Appropriate Relevancy and Reliability of Real-World Data for the Utilization of Regulatory Submission

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Abstract

The extraction of data that contribute to regulatory approval from real-world data (RWD) is difficult because of the lack of a standardized data format and extraction methodology. Additionally, when real-world evidence (RWE) is used as an external control group, the similarity between internal and external control data is not evaluated. To investigate the data extraction methodology for the external control data of rare molecular subtypes, we have initiated the "REALISE" study. In this study, we aim to elucidate the "relevance" and "reliability" of RWD/RWE necessary for regulatory approval. As most databases are not designed for regulatory use in the creation phase, we will investigate retrospective methodologies to ensure RWD/RWE reliability. This study will compare the "relevance" and "reliability" of the ARCAD global database, SCRUM-Japan Registry, SCRUM-Japan observational study, and Flatiron Health RWD, and statistically analyze the differences and similarities among the four databases. We will also examine the methodology for extracting sufficiently relevant data from the SCRUM-Japan observational study. Additionally, if the reliability of the RWD/RWE does not reach the required level for regulatory approval, we will examine the methodologies to ensure the "reliability" of the SCRUM-Japan observational study for regulatory approval. The obtained results will be submitted to the "Consultation for Development of Registry" in the Pharmaceuticals and Medical Devices Agency, and we will discuss the standard methodology. The procedures and findings identified in the REALISE study will be organized from the perspectives of "database construction," "data analysis," and "outcome evaluation" and will be issued as "the draft guidelines."

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Efforts to Utilize Real-World Data/Real-World Evidence in Each Country

According to the US Food and Drug Administration (FDA), real-world data (RWD) relate to patient health status and/or the delivery of health care routinely collected from several sources, including data derived from electronic health records (EHRs), medical claims data, data from product or disease registries, and data gathered from other sources that can inform on health status.[1,2] Real-world

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evidence (RWE) is the clinical evidence of the usage and potential benefits or risks of a medical product derived from RWD analysis.[1]

In recent years, regulatory authorities have promoted various policies for the utilization of RWD worldwide, and the use of RWD for the implementation of efficient clinical trials and regulatory submissions is expected. Pharmaceutical companies also promote the utilization of RWD based on the increased cost of drug development, issuance of various guidelines from regulatory authorities, and accumulation of use cases.[3] In fact, registry and/or EHR data were utilized for the regulatory approval of blinatumomab,[4] tisagenlecleucel,[5] and cerliponase alfa.[6] In the United States, the 21st Century Cures Act was enacted in 2016 to accelerate the approval process of the US FDA and to promote the introduction of new medical therapies. The FDA also published a framework for utilizing RWD/RWE in the process of drug approval.[1] Subsequently, various guidelines, including "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products," have been continuously issued.[7] In Europe, the European Medicines Agency (EMA) has also actively discussed the use of RWD in drug development, and the guidelines on registry-based studies have been issued.[8,9] The EMA and Heads of Medicines Agencies set up a joint task force to describe the big data landscape from a regulatory perspective and identify practical steps for the European medicines regulatory network to make best use of big data in support of innovation and public health in the European Union.[10]

In addition, the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use published the "Reflection Paper for GCP Renovation" in January 2017, and proposed the modernization of ICH E8 (General Considerations for Clinical Trials) and subsequent revision of ICH E6 (Guideline for Good Clinical Practice) in light of diversified study designs and data sources. The ICH also issued a reflection paper on the proposed international harmonization of RWE terminology, and the convergence of general principles regarding the planning and reporting of studies using RWD was issued in 2023.[11]

In Japan, the Clinical Innovation Network was constructed to improve the environment for efficient clinical development according to the 2016 Japan Revitalization Strategy. Since April 2019, the Pharmaceuticals and Medical Devices Agency (PMDA) has been operating the "Consultation for Development of Registry," which advises registry holders on the concept of planning based on the premise of using the registry and the general concept for improving quality and ensuring the registry's reliability. The PMDA also provides the "Consultation for Pre-inspection on Registry Data Reliability," which provides advice primarily to marketing authorization holders on the concept of registry reliability assurance or confirms the reliability of the survey before application. As a result, the Ministry of Health, Labour and Welfare (MHLW) has put in place a system for utilizing RWD/RWE for approval applications and postmarketing surveillance. In addition, in March 2021, the MHLW also issued notifications for the "Basic Principles on Utilization of Registry for Applications" and "Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications."[12,13]

