In addition, chronological changes in the situation can be confirmed efficiently by repeating the same examinations at certain intervals.

(1) Examination of actual status of use

An examination of actual status of use is intended to clarify the characteristics of the patient population for whom the drug of interest is prescribed or the patient population of the disease of interest. This examination is useful for identification or clarification of research questions or collection of basic information to formulate plans for confirmatory examinations, and it is often conducted for exploratory purposes. By utilizing the medical information database, it is possible to efficiently confirm the actual status of the use in clinical settings including the presence or absence of patients generally not enrolled in clinical studies (e.g., elderly patients, patients with renal impairment, etc.) and the past treatment history of patients. Concrete examples of examination of actual status of the use are shown below.

- Confirmation of the actual status of drug prescriptions

  To confirm the patient background (e.g., age, gender, comorbidity, concomitant drugs, etc.), details of the prescriptions of the drug of interest (e.g., prescribed dose, number of days of prescription, etc.) in the patient population to which the drug of interest is prescribed, and to obtain insights on the actual prescription details of the drug in actual clinical settings.
- Confirmation of implementation of laboratory tests

  To confirm the implementation (e.g., frequencies, intervals, etc.) of laboratory tests that are important in the risk management of drugs, and to obtain insights about the implementation of laboratory tests in actual clinical settings.

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2 " Procedures for Developing Post-marketing Study Plan" (PSEHB/PED Notification 0314 No.4 and PSEHB/SD Notification 0314 No.4 dated March 14, 2019, Joint Notification by the Director of Pharmaceutical Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

3 "Periodic Benefit-Risk Evaluation Report (PBRER)" (PFSB/ELD Notification 0517 No.1, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated May 17, 2013)

- Confirmation of epidemiological characteristics of the disease

  To confirm the natural course of the target disease, for which drugs are to be prescribed, and the background incidence rate, etc. of adverse events of interest, and to obtain insights necessary for the safety evaluation of drugs in actual clinical settings.

(2) Examination of safety signals

Examination of safety signals is intended to obtain insights on the association between the drug and events that occur after the prescription in the patient population to whom the drug of interest is prescribed, and it is useful in judging the necessity, etc. of issuing precautions for the safety of the drug. Drug safety signals can be identified for exploratory or confirmatory purposes, depending on the information available at the time of planning. Concrete examples of examination of safety signals are shown below*.

- Assessment of association between drug and unexpected events (signal detection)

  If there is no information suggesting the association between the drug and the events that occur after the prescription, not one individual event but multiple events will be targeted, and the incidence proportion, etc. of each targeted event will be assessed exploratorily in patients prescribed with the drug of interest to obtain insights in actual clinical settings about unexpected events to which the relationship of the drug is unclear.
- Exploratory assessment of association relationship between drug and specific events (signal enhancement)

  Although there is some information on the association between the drug and the events that occur after the prescription, if the association between the drug and the events is not clear and sufficient information for the assessment of the causal relationship is not available, the incidence proportion, etc. of target events will be assessed exploratorily in patients prescribed with the drug of interest to obtain insights about the association between the drug and the event in actual clinical settings.
- Confirmatory assessment of association between drug and specified events (signal verification)

* Considering that this document summarizes the utilization of the medical information database, the terms "signal detection," "signal enhancement," and "signal verification" were used in this section. Note that these terms are different from signal management terms in "Standard Workflow for Consideration of Safety Measures such as Revision of Electronic Drug Product Package Inserts" (Administrative Notice of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated September 27, 2021).

If a certain degree of information has been accumulated regarding the causal relationship between the drug and the events that occur after the prescription, the incidence proportion, etc. of the target event will be evaluated quantitatively and accurately in patients prescribed with the drug of interest in comparison to an appropriate control group after adjustment of the patient background, etc. to obtain insights about the association between the drug and the event in actual clinical settings.

(3) Examination of risk minimization activities

Examination of risk minimization activities is intended to evaluate the effects of ongoing risk minimization activities and to confirm the contents of risk minimization activities to be conducted concerning the target risks of drugs of interest, and the examination is useful for implementation of appropriate risk minimization activities. By utilizing a medical information database, it is possible to evaluate the effects of risk minimization activities comparing them with the status before the implementation of risk minimization activities and to efficiently collect information necessary for optimizing safety measures (e.g., addition, completion, etc. of safety measures) considering the actual treatments in clinical settings. Concrete examples of examination of risk minimization activities are shown below.

