RWE-based Platform Model Development for Ecosystem in the Life-Cycle Management of Medical Devices

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This study aimed to propose the establishment of a platform for generating real-world evidence (RWE) using real-world data (RWD) to create an empirical ecosystem in medical device life-cycle management.

To conduct this study, we examined international examples of platforms or databases for RWD/RWE in the United States and Japan. Subsequently, we examined the regulation in which RWD/RWE is utilized in policy decision-making related to medical devices in South Korea and identified the

main components that should be included in the platform.

The proposed Korean domestic medical device RWD/RWE platform consists of an application and reception system, safety reporting system, effectiveness reporting system, cost collection system, and RWE generation system. The platform allows researchers to create studies through application, and collect safety, effectiveness, and cost from the created RWD studies, and the collected data can be used by researchers to create RWE through a statistical analysis of medical devices and medical practices and provide better medical services to patients.

It is important to build RWD/RWE platforms to provide a better healthcare experience for patients, and we hope that this study can be used as a basis for future RWD/RWE platforms. In order to establish an RWD/RWE platform for medical devices, a study on the common data model for Korean medical devices for data standardization should be conducted.

Keywords: Real-world Data, Real-world Evidence, Platform, Medical Device

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I. INTRODUCTION

1. Backgrounds

Following the enactment of the 21st Century Cures Act in the United States in 2016, which aims to accelerate medical product development and increase the efficiency of medical product delivery, and the publication of guidelines on the use of real-world evidence to support regulatory decision-making for medical devices in 2017, the interest in real-world data (RWD) and real-world evidence (RWE) has continued to increase [1, 2].

Real-world data (RWD) refers to the patient health status or healthcare delivery data that are not collected in traditional clinical trials but are routinely collected from a variety of sources, including healthcare organizations, insurers, and patients. It includes electronic medical records (EMRs), electronic health records (EHRs), registries, and claims data from healthcare organizations, such as the Health Insurance Review and Assessment Service and the National Health Insurance Service [3, 4, 5].

Real-world evidence (RWE) refers to the clinical evidence of a medical device derived from the processing and analysis of various RWD [3, 4, 5]. Medical devices are often used for purposes other than their licensed indications; however, the data collected from medical devices are not recognized as medical practice because they lack reliability for regulatory decisions [3, 5]. However, the data from clinical practice under the right conditions can be used to support regulatory decisions and can provide a valid scientific basis depending on the nature of the data [3, 5].

According to the Korean Ministry of Food and Drug Safety's Guidance on the Application of Real-World Evidence in Medical Devices, revised July 2023, RWE can be used to support medical device regulatory decisions throughout the life-cycle, including approval, reassessment, and post-market surveillance [4].

In addition, on June 1, 2023, the "Regulations on Medical Device Approval, Examination, and Notification" were amended to allow medical devices that require orphan or urgent introduction, medical devices produced using 3D printers, and medical devices with digital technologies, such as big data and artificial intelligence to replace clinical trials to confirm the safety and effectiveness using evidence from RWE [4].

However, when using RWD and RWE to validate the safety and effectiveness of a medical device, it is important to consider the relevance and reliability of the data. Data relevance can be useful in determining whether regulatory questions and requirements could be partially or fully handled. Moreover, when it comes to data reliability, it is important to ensure that the data quality and integrity is sufficient through the minimization of errors in how it is collected and analyzed [3, 4, 5].

To obtain RWD, we use billing data and electronic medical records; however, in the case of electronic medical records, the patient information is fragmented because they are used by multiple medical institutions and each medical institution handles different data. Therefore, in order to use RWD in medical device regulatory decisions, it is necessary to create a platform to expand the data access and sharing, and engage stakeholders, including governments, hospitals, companies, and others [6].

In the First Comprehensive Plan for Drug Safety Management released by the Ministry of Food and Drug Safety in 2020, it was suggested in the 5-year roadmap that an active pharmacovigilance system based on big data, including RWD, should be established [7]. A study mentioned that in order to promote the utilization of domestic RWD for pharmaceuticals, it is necessary to build an integrated platform to increase the utility value of data sources [1].

In the life-cycle management of medical devices, such as in pharmaceuticals, it is necessary to build an integrated platform to collect RWD and use it for actual regulatory decision-making, and this study proposes to do so.

2. Objectives

This study was aimed to propose the establishment of a platform for generating RWE using RWD to create an empirical ecosystem in medical device lifecycle management.

3. Scope of Study

This study proposes to build a platform for generating RWE, for which we intend to conduct research in the following scope.

First, we will examine the international cases of the platform with RWD/RWE in the United States and Japan.

Subsequently, this study is aimed to identify the main elements that should be included in the platform by examining the regulation in which RWD and RWE are utilized in policy decision-making related to medical devices in Korea and then to propose a platform for RWD/RWE of medical devices in South Korea.

II. Review of Previous Studies

Prior to this study, we conducted a literature review to understand RWD/RWE in general, the current issues and suggestions, and overseas platforms.

1. General information of RWD/RWE

RWD provides data about a patient's health status and/or routine health care, which can be obtained from electronic health records, claims databases, product and disease registries, wearable devices, or electronic applications, and can be collected prospectively, such as disease registries. RWE refers to the clinical evidence from the RWD analysis of the use and potential benefits or risks of an intervention, which can be analyzed and generated through large-scale randomized controlled trials (RCTs), pragmatic studies, and prospective or retrospective observational study designs [9].

According to Dang (2023), RWEs are not subject to stringent criteria; therefore, patients may not be excluded based on concomitant medications or comorbidities. RWEs require less time to recruit/enroll patients and complete the study compared to clinical studies; and they allow for studies that are not possible with RCTs in high-risk populations, such as pregnant women and children. Additionally, it has the advantage of being able to track real-world patient behavior. The data are quick, easy to retrieve and access, and the large sample size allows for subgroup analysis and facilitates generalization and modeling [10].

From the perspective of pharmaceutical and medical device companies, RWE is needed throughout the life cycle of a product to design clinical trials, understand clinical guidelines and diseases, facilitate financial discussions and decisions, support regulatory decisions, and promote the further use of products already on the market. Healthcare providers have easy access to a wealth of patient data and can leverage RWE to provide customized support tools to help patients and doctors make informed, shared decisions. Payers are utilizing claims data to strengthen the affordability of healthcare, and regulators can use RWE to periodically report on the safety of drugs and other products [10].

2. RWD/RWE in Medical Devices

The use of RWE has been emphasized for the validation of the safety and effectiveness of medical devices [3]. In the United States, RWE was utilized in 2016 to establish the National Evaluation System for Health Technology (NEST), a multi-stakeholder partnership with a mission to accelerate the development and translation of new and safer health technologies. NEST has established formal partnerships with healthcare providers, healthcare payers, and specialty registries to collect and analyze RWD from electronic medical records, claims, medications, and other sources, including registries [11].

According to Li (2023), in China, RWD is generated in the 'Boao Lecheng Pilot Zone'. Innovative medical devices and pharmaceuticals that are not licensed in China are available in these areas, and comprehensive RWD information is

collected from a variety of data sources inside and outside the pilot zone. However, RWE's research in the Boao Lecheng Pilot Zone is still in its early stages, and they note that collaboration between stakeholders, such as government agencies, hospitals, and the medical industry is needed to improve the data quality [6].

According to Dhruva (2023), a unique device identifier (UDI) for a medical device contains both a device identifier, which includes the name of the manufacturer and the model of a particular device, and a production identifier, which includes lot and serial numbers, date of manufacture. While this ensures accurate and reliable identification and traceability of medical devices, the study noted that UDIs are often not available within an effective data source for RWE research. Therefore, there is a need to support and advance the implementation of UDI in health systems in order to realize the goal of using RWD to assess the safety and effectiveness of medical devices [2].

3. Recommendations for activating RWD/RWE

A previous study compared the recent guidelines on research design and data analysis using RWD/RWE in the United States, Europe, and South Korea and discussed the future direction. In addition, six recommendations were made for the future promotion of RWE in South Korea: publication of a framework, development of guidelines for regulatory decision-making purposes, development of a public website to register research protocols, establishment of internal and

external organizations, establishment of a domestic and international RWD/RWE knowledge system, and the development of educational programs [8].