Database Projects in the National Cancer Center Hospital East

In the era of the data-driven society, the National Cancer Center Hospital East (NCCHE) has been actively accumulating high-quality clinical data combined with genome and various types of omics data. SCRUM-Japan is the largest nationwide cancer genome screening project in Japan based on industry-academia collaboration. In 2015, SCRUM-Japan was launched by combining "LC-SCRUM-Japan" and "GI-SCREEN-Japan (UMIN000016343 and UMIN000016344)" platforms, as Japan's first industry-academia nationwide cancer genome screening project. Since then, we have launched various studies, including the "GOZILA Study (UMIN000029315)" in 2018, "MONSTAR-SCREEN-1 project" (UMIN000036749) in 2019, and "MONSTAR-SCREEN-2 project" (UMIN000043899) in May 2021.[14]

The SCRUM-Japan Registry was launched in November 2017 as a prospective registry to construct external control data contributing to the application for drug approval. In the SCRUM-Japan Registry, we prospectively collect clinical data on standard therapies in patients with rare genetic alterations for whom new drug approval applications are expected. Patients with specific genetic alterations detected in the SCRUM-Japan observational studies are registered with the individual patient's informed consent. After the registration, the efficacy of standard therapy in clinical practice is evaluated by computed tomography scan within 6 weeks before the start of each treatment regimen and every 8 $\pm$ 2 weeks after the start of the regimen according to the registry protocol. The response rate, disease control rate, progression-free survival, duration of response, and time to treatment failure are evaluated using prospectively collected computed tomography images. Overall survival is periodically tracked under the provisions of the registry protocol.[15]

The NCCHE has also been conducting the ARCAD Asia Project, an Asian version of the ARCAD database project that collects clinical trial data on metastatic colorectal cancer (mCRC) in the Asian region. Upon the signing of a data provision agreement between the data provider and the NCCHE, the supplied data are processed and integrated into the ARCAD Asia database using a standardized structure that is consistent with the ARCAD global database.[16] ARCAD Asia data are regularly transferred to the ARCAD global database project, which is conducted by the French ARCAD Foundation and Mayo Clinic in the United States, and the ARCAD Asia data are integrated into the ARCAD global database. Because the integrated global database is simultaneously shared with all French, US, and Japanese data centers, we can utilize the ARCAD global database based on our preferences.[16] Utilizing the consolidated database, analyses were conducted following the approval process of the internal committee, with stringent precautions to avoid violating the rights of the original trial sponsors.

Furthermore, the NCCHE and Flatiron Health Japan started a joint research partnership in January 2022, with a shared mission

to address the critical need for oncology RWD in Japan. As the NCCHE is one of the flagship hospitals for cancer care and research in Japan, 12,000 new patients with cancer are annually treated. We are now constructing a database that includes high-quality structured and unstructured data from patients with gastrointestinal, breast, and hematological malignancies.[17]

Requirements of Real-World Data/Real-World Evidence for Application of Drug Approval

When we attempt the utilization of RWD for the application of regulatory approval based on the fitness-for-purpose, the "relevance" and "reliability" of data should be considered.[18,19] The "relevance" of the data includes the availability of key data elements (exposure, outcome, and covariate), representativeness, sufficient subjects, and longitudinality. The "reliability" of data includes accuracy, completeness, provenance, and traceability of data processing.[18,19]

According to the "Basic Principles on Utilization of Registry for Applications," from the MHLW in Japan, "General points to consider for utilizing registry data for the applications" are as follows: (1) Considerations for the protection of personal information and patient consent, (2) reliability of registry data utilized, (3) appropriateness of registry data utilized, and (4) early consultation with those who construct the registry (registry holder). In addition, the points to consider when utilizing registry data as an external control of clinical studies for efficacy and/or safety evaluation are as follows: (1) registry patient population, (2) endpoints, (3) evaluation period, (4) statistical method, and (5) type of observational study for natural history (prospective or retrospective).