- Evaluation of effectiveness of safety measures

  To confirm the events (e.g., onset of adverse events), which may be affected by the safety measures, in the period before and after the implementation of safety measures, such as release of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications, in order to obtain insights on the effectiveness of the measures in actual clinical settings.
- Evaluation of the effectiveness of ongoing risk minimization activities

  To confirm the effectiveness expected from the risk minimization activities (e.g., implementation of periodic tests, reduction of dosage , etc.) to obtain insights on the effectiveness of risk minimization activities.
- Confirmation of the contents of risk minimization activities to be implemented

  To check the characteristics of the patient population susceptible to adverse events, factors affecting the onset of adverse events, etc., and to obtain insights on additional risk minimization activities to be conducted based on the identified risk factors.

2) General points to consider for utilization of medical information database

For general points to consider in the examination using the medical information database, refer to "Guideline for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases" (dated March 31, 2014, by the PMDA) and "Basic Principles on the Use of Medical Information Databases in Post-marketing Pharmacovigilance" (PSEHB/PED Notification 0609 No.8 and PSEHB/SD Notification 0609 No.4 dated June 9, 2017, Joint Notification by the Director of Pharmaceutical Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

For examinations using databases, measures to ensure the reliability of the database are also required taking into account the purpose of the examinations as well as examinations falling under post-marketing database studies, which must comply with the standards specified in the GPSP Ordinance. "Points to Consider for Ensuring the Reliability of Post-marketing Database Study" (PSEHB/PED Notification 0221 No.1, issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated February 21, 2018) should be referred to for items, etc. to be confirmed for securing reliability when utilizing medical information databases.

In addition to the above, since the actual medical system, legal regulations, etc. differ between Japan and overseas, it is necessary, in principle, to utilize medical information databases that reflect the medical environment in Japan from the viewpoint of examining the safety of drugs in the actual clinical settings in Japan. In some cases where it is difficult to utilize a medical information database that reflects the medical environment in Japan, it is possible to utilize an overseas medical information database which enables appropriate examination. However, it is necessary to pay attention to the characteristics of the database when planning a study, and the results should be interpreted carefully.

In the examinations conducted for exploratory purposes, results obtained should be carefully evaluated because there are cases where an unvalidated[4] outcome definition is used or adjustment for confounding factors, etc. has not been performed sufficiently. In some cases, additional examinations for confirmatory purposes may be necessary to obtain further information about concerns.

[4] "Basic Principles on validation of outcome definition used in post-marketing database studies" (Pharmaceuticals and Medical Devices Agency dated July 31, 2020)

3) Concrete example cases of utilization of medical information databases in pharmacovigilance

Example cases of utilization of the medical information database in pharmacovigilance are shown in the appendix. The results of the examination appropriately conducted by utilizing the medical information database not only serve as the basis for the revision of information on PRECAUTIONS, etc. in (e-) package inserts but also may be utilized from various viewpoints, such as confirming the appropriateness of the current safety measures, correctly understanding the current status in actual clinical settings regarding implementation of laboratory tests, dose adjustment, etc. indicated in the information on PRECAUTIONS, etc., contributing to the assessment on the necessity of further examination, and drawing up an appropriate plan. It should also be noted that the examples shown in the appendix are just for reference, since various conditions are anticipated regarding the purposes, methods, etc. of examinations.

Appendix

Examples for reference in which medical information databases were utilized in pharmacovigilance

(1) Examination of actual status of use

It may be possible to grasp the actual status of use of a drug by using the medical information database in the following cases: Cases to grasp the actual status of prescription of a drug in patients prescribed with the drug at a certain time point after marketing or in patient populations not sufficiently evaluated before marketing authorization (e.g., children, patients with renal impairment, elderly, etc.) in clinical settings; cases to grasp the implementation status of laboratory tests related to the onset of adverse events during the treatment period (e.g., implementation rate, frequency, etc.).

An example of utilizing a medical information database in an examination of the actual prescription status of a drug is shown below.

<Example 1: Confirmation of the actual status of drug prescriptions>

Background	Detection of N-nitrosodimethylamine, a carcinogen, in drug substances of some of marketed valsartan tablets
Purpose	To confirm the actual prescription of valsartan tablets to evaluate health effects
Database and reason for selection	National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB): It was selected in consideration of the number of patients included in the database, since it is highly exhaustive to obtain information on prescriptions at different medical institutions.
Method	For patients prescribed with valsartan tablets, the cumulative prescribed dose, etc. were calculated for each patient from the daily dose and length of prescription based on each prescription.
Remarks (summary of results, references, etc.)	https://www.pmda.go.jp/files/000241342.pdf (only in Japanese) https://www.frontiersin.org/articles/10.3389/fmed.2023.1096992/full (Published article in English; this information is not included in the original Japanese version and is shown here just for your reference.)