Jeon (2023) compared RWD/RWE-related systems and platforms in the United States, Europe, and Korea and recommended ways to improve them in Korea by comparing the current status of access, linkage, and the verification of medical data. The study presented the Common Data Model (CDM) in the United States and South Korea as well as the Big Data roadmap in Europe, including data standardization, quality, and linkage. The study pointed out that there are still some shortcomings in terms of the system differences between sources, privacy, data accessibility, and linkage, and recommended the establishment of a data standardization system to build an integrated platform, developing guidelines for data linkage and verification, improving the segmentation and operation of data access systems, and holding regular forums between stakeholders [1].

III. Methods

To conduct this study, we examined the cases of RWD/RWE platforms in the United States and Japan. Subsequently, we identified the necessary elements for platform construction through a review of the medical device-related regulations in South Korea where RWD/RWE can be used. Finally, we propose a platform construction (draft). Here, we discuss how to do it specifically.

1. RWD/RWE Platform Cases of Overseas

To propose a platform for RWD and RWE, we reviewed overseas platform cases through literature and websites. However, considering that platforms for pharmaceuticals are being built in advance, we included platforms for pharmaceuticals in addition to the RWD and RWE platforms for medical devices. We searched the literature in PUBMED and GOOGLE using a combination of “real-world data,” “real-world evidence,” “medical information database,” “platform,” and ”system” to learn about Observational Health Data Sciences and Informatics (OHDSI) and Japan's MID-NET, which are used in multinational countries.

2. Reviewing the Regulatory for Identifying Platform Components

To build the content of the RWD and RWE platform on medical devices, we examined the current Korean medical device regulations for which RWD and RWE can be used for regulatory decision-making, and gathered essential information from each regulation to identify the components of the platform.

We first examined the cases that can be applied to RWD and RWE of medical devices based on the Guidelines for Application of Evidence of Real Use of Medical Devices (Guideline for complainant) published by the Korean Ministry of Food and Drug Safety in 2023 [4].

These areas include ① specifying the purpose of use, method of use, and precautions for use of licensed (certified) medical devices; ② identifying safety (adverse event) issues with products after market; ③ establishing objective criteria for evaluating the safety and effectiveness of medical devices; ④ establishing control groups in clinical trials of medical devices; ⑤ re-examining and re-evaluating data for medical devices; and ⑥ licensing medical devices for orphan and urgent introduction [4].

In addition, the generation of RWEs is also required for pre-entered health technology assessment conducted as part of the new health technology assessment in the health technology assessment involving medical devices in South Korea. The pre-entered health technology assessment programs include Conditional Approval for Evidence Development, Innovative Health Technology Assessment, and Postponement of new Health Technology Assessment. Basically, the Conditional Approval for Evidence Development is applied in the form of

research, while Innovative Health Technology Assessment and Postponement of new Health Technology Assessment are applied in the form of research/clinical practice and clinical practice, respectively. Moreover, since these regulations conduct new health technology assessment evaluations after the procedure/test authorization period ends, the RWE obtained during research and clinical practice is essential. Therefore, the platform should be able to collect data on the safety and effectiveness for the above-mentioned Korean domestic medical devices and health technology regulations by default.

2.1. Managing adverse events of Medical Devices

The adverse event information of medical devices refers to adverse events or cases of adverse events that occurred in South Korea or other countries when handling or using medical devices and should be collected and reported. When a medical device handler is aware that a death or serious adverse event has occurred or is likely to occur during the use of a medical device, he or she must report it to the Minister of Food and Drug Safety. Additionally, the Korea Institute of Medical Device Safety Information must request data for the collection, analysis, and evaluation of the reported adverse events and report the results of the analysis and evaluation to the Ministry of Food and Drug Safety. Depending on the results of the evaluation, the Ministry of Food and Drug Safety may take measures, such as providing safety information, recalling the product, and suspending manufacturing and sales operations [13-14]. The information that should be collected in a medical device adverse event report is shown in Table 1.

Table 1. Required documents of Managing Adverse Events of Medical Devices

Contents
▪ Whether and what types of medical devices are being handled ▪ Reporter information (organization name, name, phone number, etc.) ▪ Medical device information (item name, model name, classification number and grade, license number, manufacturing number (lot number), whether it is a human implantable device, UDI code, company name/manufacturer (for imports)). ▪ Patient information: patient name (de-identified), date of birth (can be omitted if the patient does not consent), sex and age, and date of implantation (if human implantable device), Other (past medical history, medications, and complications, etc.) ▪ Adverse event information (date of recognition and date of occurrence), outcome (death, hospitalization, extended hospitalization, etc.), cause (adverse event due to medical device, adverse event due to procedural issue, adverse event due to patient's condition, etc.), details (how it happened and patient symptoms, etc.), progress (safety measures taken for the patient and the product), adverse event standard code, and action plan. ▪ Attachments (medical reports, analysis reports, etc.)

2.2. Medical Device Post-Market Surveillance

The post-market surveillance of medical devices is a regulation that collects, reviews, confirms, or verifies information on the safety and effectiveness of the

medical device for a certain period after the release for newly developed medical devices, and orphan medical devices. The post-market surveillance period is 4 years from the date of marketing for new and follow-up medical devices and 6 years for orphan medical devices. For new medical devices, more than 600 cases are required, and for surveillance and orphan medical devices, a complete enumeration survey [12, 15]. The information collected in the protocol and results report for the post-market surveillance of medical devices is shown in Table 2.

Table 2. Required documents of Medical Device Post-Market Surveillance

Category	Contents
Post-Market Surveillance Plan	▪ Application information (plan approval, modified plan approval, minor modification, etc.) ▪ Applicant (representative) information (name, date of birth, address, application date) ▪ Contact information (name, phone number, cell phone) ▪ Manufacturer/importer (name (trade name), business license number, address) ▪ Details (product name (trade name and type), classification number and grade, approval number, approval date, expected market date, post-market surveillance period, post-market surveillance title) ▪ Post-market surveillance agency information (name, address, investigator signature, phone number) ▪ Source of manufacture (for imports, list the name, country of manufacture, and address) ▪ Surveillance Period ▪ Individuals responsible for the surveillance (e.g., personnel)

Category	Contents
	▪ Name of the outsourcing organization (including personnel if outsourced) ▪ Number of cases ▪ Surveillance Agencies ▪ Purpose of surveillance ▪ Surveillance methods (selection of subjects for data collection and analysis, baseline information on selected subjects, safety and effectiveness endpoints by time point, etc.) ▪ Surveillance details (background, baseline information, inclusion/exclusion criteria, safety and effectiveness endpoints, etc.) ▪ Interpretive items (subject information, procedure (use) information, safety and effectiveness endpoint items, etc.) ▪ Interpretation methods (statistical methods and comprehensive analysis results, including clinical significance, annual reports, final reports, etc.) ▪ Safety issues (issues considered during development, similar medical devices, experiences in different countries, etc.) ▪ Plan change overview (when submitting a plan of amendment)
Post-Market Periodic Reports	▪ Reporting information (enter "the 6th Month" for the first report, and years 1-7 depending on the number of reports) ▪ Reporter information (name, date of birth, address, and report date) ▪ Contact information (name, phone number, and mobile number) ▪ Manufacturer/importer (name (trade name), business

Category	Contents
	license number, address) ▪ Post-market surveillance overview (product name (trade name and type), classification number and grade, approval number, approval date, plan approval number, and plan approval date) ▪ Overview of Post-market surveillance (market date, reportable period, number of cases collected, sales performance, and post-market surveillance period) ▪ Post-market surveillance agency information (name, address, investigator name, and phone number) ▪ Country of origin (in case of for imports, name, country of manufacture, and address) ▪ Attachments (basic data, post-market surveillance evaluation and analysis results, adverse event reports, etc.)
Application for Review of Post-Market Surveillance Report	▪ Applicant (name, date of birth, address, contact name, contact phone number, and date reported) ▪ Manufacturer/importer (name (trade name), business license number, address) ▪ Details (product name (trade name and type), classification number and grade, approval number, approval date, and post-market surveillance period) ▪ Country of origin (in case of for imports, name, country of manufacture, and address)

2.3. Re-evaluation of medical devices

Of the medical devices that have been licensed, certified, and notified, re-evaluation may be carried out for those deemed necessary to be reviewed for the safety and effectiveness at the latest scientific level, and the subject of reevaluation shall be a medical device recognized by the Minister of Food and Drug Safety. The requirements and guidelines for submitting data for re-evaluation are in accordance with the Regulations on Medical Device Approval, Examination, and Notification and must include data on safety information, such as adverse events [12, 16].