In clinical trials aimed at rare (1%-5% of the total population) molecular subtypes, a sufficient sample size for randomized controlled trials (RCTs) is difficult to achieve owing to cost and time constraints. In the SCRUM-Japan Registry, we have prospectively collected the clinical data of standard therapies in patients with rare genomic alterations, where new drug approval applications are expected, since 2017.[15] The TRIUMPH study, an investigator-initiated phase 2 trial conducted by the NCCHE (UMIN000027887), was the first significant experience in using the SCRUM-Japan Registry.[20] The trial evaluated the efficacy and safety of pertuzumab and trastuzumab as salvage-line therapies in patients with human epidermal growth factor receptor 2 (HER2)-positive and *RAS* wild-type mCRC. Based on the results of the phase 2 TRIUMPH study and data extracted from the SCRUM-Japan Registry, the pharmaceutical company submitted an application for pertuzumab and trastuzumab for patients with HER2-positive mCRC in April 2021.

As the "Basic Principles on Utilization of Registry for Applications" was issued after the start of construction of the SCRUM-Japan Registry (in March 2021), we reviewed the systems of our registry in terms of the data quality and reliability. For "GCP On-site Inspection and Document-based Conformity Inspection" conducted for the TRIUMPH study, the standard operating procedures and documentations were revised. Pertuzumab and trastuzumab were approved as expanded indications on March 28, 2022, for "HER2-positive unresectable advanced/recurrent colorectal cancer exacerbated after cancer chemotherapy." To the best of our knowledge, this is the first regulatory approval for HER2-positive colorectal cancer worldwide and represents a remarkable success in obtaining regulatory approval utilizing regulatory-grade registries for rare molecular subtypes.

REALISE Study

Although it is ideal to extract data that contribute to regulatory approval from RWD/RWE, such as data from EHRs in the future, the EHR data format has not been standardized, and the extraction methodologies have not been clarified. In addition, when RWD/RWE is used as an external control group instead of an internal control group in an RCT, a similarity between the internal and external control data should be assumed. However, the quality and feasibility of RWD/RWE have not yet been fully evaluated. Based on these backgrounds, we have initiated the "REALISE study" to investigate the data extraction methodology for external control data of rare molecular subtype. We also evaluate the "relevance" and "reliability" of RWE generated from RWD as evidence for regulatory approval. As most databases are not designed for regulatory use in the creation phase, the additional assurances of "reliability" will be retrospectively expected. In this study, we will investigate retrospective methodologies to ensure the "reliability" of RWD/RWE.

In the SCRUM-Japan observational studies, we have already accumulated data on 40,000 cases of solid tumors. We have obtained consent from these patients, including the secondary use of data. Using data from the SCRUM-Japan observational studies, we will examine the methodology for the appropriate extraction of RWD. Because the database of SCRUM-Japan observational studies collects predetermined data using electronic data capture, the "relevance" and "reliability" of data may differ from RWD retrospectively extracted from EHRs. The differences between the two are also summarized, and the generalizability of the results is discussed. The RWD of Flatiron Health Japan, which is currently being prepared based on the EHRs of the NCCHE, will also be utilized. The extracted patients' data will be compared with the data of SCRUM-Japan Registry, and the "relevance" and "reliability" of data will be examined. Furthermore, we will compare the external control data extracted from the SCRUM-Japan observational studies with the data from ARCAD global database and will examine whether the data with sufficient "relevance" and "reliability" contributing to the regulatory submission can be extracted from the SCRUM-Japan observational studies (Figure 1).

Databases for the REALISE Study

In the REALISE study, we evaluate various types of databases for appropriate "relevance" and "reliability" that can be utilized as external control data for the application of regulatory approval. The following databases will be integrated into our analysis (Table 1).