(2) Examination of safety signals

It may be possible to assess a safety signal of a drug by using the medical information database in the following cases: Cases to comprehensively assess adverse events, including unexpected ones, in actual clinical settings, although there are no specified safety concerns for a drug; cases to clarify the causal relationship with events for which a certain amount of adverse drug reaction reports in Japan, etc. have been accumulated and safety signals have been observed. An example of utilizing a medical information database in an examination on the safety signals of drugs is shown below.

<Example 2: Assessment of an association between drug and unexpected events (signal detection)>

Background	The causal relationship between fluoroquinolone antibiotics and retinal detachment is unexpected, and there have been no case reports in Japan.
Purpose	To assess exploratorily the association between fluoroquinolone antibiotics and retinal detachment
Database and reason for selection	National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB): It was selected in consideration of the number of patients included in the database, since the incidence of the target outcome is low and it is highly exhaustive to obtain information on prescriptions at different medical institutions.
Method	For patients who were prescribed with fluoroquinolone antibiotics and developed retinal detachment, the sequence ratio (the number of patients whose prescription date of fluoroquinolone antibiotics preceded the onset date of retinal detachment divided by those of patients whose onset date of retinal detachment preceded the prescription date of fluoroquinolone antibiotics), etc. were calculated using a sequence symmetry analysis, a self-controlled design.
Remarks (summary of results, references, etc.)	https://www.pmda.go.jp/files/000240294.pdf (only in Japanese) https://www.frontiersin.org/articles/10.3389/fmed.2023.1096992/full (Published article in English; this information is not included in the original Japanese version and is shown here just for your reference.)

<Example 3: Assessment of an association between drug and specific events (signal verification)>

Background	There have been multiple case reports of adverse drug reactions involving decreased platelet counts after the use of G-CSF (granulocyte-colony stimulating factor) preparations, but it is difficult to assess the causal relationship based on case reports alone because of the possible effects of antineoplastic agents, etc.
Purpose	To confirm the association between G-CSF preparations and decreased platelet counts by comparing the occurrence of decreased platelet counts in the presence or absence of G-CSF preparations in patients who are prescribed antineoplastic agents
Database and reason for selection	MID-NET: It was selected to evaluate laboratory test results as indices
Method	Based on the nested case-control design, adjusted odds ratios, etc. were calculated by comparing the patients with or without G-CSF preparations, focusing on the onset of decreased platelet counts in patients prescribed with the same antineoplastic agents.
Remarks (summary of results, references, etc.)	https://www.pmda.go.jp/files/000234445.pdf (in Japanese) https://www.pmda.go.jp/files/000234698.pdf (in English) DOI:10.1002/cpt.2263

(3) Examination of risk minimization activities

It may be possible to obtain insights related to risk minimization activities using the medical information database in the following cases: Cases where safety measures such as release of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications were taken for a drug and where it is necessary to confirm whether the risk has decreased as an effect of such measures; cases where it is necessary to check which patients are at high risk of developing adverse events.

An example of utilizing a medical information database in an examination on the risk minimization activities for drugs is shown below.

<Example 4: Evaluation of effectiveness of safety measures>

Background	After marketing, cases of serious hypocalcaemia were reported in patients prescribed with denosumab, and safety measures such as issuance of Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter) were taken. It was necessary to quantitatively confirm the effect.
Purpose	To evaluate the effects of safety measures by comparing the occurrence of serious hypocalcaemia, before and after taking safety measures, in patients prescribed with denosumab
Database and reason for selection	MID-NET: It was selected to evaluate laboratory test results as indices.
Method	The incidences of hypocalcaemia before and after taking safety measures were compared based on the interrupted time series design, etc.
Remarks (summary of results, references, etc.)	DOI:10.1002/pds.4777#

<Example 5: Confirmation of the contents of risk minimization activities to be implemented>

Background	Although precautions were issued to perform periodic blood tests when thiamazole is prescribed, there are still a certain number of case reports of serious granulocytopenia after prescription.
Purpose	To explore risk factors for thiamazole-induced granulocytopenia
Database and reason for selection	MID-NET: It was selected to evaluate laboratory test results as indices.
Method	Based on the nested case-control design, focusing on the presence or absence of granulocytopenia in patients with hyperthyroidism being treated with antithyroid drugs, the association between thiamazole and granulocytopenia was assessed. Adjusted odds ratios, etc. for granulocytopenia in the presence or absence of each assumed effect modifier were calculated.

Remarks (summary of results, references, etc.)	https://www.pmda.go.jp/files/000244990.pdf (only in Japanese)