2.4. Orphan and Urgent Medical Devices

'Orphan and Urgent Medical Devices' is a regulation that monitors the supply and demand status of medical devices that are essentially used for those with pediatric, rare, and incurable diseases. However, it requires importation and supply because there is no substitute in South Korea, or medical devices whose supply is unstable or interrupted in South Korea, so that they can be supplied stably in the country. The medical devices to be supplied are medical devices used for the diagnosis and treatment of rare diseases, for which there are no substitute products in South Korea, and medical devices requested by the Minister of Food and Drug Safety, or the head of the relevant central administrative agency for urgent introduction or stable supply support for public health [12, 17].

2.5. Conditional Approval for Evidence Development

Conditional Approval for Evidence Development is a health technology whose safety has been recognized; additionally, it is necessary to introduce it into clinical practice quickly for the treatment and examination of diseases or illnesses. Therefore, it can be used in clinical practice for research purposes only if it meets the conditions for the period of use, intended use, target of use, and procedure/test method separately specified and notified by the Minister of Health and Welfare. Conditional Approval for Evidence Development is limited to research-stage technology that has been reviewed as a Conditional Approval for Evidence Development as a result of a new health technology assessment [18, 19]. The documents required for Conditional Approval for Evidence Development are listed below (Table 3).

Table 3. Required documents of Conditional Approval for Evidence Development

Category	Contents
For the application of Conditional Approval for Evidence Development	▪ Conditional Approval for Evidence Development Application (including applicant information and medical technology information) ▪ Conditional Approval for Evidence Development Plan ▪ Executive Summary of Conditional Approval for Evidence Development Plan ▪ Implementing hospitals information ▪ Researcher status

Category	Contents
	▪ Patient case report form ▪ Institutional Review Board deliberation report and all documents submitted during the deliberation ▪ Resume of principal investigator and research records ▪ Required equipment list of MFDS clearance checks ▪ MFDS license for medical devices and major drugs ▪ Status of the medical device equipment and facilities ▪ How to apply for and plan to use national support funding types ▪ Research Feasibility Questionnaire ▪ Conflict of interest reports ▪ Personal Information Collection and Use Agreement ▪ References, other attachments, etc.
Management of Conditional Approval for Evidence Development courses	▪ Application to amend a Conditional Approval for Evidence Development plan ▪ Report of the first enrolled patient (Conditional Approval for Evidence Development name, hospital name, principal investigator, clinical study duration, and date when the first patient was enrolled) ▪ Report of the end of final patient observation period (Conditional Approval for Evidence Development name, hospital name, principal investigator, clinical study duration, and end date of final patient observation period)

Category	Contents
	▪ Safety-related information (report type [initial, additional, final], reporter type, reporter information, medical technology name, medical device information, patient information, adverse event name, onset and end time of adverse event, adverse event outcome, severity, predictability, causal relationship to medical technology, basis for determining relevance, details, follow-up, cause classification, causal relationship to medical device, final report result, attachments) ▪ State support cost calculation statement, claim application, usage plan, etc. ▪ Monitoring and inspection documentation ▪ Conditional Approval for Evidence Development interim (termination, final) report (name of Conditional Approval for Evidence Development, hospitals and physician in charge of implementation, period of implementation, government funding, patient registration results, document retention period, changes to the Conditional Approval for Evidence Development plan, reports of serious adverse events and adverse physical reactions, implementation of monitoring, implementation of inspection, study results (description of research background, research objectives, and research methods)

2.6. Innovative Health Technology Assessment

Innovative Health Technology Assessment is a health technology with recognized safety and potential that can be used clinically for 3 to 5 years only if it meets the conditions of use during the period, intended use, target of use, and procedure that the Minister of Health and Welfare specifically establishes and notifies. Currently, an Health Technology Assessment can be conducted as a study and subsequently used for treatment purposes for the remainder of the notice period once the number of study subjects has been fulfilled. When used for research and treatment purposes, Health Technology assessment may be used on a non-covered technology before the Committee by experts of medical treatment management procedure in Health Insurance Review and Assessment Service determines whether they are covered or not covered [20, 21]. The documents required for Innovative Health Technology Assessment are listed below (Table 4).

Table 4. Required documents of Innovative Health Technology Assessment

Category	Contents
When reporting the use of an Innovative Health Technology Assessment	▪ Application of Use of Innovative Health Technology Assessment ▪ Summary of Innovative Health Technology Assessment Proposals ▪ About Innovative Health Technology Assessment Implementing hospitals and Implementers ▪ Manufacturing (import) license for equipment

Category	Contents
	▪ Institutional Review Board approval letter and submission documents for each site ▪ Other documents
For Innovative Health Technology Assessment research purposes	▪ Innovative Health Technology Assessment Research (Change) proposal ▪ Safety-related information (report type [initial, additional, final], reporter type, reporter information, medical technology name, medical device information, patient information, adverse event name, onset and end time of adverse event, adverse event outcome, severity, predictability, causal relationship to medical technology, basis for determining relevance, details, follow-up, cause classification, causal relationship to medical device, final report result, attachments) ▪ Report on the status of Innovative Health Technology Assessment implementation (medical technology name, reporting person, health insurance code, period of implementation, total implementation status, registration status by implementing organization, research method, major changes, implementation contents and results [patient registration status, adverse event report, serious adverse event/adverse physical reaction report, quality control status report, research presentation and publication status, etc.], attachments)

Category	Contents
	▪ Results (final) report
For Innovative Health Technology Assessment clinical practice purposes	▪ Safety-related information (report type [initial, supplemental, final], reporter type, reporter information, medical technology name, medical device information, patient information, adverse event name, onset and end time, adverse event outcome, severity, predictability, causality to medical technology, basis for determining relevance, details, follow-up, cause classification, causality to medical device, final report outcomes, attachments) ▪ Innovative Health Technology Assessment implementation status report (medical technology name, reporting person, health insurance code, implementation period, total implementation status, number of medical device sales and procedures [tests] by implementing organization, total adverse event report status, total serious adverse event and adverse physical reaction report status) ▪ Results (final) report

2.7. Postponement of nHTA

The Postponement of nHTA is a regulation introduced to defer the evaluation of new health technology assessment for 2 years for use in clinical practice if the medical technology using a medical device licensed by the Ministry of Food and

Drug Safety meets the requirements for a deferred application and is not covered by insurance. The documents for applying for a Postponement of nHTA and gathering information include [22, 23] (Table 5).

Table 5. Required documents of Postponement of nHTA

Category	Contents
When applying for Postponement of nHTA	▪ Applicant information, address, applicant organization, address, and contact information ▪ Postponement of nHTA Name, Technical Overview. ▪ Results of eligibility check for insurance coverage ▪ Comparative clinical literature with existing technologies ▪ Authorization materials, including equipment
For the application of Postponement of nHTA	▪ Report for Sales and Lease of Postponement of nHTA Medical Device (Postponement of nHTA Name, Reporter Type, Reporter Information, Medical Device Information, Sale-Lease Information) ▪ Monthly status report of Postponement of nHTA (name of institution, address, type of provider, hospital code number, date of first shipment (sale), quantity sold, amount sold, date of first use, number of procedures/tests (or number of patients), cost of procedures/tests, and number of adverse events). ▪ Status of adverse events by Postponement of nHTA (name of implementing hospitals, address, type of medical institution, hospital code number, adverse events

Category	Contents
	and adverse reactions, period of occurrence, treatment status, progress, and final outcome) ▪ Safety-related information (report type [initial, additional, final], reporter type, reporter information, Postponement of nHTA name, medical device information, patient information, adverse event name, onset and end time of adverse event, adverse event outcome, severity, predictability, causal relationship to health technology, basis for determining relevance, details, follow-up, cause classification, causal relationship to medical device, final report result, attachments) ▪ Results (final) report ▪ Informed Consent Form Postponement of nHTA

IV. Results

1. RWD/RWE Platform Cases of Overseas

Overseas platforms include Observational Health Data Sciences and Informatics (OHDSI) and Japan's MID-NET, which are in use in several countries.

