Provisional Translation (as of December 2021)*

PSEHB/MDED Notification No. 1219-4
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To: Director, Prefectural Health Department (Bureau)

Director, Medical Device 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 Medical Devices

In the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145. 1960), marketing authorization holders of medical devices or designated holders of marketing authorization for foreign-manufactured medical devices, etc. (hereinafter referred to as "MAH, etc.") shall conduct post-marketing surveillance and post-marketing clinical studies based on "Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices" (Ministry of Health, Labour and Welfare Ordinance No.38 of 2005) (hereinafter referred to as the GPSP ordinance).

"Ordinance for Partial Revision of the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs" (MHLW Ordinance No. 116 of 2017) was promulgated, and a "post-marketing database study" was explicitly specified in Article 2 of the GPSP ordinance as one of "post-marketing surveillance, etc." A "post-marketing database study" is conducted to prepare application data/documents for Use-results evaluation of medical devices by utilizing Medical Information Database (hereinafter referred to as "MID") for business use provided by medical information database holders (hereinafter referred to as "DB holders"). Thus, points for MAH, etc. to consider for ensuring the reliability of the application data/documents for Use-results evaluation of medical devices in conducting a post-marketing database study are provided in the Note below. In addition, MAH, etc. who intends to submit an application for Use-results evaluation of medical devices utilizing the results of the post-marketing database study should confirm procedures, etc. of DB holders. Examples of procedures were shown as a reference in the Attachment.

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Please understand these matters and inform manufacturers and sellers placed under your administration to utilize this notification for their business operations.

Note

1. Scope of application

This notification shall be applied when MAH, etc. conducts a post-marketing database study specified in Article 2, Paragraph 1, Item 2 of the GPSP ordinance utilizing MID specified in Paragraph 2 of the same article of the GPSP ordinance provided by a DB holder specified in Paragraph 3 of the same article of the GPSP ordinance and prepares application data/documents for Use-results evaluation of medical devices. Under Article 2, Paragraph 2 of the GPSP ordinance, MID is defined as "An aggregate of information related to medical records and other records of medical practices, claims for medical fees, and disease registration which is collected for a certain period of time and systematically constructed so that the information can be retrieved utilizing a computer." Specifically, the following databases consisting of systematically collected electronic medical information (hereinafter referred to as "medical information") are assumed MID:

- The hospital information system (Electronic medical records, Diagnosis procedure combination [DPC], etc.)
- Claims for medical fees and dispensing fees (Receipt data of health insurance associations, etc.)
- Disease registry

The contents of this notification will be revised appropriately based on further consideration in the future.

2. Definitions of terms

The definitions of terms in this notification are as follows.

Term	Definitions
DB holder	An MID holder who provides MID for business use as specified in Article 2, Paragraph 3 of the GPSP ordinance
Applicant	An MAH, etc. who intends to submit an application for Use-results evaluation of medical devices utilizing the results of post-marketing database studies
Medical information	Electronic medical information such as data from the hospital information system (electronic medical record, diagnosis procedure combination [DPC], etc.), data of claims for medical fees and dispensing fees (receipt data of health insurance associations, etc.), and disease registry data

Medical Information Database (MID)	An aggregate of information related to medical records and other records of medical practices, claims for medical fees, and disease registration which is collected for a certain period of time and systematically constructed so that the information can be retrieved utilizing a computer as specified in Article 2, paragraph 2 of the GPSP ordinance.
Information source	Medical institutions, etc. providing medical information to DB holders
Data cleaning	Data management of MID by deleting or correcting medical information, etc.
Coding	Data management of MID by replacing medical information with numerical values/code, etc. to process medical information efficiently on a computer
Statistical Analysis Plan (hereinafter referred to as "SAP")	A plan specifying methods of extracting datasets for analysis from MID and details of statistical analysis utilizing datasets for analysis in accordance with a post-marketing database study protocol
Datasets for analysis	Datasets necessary for analysis extracted from MID in accordance with a post-marketing database study protocol or an SAP prepared based on the protocol

3. Points to consider for ensuring the reliability of application data/documents

An applicant shall be responsible for the following duties as usual:

- Preparation of application data/documents for Use-results evaluation of medical devices
- Ensuring reliability of application data/documents

(1) Selection of MID and contract with DB holders

a An applicant shall conclude a contract with the DB holder after confirming that the MID can adequately fulfill the purpose of the post-marketing database study by reviewing the following matters:

- An internal system and governance by the DB holder
- Business plan for handling MID held by the DB holder
- Details of operations outsourced by the DB holder to external contractors for handling MID
- Design and outline of MID
- Contents and status of operation of the following procedures for MID
  - Rules for construction and management

- Standards and procedures for data cleaning
- Standards and procedures for coding
- Rules and procedures for security
- Rules and procedures for data backup and recovery
- Rules for quality management of medical information collected from information sources
- Rules to verify that datasets for analysis or analysis results are appropriately prepared
- Rules for reporting of plan and confirmation results of quality management
- Rules for quality assurance
- Rules for storage of records related to preparation of application data/documents for Use-results evaluation of medical devices.
- Rules for education and training provided for persons involved in construction/management

b An applicant shall clarify the scope of operations to be outsourced or requested to DB holders.

(2) Quality management of medical information collected from the information sources

a An applicant shall confirm that the MID has been appropriately constructed based on the collected medical information by confirming the following matters:

- The standards and procedures of the DB holder to collect medical information from information sources
- The methods for the DB holder to confirm that medical information has been entered/captured correctly

If a DB holder implements data cleaning and/or coding of MID, an applicant shall confirm the standards and procedures for data cleaning and/or coding, and then shall confirm that the relevant operations have been implemented appropriately. An applicant shall confirm these matters not only at the selection of MID but also at other timing as needed.

b An applicant shall confirm the rules and procedures of MID operated and managed by a DB holder for the following matters:

- Security
- Data backup and recovery

Then an applicant shall confirm that medical information is appropriately

maintained.

c During the contract period, an applicant shall confirm that a DB holder continuously manages the quality of MID by receiving the quality management records periodically related to medical information provided by the DB holder.

(3) Analysis utilizing medical information extracted from MID

a An applicant shall consider the following matters in preparing datasets for analysis:

- An applicant shall confirm that operations to prepare datasets for analysis (including extraction and processing) from MID are appropriately implemented by the DB holders.
- An applicant shall present the post-marketing database study protocol and/or SAP to a DB holder, and confirm the scope of medical information stored in MID that the applicant can access and obtain as needed.
- When an applicant outsources a part or all of the operations for preparation of datasets for analysis to a DB holder or a contract research organization (hereinafter refer to "CRO"), etc., an applicant shall clarify the scope of operations to be outsourced.

b An applicant shall consider the following matter related to analysis results.

- When an applicant outsources a part or all of the operations for analysis to a DB holder or a CRO, etc., an applicant shall confirm that appropriate analysis has been executed based on the post-marketing database study protocol or SAP.

(4) Storage of records related to preparation of application data/documents for Use-results evaluation of medical device.

An applicant shall establish governance that allows the following records to be appropriately stored:

- Datasets for analysis
- Analysis Results
- Data/documents indicating that MID has been appropriately constructed
- Data/documents indicating that the datasets for analysis and analysis results have been appropriately prepared
- Other documents necessary to ensure the reliability of application data/document

(e.g., if a survey to investigate MID to be utilized, study design, analysis methods, and feasibility, etc. is conducted prior to development of the protocol for the post-marketing database study [including a validation study to define the outcome of the post-marketing database study], the results and protocol of the relevant survey and/or SAP, etc., or records of the survey progress if the protocol of the survey or SAP is not prepared)

The applicant shall keep space to appropriately manage these records and specify the location to review the records as needed.

(Attachment)

Examples of procedures, etc. of DB holders related to MID that applicants should confirm

1. Rules for construction and management
   - Governance:
     Responsibility and system related to the following matters within DB holders:
     - Supervisor
     - Managers
     - Facilities
     - Education and training, etc.
   - Management of external contractors (if the DB holder outsources a part of operations related to construction and management to the external contractor):
     Procedures and plans to confirm that a DB holder appropriately manages an external contractor

2. Standards and procedures for data cleaning
   - Departments and roles of persons in charge of data cleaning:
     Departments where supervisor, managers, and persons in charge of data cleaning belong and their responsibilities
   - Standards and procedures for data cleaning:
     Data items and contents of data cleaning implemented by a DB holder specified for each stage of the data cleaning like below
     - A stage when medical information collected from information sources is captured into MID
     - A stage when datasets for analysis are prepared
   - Procedure for changing the standards for data cleaning:
     Procedure and process of DB holders to change the standards for data cleaning
   - Management of external contractors (if the DB holder outsources a part of operations related to data cleaning to the external contractor):
     Procedures and plans to confirm that a DB holder appropriately manages an external contractor

3. Standards and procedures for coding
   - Departments and roles of persons in charge of coding:
     Departments where supervisor, managers, and persons in charge of coding belong and their responsibilities

- Standards and procedures for coding:
  Data items and contents of coding implemented by a DB holder specified for each stage of the data coding like below
  - A stage when medical information collected from information sources is captured into MID
  - A stage when datasets for analysis are prepared
- Maintenance of code lists, etc. (masters) for coding:
  Frequency and means of updating the masters to be concerned
- Procedure for changing the standards for cording:
  Procedure and process of DB holders to change the standard for coding
- Management of external contractors (if the DB holder outsources a part of operations related to coding to the external contractor) :
  Procedures and plans to confirm that a DB holder appropriately manages an external contractor

4. Rules and procedures for security
   - Departments and roles of persons in charge of security:
     Departments where supervisor, managers, and persons in charge of security belong and their responsibilities
   - Rules for information security:
     [1] Rules for management of log-in /log-out of MID system:
     The rules for entering/exiting the server room of the MID system, and the rules for preparation, operation, storage of log-in/log-out records shall be specified at required levels in light of the contents of medical information handled in MID, system configuration and operation method of MID.
     [2] Rules for user management:
     The methods of the following user management shall be specified.
     - The scope of users
     - Account settings for users

     [3] Rules for access control:
     The settings and controls shall be specified so that DB holder grants access authority to users according to the criticality of medical information.
     [4] Rules for network security:
     Rules for network security shall be specified.
   - Other rules for security:
     Business Continuity Plan, etc.

5. Rules and procedures for data backup and recovery
   - Departments and roles of persons in charge of data backup and recovery:
     Departments where supervisor, managers, and persons in charge of data backup and recovery belong and their responsibilities
   - Scope, frequency, version control and destination to save for backup of MID:
     Rules related to the following matters for backup of MID
     - Frequency and the number of version to save of whole or differential backup
     - Utilized media, storage location and storage period for backup
   - Recovery plan and procedure:
     Plan, specific contents and procedure of recovery
   - Recovery test:
     A record of recovery test results

6. Rules for quality management of medical information collected from information sources
   - Department and roles of persons in charge of quality management:
     Persons in charge of quality management in information sources and DB holders and their responsibilities
   - Migration, input and capture of medical information:
     - Methods of migration of medical information (via network or media, etc.)
     - Procedures for input and capture (input reference [dictionary], etc.)
   - Input to and output from MID:
     Method to confirm that medical information has been entered and captured appropriately

7. Rules for verification of datasets for analysis or analysis results are appropriately prepared
   - Departments and roles of persons in charge of verification:
     Departments where supervisor, managers, and persons in charge of verification belong and their responsibilities
   - Scope, method, procedures of verification:
     Period, and specific methods, etc.
   - Report of results of verification
   - Management of external contractors (if the DB holder outsources a part of operations related to verification to the external contractor):
     Procedures and plans to confirm that a DB holder appropriately manages an external contractor

8. Rules for report of plan and confirmation results of quality management
   - Departments and roles of persons in charge of quality management:
     Departments where supervisor, managers, and persons in charge of quality management belong and their responsibilities
   - Rules for plan (including rules for the scope of quality management) and report (including confirmation of results) of quality management

9. Rules for quality assurance
   - Departments and roles of persons in charge of quality assurance:
     Departments where supervisor, managers, and persons in charge of quality assurance belong and their responsibilities
   - Rules for quality assurance (including rules related to the way the quality assurance ought to be)

10. Rules for storage of records related to preparation of application data/documents for Use-results evaluation of medical device.
    - Departments and roles of persons in charge of storage of records:
      Departments where supervisor, managers, and persons in charge of storage of records belong and their responsibilities
    - Scope of storage:
      Rules for storage of the following documents
      - Documents prepared for preparing datasets for analysis and/or analysis results
      - Documents prepared for conducting the study
    - Storage procedure:
      Rules for storage location, procedure and storage period, etc.
    - Transfer procedure:
      Rules for the location and procedure of transfer, if applicable
    - Disposal procedure:
      Rules for disposal procedure, etc.

11. Rules for education and training for persons involved in construction and management
    - Timing and required hours for education and training:
      Rules on timing and required hours for implementation of education and training
    - Target of education and training:

Rules for trainees of each education and training item

- Persons in charge of education and training:
  Rules for the persons in charge of each education and training item
- Contents of education and training:
  Rules for contents of each education and training item
- Evaluation of education and training:
  Rules for records summarizing results of education and training

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