Both OHDSI and MID-NET apply their own common data model (CDM) to standardize data and operate their databases with a focus on consistency, accuracy, and completeness of large-scale real-world data.

1.1. Observational Health Data Sciences and Informatics

OHDSI is an international collaboration of academia, industry, healthcare providers, and regulatory agencies that aims to improve health and well-being by building and applying open source data analytics solutions to a large network of health DBs [24].

OHDSI has developed the OMOP CDM, which is built to have a data structure that can contain the broadest range of clinical information; additionally, it applies a distributed network approach to collect more than 1 billion patient records [8] (Figure 1).

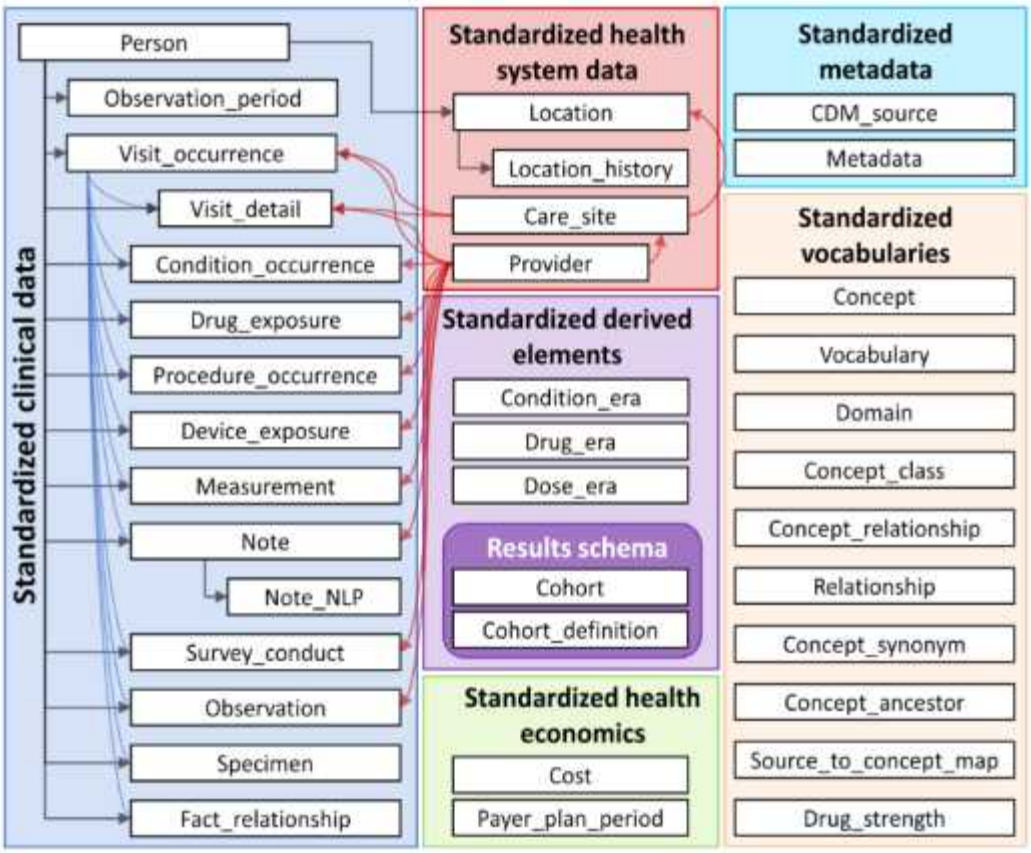

Figure 1. OMOP CDM
(Cite: The Book of OHDSI)

The OHDSI developer community has created an open source library of analytical tools in the OMOP CDM to support practices, such as clinical characterization of disease natural history, treatment delivery and quality improvement, application of causal inference methods for medical product safety surveillance and comparative effectiveness, and patient-level prediction for precision medicine and disease surveillance [25].

The simultaneous evaluation and analysis of multiple data sources requires the

harmonization of data into common data standards and a high level of security of patient data. To this end, OHDSI has created the OMOP CDM, which systematically applies research methods to produce comparable and reproducible results [25].

1.2. MID-NET

Launched in April 2018, MID-NET is a medical information database for RWD-based drug safety assessment designed and developed by Japan's Ministry of Health, Labor and Welfare, and PMDA in collaboration with 23 hospitals across Japan [26]. MID-NET employs a CDM that stores a vast array of hospital information systems, which are installed at each of its partner institutions. The data stored in MID-NET undergo the following processes to provide up-to-date clinical information [27]:

① A user writes a program to extract and summarize the target data.
② The user sends a request for approval to run the program to the collaborating organization for analysis.
③ The technical staff from the relevant partner organization approves the request.
④ The executed program is used to extract the target data from MID-NET and collect summarized data.
⑤ The technical staff from the relevant partner organization approves the transfer of the extracted data to the central data center.
⑥ The extracted data are to be sent to a central data center.

⑦ The user remotely accesses the extracted data and performs analyses using statistical programs as needed.

⑧ The user only has local access to the summarized data after the analysis is complete.

MID-NET contains RWD collected from about 4.7 million patients as of December 2018, and to maintain the high quality of large-scale data, the data are received from medical institutions on a daily basis and monitored daily, and various quality control systems are in place, including periodic data consistency checks [27].

2. Component of the Platform

The components of the platform were identified through a review of medical device-related regulations that can be applied to RWD/RWE, as well as guidelines and instructions for each regulation, and information obtained through the Ministry of Food and Drug Safety's medical device information portal (udiportal.mfds.go.kr). Since the purpose of this study was to develop a platform for collecting and analyzing RWD/RWE, and not to configure a platform for medical device license application, the components of the platform were divided into basic information, safety, effectiveness, cost, and stakeholder analysis.

2.1. Basic Information

When reviewing the regulations mentioned in the method, we set the following

elements as basic information: whether and what kind of medical device is handled, contact information, and medical device information.

- Medical Device Operator Information
- Information of Applicant and Person in Charge
- Manufacturer/importer information
- Medical device information (product name, item name, classification number, grade, approval number, and approval date, UDI code, etc.)
- Source of manufacture (for imports, list the name, country of manufacture, and address)
- Medical Device Sales status
- Name of the institutions using the medical device, hospital code number

2.2. Safety

All of the reviewed regulations require the collection of safety data and report on it regularly and frequently. The collection of information on safety must also include de-identified patient information; additionally, the information on human implantable devices and orphan and urgent medical devices that are not yet licensed is required.

- Patient de-identified information (gender, age, underlying diseases, etc.)
- Report type (initial, additional, final)
- Adverse event case name
- Time that adverse events occurred and ended
- Adverse event outcomes

- Severity
- Predictability
- Causation with medical devices/health technology
- Rationale for determining relevance
- Details
- Follow up
- Categorizing causes
- Final Reporting Results

2.3. Effectiveness

Most of the reviewed regulations require effectiveness information for their medical devices and medical technologies. An effectiveness analysis requires pre-designed effectiveness assessment endpoints, effectiveness assessment methods, and statistical analysis methods.

- Number of target patients
- Patient inclusion/exclusion criteria
- Effectiveness end points
- Statistical analysis methods
- Case reports Form

2.4. Cost

The costs should include not only the sale/lease price of the device but also the cost of the procedure/test, whether covered or not covered. The accumulation of cost data can be used as a basis for future economic evaluations of medical devices and medical technologies

- Amount of medical device sales
- Insurance covered/not-covered status and medical treatment / medical material code number
- Procedure/Test Costs

2.5. Stakeholder analysis

It is important to know what stakeholders are involved in building a RWD/RWE platform. Overall, the industry, healthcare, and government should be included. The healthcare should be inclusive of primary and secondary care providers, not just tertiary hospitals. For the government, it should include the Ministry of Food and Drug Safety and the Korea Institute Medical Device Safety Information, as well as the National Evidence-based Healthcare Collaborating Agency, which conducts medical technology assessments, and the Health Insurance Review and Assessment Service, which determines the appropriateness of benefits and conducts affordability assessments. The stakeholder block diagram is shown in Figure 2.

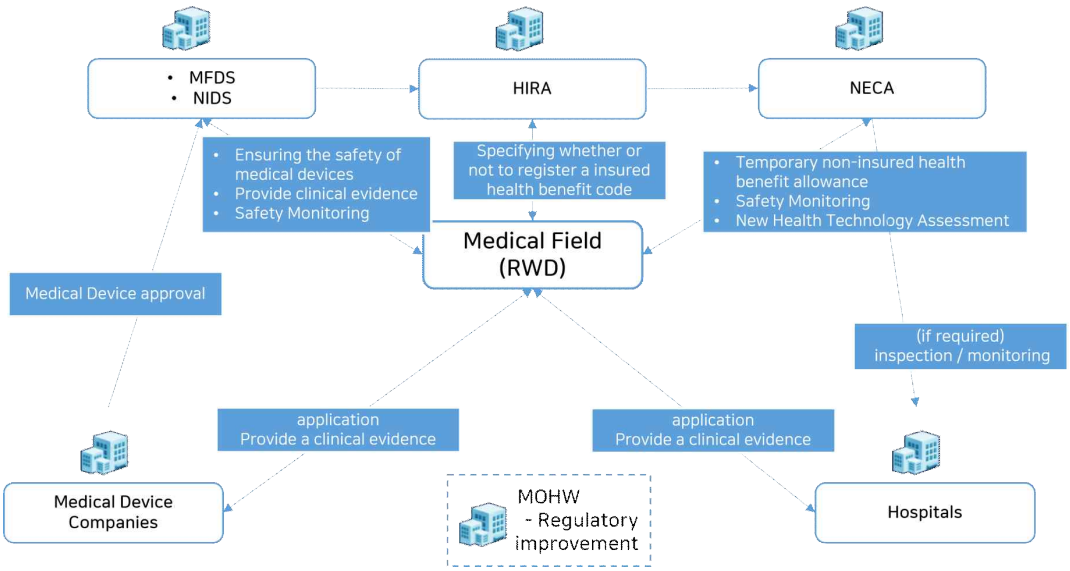

Figure 2. Stakeholder analysis for RWD/RWE of Medical Device

3. Development of RWD/RWE Platform for Medical Device

Based on the platform components derived above, a Korean RWD/RWE platform for medical devices was derived as follows, consisting of application/reception, safety reporting, effectiveness reporting, cost reporting, and RWE generation.

3.1. Application System

The most fundamental system for organizing the RWD/RWE platform is the application and reception system for using the platform.

Members who can access the system include platform administrators, applicants,

such as medical device importers, manufacturers, and medical technology application organizations, implementing organizations, such as tertiary hospitals, general hospitals, and hospitals/clinics, government agencies, such as the Ministry of Health and Welfare, the Korea Food and Drug Administration, the National Evidence-based Healthcare Collaborating Agency, and the Korea Health Insurance Review and Assessment Service, and the public, such as patients. They can access the system through a PC, tablet, or smartphone.

After signing up and logging in, the system will show a list of projects that are currently collecting RWD. RWD project management is tied to patient data collection, including safety, effectiveness, and cost.

To apply for RWD data collection for RWE generation, the members need to fill out an application form, enter the information of the applicant's organization, such as the type of medical device operator and manufacturer/importer, the license and details of the required equipment for which RWD needs to be collected, the sales status of the medical device, the name under which the medical device was sold, the information of the implementing organization, such as the medical institution number and address, the information of the implementer, and related documents.

The diagram of the application and reception system for using the RWD/RWE platform is shown in Figure 3.

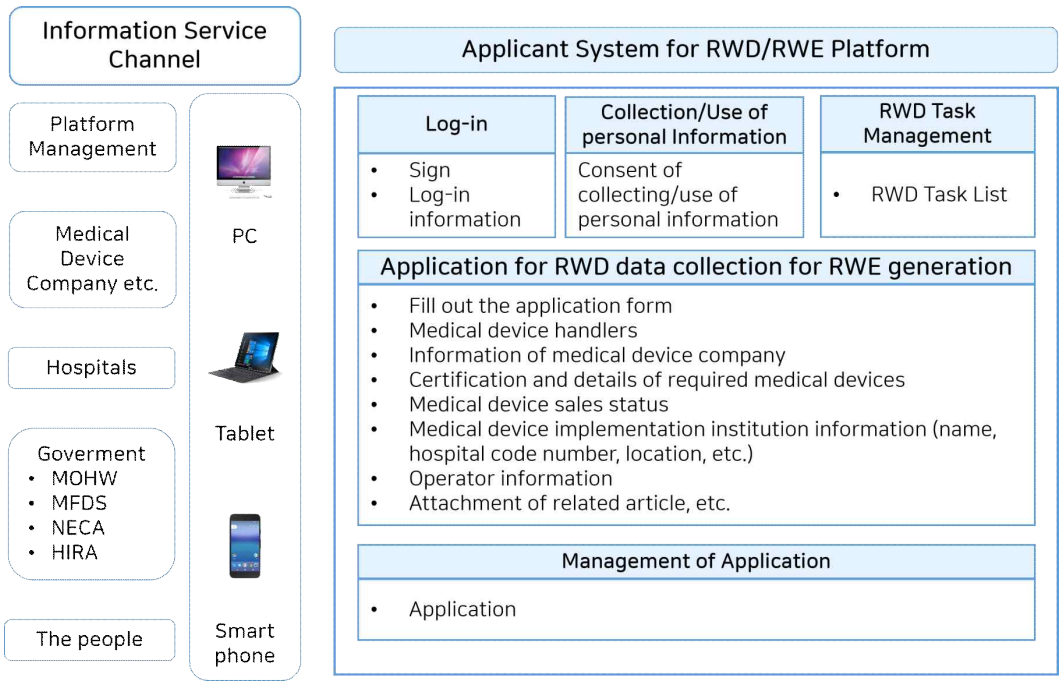

Figure 3. Application System for using the RWD/RWE Platform

3.2. Safety System

It is important to collect information about the safety of medical devices through the RWD/RWE platform.

Adverse event reporting is available not only to medical device manufacturers but also to implementing organizations and patients, and the adverse event reporting system is designed to be accessible to the public, including platform administrators, applicants, implementing organizations, governments, and patients.

Adverse event reports should include de-identified information, such as the patient's sex, age, and underlying diseases, and identify whether the report is a first, additional, or final report. The name of the adverse event, the time of

occurrence and termination, and the outcome shall be described in detail, and the severity and predictability of the adverse event, the causal relationship with the medical device or medical technology, the basis for determining the relevance, the details, follow-up actions, cause classification, final report, and other attachment s shall be implemented on the platform.

The diagram of the adverse event reporting system of the RWD/RWE platform is shown in Figure 4.

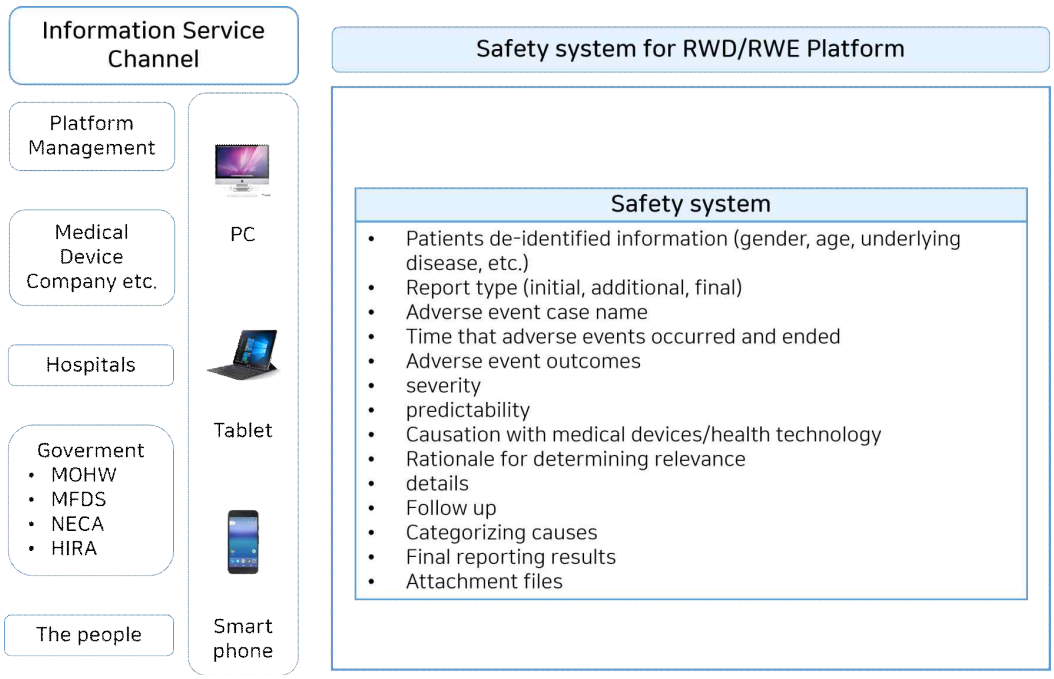

Figure 4. Safety System for using the RWD/RWE Platform

3.3. Collecting and Managing Effectiveness Data System

The collecting of effectiveness information through the RWD/RWE platform plays an important role in several fields, including post-marketing surveillance of medical devices and medical practices, and can provide better medical services to patients based on the effectiveness information collected using real-world data.

The effectiveness data collection and management system is accessible to platform administrators, applicants, implementing organizations, and governments. However, priority should be given to implementing organizations that are familiar with the clinical implications of the medical device/medical technology when entering effectiveness data.

In the above review of regulations, all of the regulations that collect effectiveness data were observed to collect effectiveness data in accordance with their respective proposals. Therefore, in order to collect effectiveness data, a proposal should be designed first accordingly. The proposal must describe the number of patients to be included, patient inclusion/exclusion criteria, effectiveness endpoints, definitions of effectiveness endpoints, and methods of statistical analysis. In addition, the implementation of a patient case report format will allow for the systematic management of effectiveness data collection, and an informed consent form should be prepared in advance.

To collect the effectiveness data, de-identified patient information and the institution where the patient received the procedure or test must first be entered. In addition, the patient visit record must be entered, and the effectiveness variables must be entered accordingly. Case reports must be uploaded as a file if they

cannot be typed, and patient consent must be verified.

Effectiveness data verification is for controlling the errors in the input data during the data collection process. It should be able to control errors, such as entering values that are too large or too small compared to the average value. Additionally, if the input data are changed, there should be change tracking, including why it was changed and when it was changed.

The diagram of the RWD/RWE platform effectiveness data collection and management system is shown in Figure 5.

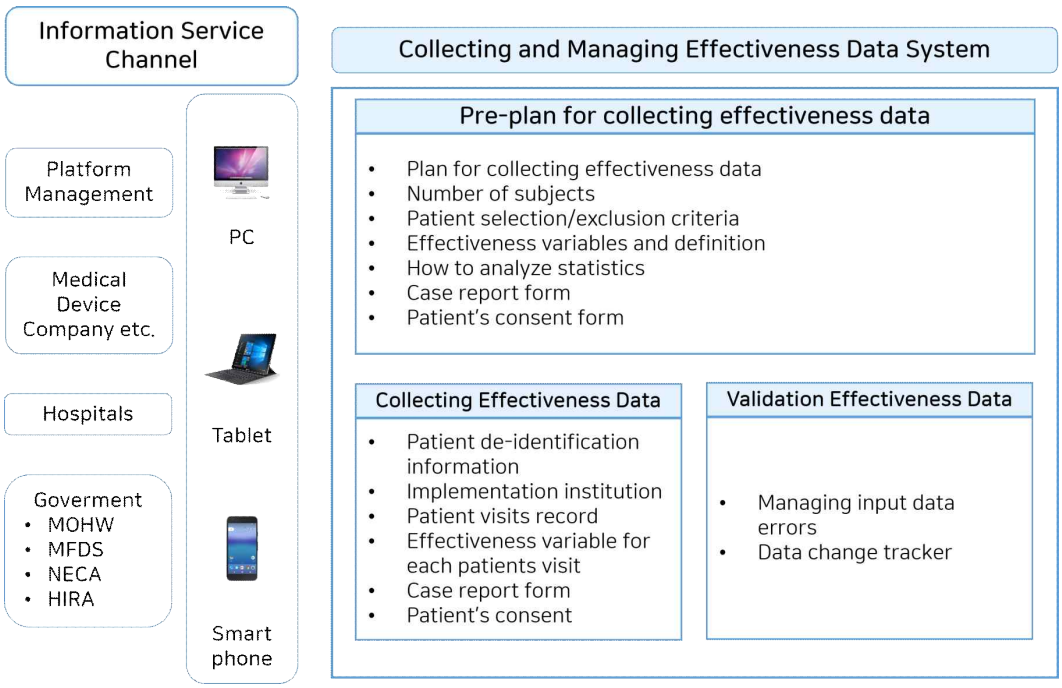

Figure 5. Collecting and Managing Effectiveness Data System

3.4. Collecting Cost Data System

The cost information collected through the RWD/RWE platform can be used as a source for future decisions for insurance covered/not covered and its appropriateness.

The cost management system is accessible by platform administrators, applicants, implementing organizations, and governments. Patients were excluded because they do not know the exact cost of the medical procedure/treatment material.

The system must first be linked to de-identified patient information and include the number of patients who have used the medical device and medical technology. To collect the cost data, it should be determined whether the medical procedure or therapeutic material for the device is covered or not covered; if covered, the payment code for the medical procedure/therapeutic material should be entered. However, if not covered, medical institutions charge different amounts even for the same medical procedure and treatment materials; therefore, it is necessary to collect "not-covered cost per patient by medical institution." The diagram of the RWD/RWE platform cost data collection system is shown in Figure 6.

3.5. Create RWE

The data on safety, effectiveness, and cost collected through the platform can be linked to data analysis systems to generate RWE. The data analysis system is equipped with statistical package programs, such as SPSS and SAS, allowing researchers to download and analyze the data directly.

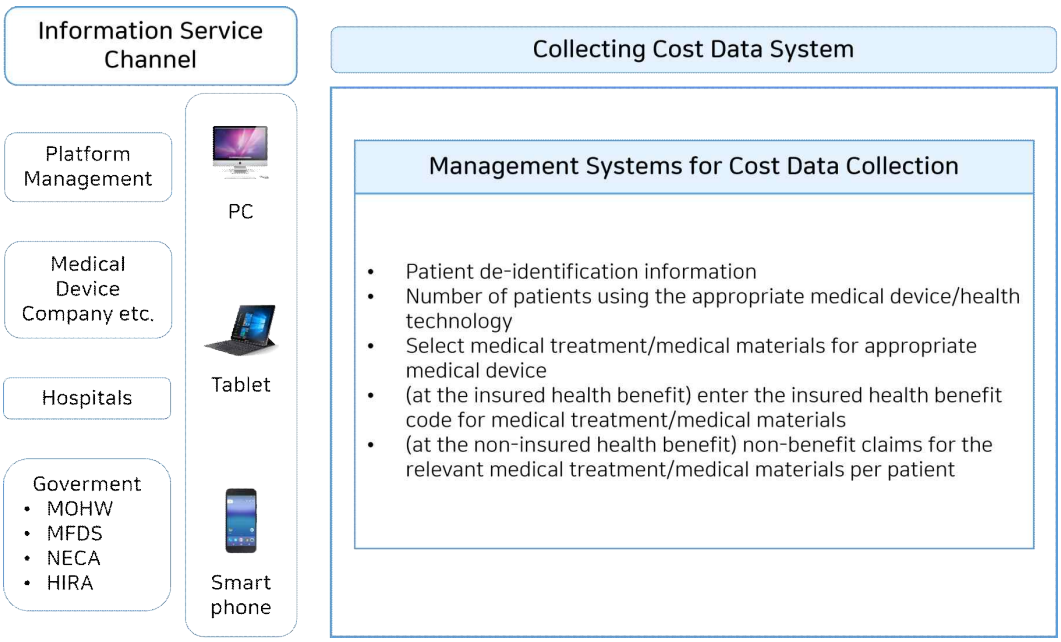

Figure 6. Collecting Cost Data System

3.6. Proposal of RWD/RWE Platform System Model

The final proposed RWD/RWE platform system model, which integrates the above-mentioned application and reception system, safety system, effectiveness system, cost collection system, and RWE generation system, is shown in Figure 7.

On this platform, the users can apply to create a study of their choice and see what RWD studies are currently being conducted. The generated RWD studies can collect safety, effectiveness, and cost and the data collected can be used by researchers to generate RWE through the statistical analysis of medical devices and medical practices, and utilize the generated RWE to provide better medical services to patients.

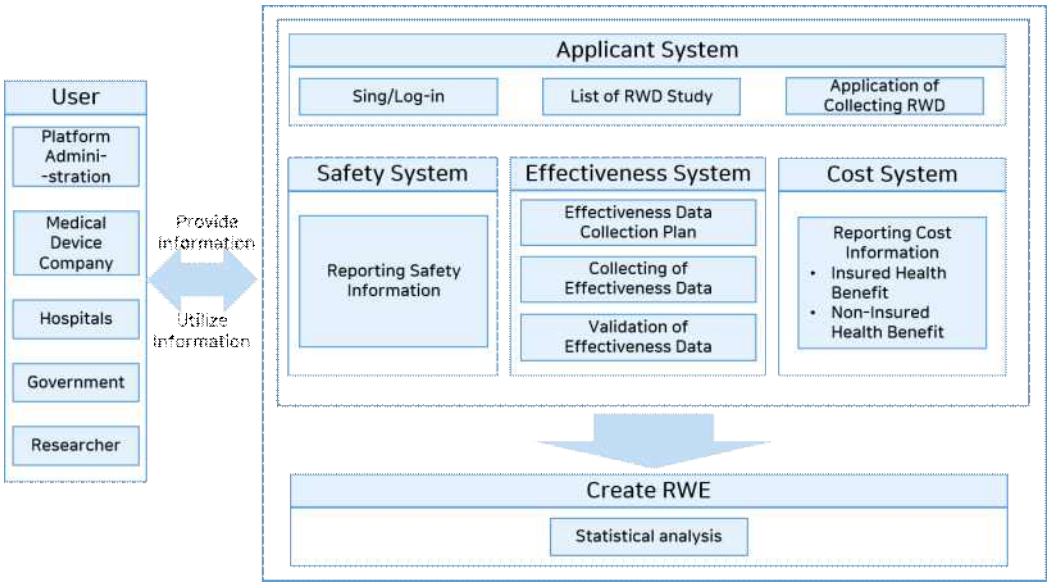

Figure 7. Proposal of RWD/RWE Platform System Model

V. Discussion

This study proposed the establishment of a platform for generating evidence using real-world data to create an empirical ecosystem in the life cycle management of medical devices through a review of the medical device regulations in South Korea.

In our review of foreign platform systems, we looked at two databases, OHDSI and MID-NET. OHDSI is a voluntary consortium of researchers from a wide range of disciplines, including several organizations around the world with clinical data. The OMOP-CDM developed by OHDSI is designed to have a data structure that can contain the broadest range of clinical information of any CDM developed to date; however, the further development of standardization techniques for unstructured data is needed [28].

Japan's MID-NET is a database for drug safety management that ensures high data quality through periodic checks of accuracy, consistency, and completeness between original and extracted data; however, it has a limitation that the sample of patients is limited because the collaborating medical institutions are only medium- to large-sized hospitals [27].

OHDSI is an international consortium that can currently collect the most structured RWD through OMOP-CDM; however, there are limitations in collecting data at the hospital and clinic level in South Korea. Since MID-NET is a database for pharmaceuticals and not for medical devices and medical practices, there is a need for a database suitable for medical devices and medical practices in South

Korea.

In addition, Wang (2019) mentioned that a national integration and data sharing platform should be created through consultation with various stakeholders [29], and the establishment of a cross-ministerial open platform to collect and analyze data is necessary to prepare RWE for the post-market assessment of digital therapeutic devices [30].

Moreover, in 2020, the Ministry of Food and Drug Safety announced a plan to establish an active pharmacovigilance system based on big data, such as real-world data [7]. Therefore, it is necessary to build a platform to monitor the safety and effectiveness of RWD/RWE-based medical devices and medical practices just like pharmaceuticals.

The FDA guidelines for RWD/RWE mentioned relevance and reliability as characteristics of RWD. RWD relevance is about whether RWD is suitable for evaluating the performance of a device in medical device regulation, while reliability is about ensuring data quality and integrity with minimal errors [3, 4, 5]. Therefore, RWD relevance and reliability, as mentioned in the FDA guidelines, should be fully considered when building a platform. UDI can be an example. UDI also affects the relevance of RWD, and other studies have noted the need to support and advance the implementation of UDI for the purpose of evaluating the safety and effectiveness of medical devices using RWD [2, 3, 4, 5]. Therefore, when building a RWD/RWE platform, information about UDI must be included, and ways to efficiently operate UDI within the platform should be explored.

In addition, FDA guidelines note that regardless of the intended purpose of RWD collection, procedures for data collection and quality assurance should be implemented during the source design and development phase to optimize the

reliability, quality, and utility of the data [3, 4, 5]. Therefore, at the same time as establishing the RWD/RWE platform, it is necessary to clearly write a Standard Operating Procedure (SOP) for data management, and fully discuss the policy for quality assurance and management of RWD, and then the procedure must be recorded.

This study has a few limitations. The first is that it is not clear who is the subject of the operations for building the platform. The platform proposed in this study covers the entire spectrum of medical device licensing to medical practice. In South Korea, however, the approval of medical devices is carried out by the Ministry of Food and Drug Safety; however, the evaluation of medical technologies is carried out by the National Evidence-based Healthcare Collaborating Agency. To build the platform proposed in this study, therefore, it is necessary to discuss whether the platform operation and supervision will be carried out in a cross-ministerial way.

The study also lacks information on the standardization of the data. For data standardization, such as OMOP-CDM, further research from multiple angles is needed to develop a model for data standardization tailored to the actual situation of medical devices in South Korea.

VI. Conclusion

In this study, we proposed the construction of an RWD/RWE platform to utilize RWE in medical device regulation in South Korea. Research on building RWD/RWE platforms for medical devices is limited globally, and Korean domestic medical device and medical practice regulatory agencies do not have much experience in utilizing RWD/RWE. It is important to build a RWD/RWE platform that addresses these limitations well, while providing a better healthcare experience for patients. However, in order to establish an RWD/RWE platform for medical devices, a study on the common data model for Korean medical devices for data standardization should be conducted. Therefore, we propose to build an RWD/RWE platform for medical devices and medical practices, and expect that this study can be used as a basis for future RWD/RWE platforms.

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APPENDIX I

Simulation of the proposed RWD/RWE Platform

It would like to simulate the platform proposed in the study for the following medical device among the devices currently designated as orphan and urgent medical devices.

Category	Contents
Manufacturer (Country)	Numed (USA)
Name of Product	Atrioseptostomy catheter
Item Category	Cardiac catheter, balloon, septostomy [4]
Name of Model	611200, 611100
Specification	Ballon Diameter 9.5mm, Length 0.95cm Ballon Diameter 13.5mm, Length 1.35cm
Medical Devices Code for Health benefit Insurance	Insured Health Benefit, J4064010
Intended Use	Medical device used for newborns or infants with congenital heart disease. It is used for cardiovascular performance and is used to maintain blood flow between atria in complex congenital heart diseases such as aortic dislocation, tricuspid valve obstruction, mitral valve obstruction, etc

After signing up for membership and logging in to the platform to collect the basis for real-world data of the medical device, an application for platform use is prepared. In the application, the medical device requiring ‘Orphan and Urgent Medical Device’, which is the regulatory purpose of the medical device, is checked, and details of the medical device are written. In the case of this medical device, a certification is not attached separately because there is no domestic approval. If there is a medical institution where medical devices have already been sold, the name of the institution, the hospital code number, location, and the operator must also be prepared. If there is no medical institution sold, it is checked for non-sale. In addition, an application is submitted with related article confirming the safety and effectiveness of the medical device.

The platform manager may review the received application for the medical device and then approve/supplement/turning back. The finally approved application is included in the RWD task list under the title of 'cardiovascular catheter for newborns and infants with congenital heart disease'. After that, when the sales and implementation institution of the medical device is confirmed, the name of the hospital, the hospital code number, location, and the operator may be added.

All adverse events occurring in the patient using the medical device, such as adverse events occurring while performing the procedure and adverse events after surgery, can be input into the safety system. Non-identification information such as gender, age, and underlying disease of the patient can be input, and adverse events, time of occurrence and end, side effect result, severity, prediction, causal relationship with medical device, judgment basis, details, and follow-up measures of the corresponding adverse reaction can be input.

For example, when the following adverse events occurs, the safety system of the platform may be prepared as shown in the table below.

"A newborn baby with congenital heart disease, who underwent surgery using the medical device at Hospital A on November 30, 2023, was admitted to the emergency room with a high fever on December 21, 2023, three weeks after surgery, and a fever reducer was administered immediately, and adverse reactions were resolved the next day. The high fever was confirmed to be caused by COVID-19, and there was no causal relationship with the medical device."

Category	Contents
Patient de-identification information	A001-Atrio C
Gender / Age	Male / 3 weeks
Adverse Event	High fever for SARS-COV-2
Time of occurrence	2023. 12. 21.
End time point	2023. 12. 22.
causality with medical devices	None

In the event of serious adverse reactions such as death or hospitalization among the safety information of patients gathered at each implementation institution, implementation institutions, medical device companies, and government agencies can receive real-time feedback on the safety information of the medical device.

It is also possible to collect the effectiveness information of the 'cardiovascular catheter for newborns and infants with congenital heart disease'. However, in the

case of effectiveness, even with the same indicator, there may be a difference in collection timing for each medical institution, so standardization requires a definition of the effectiveness indicator. For example, if you want to see the success rate of catheter insertion and re-operation rate as indicators of the effectiveness of the technology, a clear term definition and window period must be described in advance. In addition, the number of target patients and the criteria for selection and exclusion of patients through statistical analysis for validity verification should be clearly defined in advance. A preliminary design for collecting validity data according to the following example may be expressed as the table below.

"The main effectiveness variables of this medical device are 'catheter insertion success rate' and 're-procedure rate', and about 100 patients are required as a result of statistical analysis to verify the effectiveness variable. In order to verify the effectiveness variable, the patient must visit the hospital 1 day after surgery, 1 week after, 1 month after, and 3 months after, and each window period is ± 2 to 7 days. The 'catheter insertion success rate' was defined as the case where the catheter was located in the area when confirmed by echocardiography, and the 're-procedure rate' was defined as the case where the catheter was performed again within 3 months of surgery."

Category	Contents
Number of Patients for Effectiveness Validation	▪ 100 patients
Effectiveness Variables	▪ Success rate : If the catheter is located in that area ▪ Re-operation : If reoperation is performed within 3 months of surgery
Follow up	▪ one day after surgery ▪ one week after surgery (± 2 days) ▪ one month after surgery (± 7 days) ▪ three months after surgery (± 7 days)

In accordance with the pre-designed effectiveness definition, the implementation agency must enter the validity data into the platform. The patient's non-identification information, patient visit records, effectiveness variables, and case records must be entered or uploaded. In the process of entering the validity data, there are no errors such as incorrectly inputting figures, and the data corrected in the middle can be tracked and managed for what reasons and how it was modified. The collection of patient effectiveness data according to the following cases is shown in the table.

"A newborn baby with congenital heart disease who underwent surgery using the medical device at Hospital A on November 30, 2023, successfully underwent catheterization because the catheter was well located in the area. As a result of follow-up for 3 months of surgery, no complications

occurred, and no re-operation occurred."

Category	Contents
Success Rate	▪ day of surgery : Success
Re-operation	▪ one day after surgery : Nothing happened ▪ one week after surgery (± 2 days): Nothing happened ▪ one month after surgery (± 7 days): Nothing happened ▪ three months after surgery (± 7 days): Nothing happened

Cost information can also be collected on the proposed platform to analyze the cost-effectiveness analysis and evaluate the adequacy of benefits in the future. In the case of 'cardiovascular catheter for newborn and infant with congenital heart disease', the treatment material code J4064010 is entered because the treatment material has already been registered as a benefit.

The RWD information for the 'cardiovascular catheter for newborns and infants with congenital heart disease', in which all safety, effectiveness, and cost information are collected, can be downloaded by a researcher, etc. who wants to analyze the data and perform statistical analysis to generate RWE. The RWE information generated in this way can be used to regulate medical devices, such as permission of the corresponding medical device. For example, when the following results are obtained, the RWE can be generated as shown in the following table.

"For 11 months from November 2023 to December 2024, RWD collection of 'cardiovascular catheter for newborns and infants with congenital heart disease' was performed at 15 hospitals nationwide. A total of 102 children underwent the procedure during the period, and the average age was 1.2 ± 0.5 years old, and 50 males. A total of 100 adverse reactions occurred within the period, but the adverse reactions were mild and there was no causal relationship with the medical device. As a result of 3-month follow-up, 85 out of a total of 102 children successfully performed catheterization, and the reoperation rate was 10 patients."

Category	Contents
Name of Product	Atrioseptostomy catheter
Patients Characteristic	newborns or infants with congenital heart disease
Period of Collecting RWD	2023. 11. ~ 2024. 12.
Number of Hospital	15
Number of Patients	102
Characteristic of Patients	▪ average age: 1.2 ± 0.5 yr ▪ male/female : 50 / 52
Safety	100 mild adverse event (Not related to medical device)
Effectiveness	▪ Success Rate : 83.3% (85/102) ▪ Re-operation rate : 0.10% (10/102)
Insured Health benefit code	J4064010

Abstract (in Korean)

의료기기 전주기 관리에서 실증 생태계 조성을 위한 RWE 기반 플랫폼 모델 개발

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동 연구는 의료기기 전주기 관리에서 실증 생태계 조성을 위하여 실사용 데이터를 이용한 실사용 근거를 생성하기 위한 플랫폼의 구축을 제안하는 것을 목적으로 한다.

동 연구를 수행하기 위해서 RWD/RWE에 대한 플랫폼 혹은 데이터베이스의 미국 및 일본의 국외 사례를 조사하였다. 그 후, 국내 의료기기 관련 정책 의사 결정에 있어 RWD/RWE가 활용되는 제도를 고찰하여 플랫폼에 구성되어야 할 주요 요소들을 파악하였다.

국내 의료기기 RWD/RWE 플랫폼은 신청 및 접수 시스템, 안전성 보고 시스템, 유효성 보고 시스템, 비용 수집 시스템, RWE 생성 시스템의 구성으로 제안하였다. 동 플랫폼에서는 신청을 통하여 연구를 생성할

수 있으며, 생성된 RWD 연구에서는 안전성과 유효성, 비용 등을 수집할 수 있고, 수집된 데이터들은 연구자 등에 의하여 의료기기 및 의료행위 통계 분석을 통해 RWE를 생성하고 환자에게 더 나은 의료 서비스를 제공할 수 있게 해준다.

환자에게 더 나은 의료 환경을 제공하기 위해 RWD/RWE 플랫폼을 구축하는 것은 중요하며, 해당 연구가 추후 RWD/RWE 플랫폼 구축에 있어 기초자료로 활용될 수 있음을 기대하는 바이다. 다만, 의료기기를 위한 RWD/RWE 플랫폼 구축을 위해서는 데이터 표준화를 위한 한국형 의료기기 공통 데이터 모델에 관한 연구가 수행되어야 한다.

핵심 되는 말: 실사용 데이터, 실사용 근거, 플랫폼 구축, 의료기기