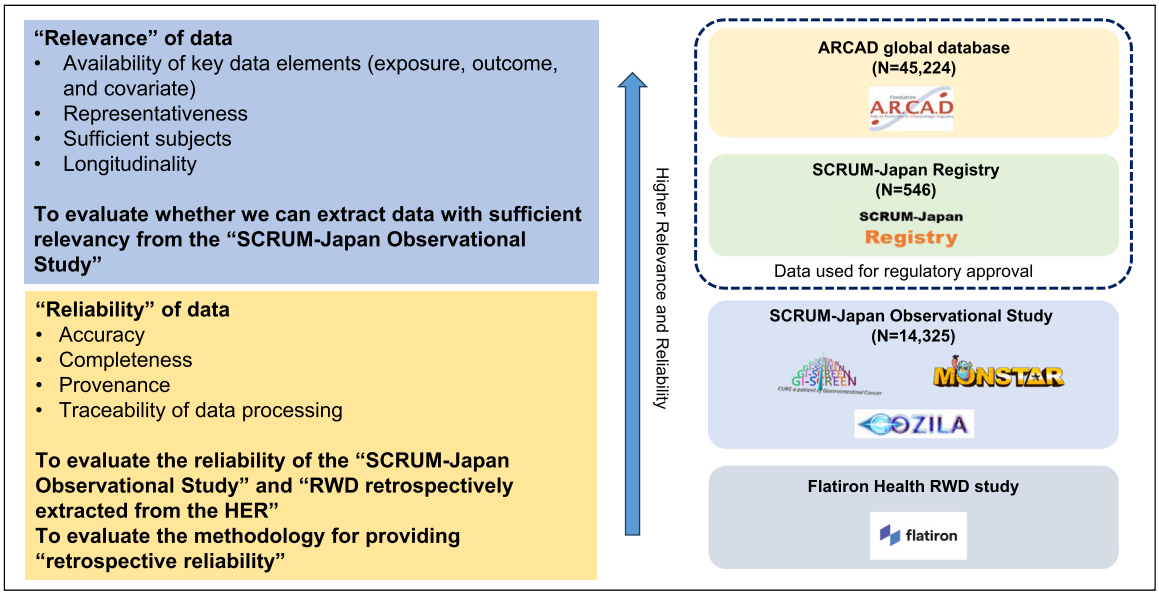
ARCAD Global Database

The ARCAD database project was established in 2006 by the French Foundation of ARCAD and Mayo Clinic in the United States. The ARCAD database project has been collecting and integrating the individual patient data (IPD) of randomized clinical trials for advanced colorectal cancer or mCRC. The NCCHE

Table 1 The List of Databases for the REALISE Study

	ARCAD Global Database	SCRUM-Japan Registry	SCRUM-Japan Observational Study	Flatiron Health Real-World Data Study
Cancer type	Colorectal cancer	Solid tumors	Solid tumors	Gastrointestinal cancers (real-word data for breast cancer, with lung cancer and hematological malignancies under development)
Sample size (as of Jannuary 2024)	ARCAD global database: 45,224 cases from 63 trials ARCAD Asia database: 4218 cases from 13 trials	546 cases	Total: 14,325 cases GI-SCREEN 2013-01-CRC: 3641 cases GI-SCREEN 2015–01-Non CRC: 2952 cases MONSTAR-SCREEN: 2224 cases GOZILA Study: 5508 cases	650 cases (Japan only)
Number of participating sites	ARCAD is the database project constructing 3 data centers.	72 sites	Total: 31 sites GI-SCREEN 2013-01-CRC: 26 sites GI-SCREEN 2015–01-Non CRC: 24 sites MONSTAR-SCREEN: 31 sites GOZILA Study: 31 sites	1 site (on track to grow to more than 5 partners within 2024 and building multi-site data products based on that network. Continuing to grow Japan network in 2025+ as needed to ensure value and representativeness of datasets).
Number of collected data points	Clinical characteristics: 72 Treatment data: 90 Efficacies: 17	Clinical characteristics: 39 Treatment data: 16 Efficacies: 12	Clinical characteristics GI-SCREEN 2013-01-CRC: 11 GI-SCREEN 2015–01-Non CRC: 15 MONSTAR-SCREEN: 21 GOZILA Study: 16 Treatment data GI-SCREEN 2013-01-CRC: 7 GI-SCREEN 2015–01-Non CRC: 7 MONSTAR-SCREEN: 17 GOZILA Study: 9 Efficacies GI-SCREEN 2013-01-CRC: 2 GI-SCREEN 2015–01-Non CRC: 2 MONSTAR-SCREEN: 4 GOZILA Study: 4	Clinical characteristics: 66 Treatment data: 19 standard data elements per drug delivered, as well as 13 additional standard data elements for radiotherapy and surgery episodes. These details are documented for every line of therapy captured throughout the patient journey. Efficacies: currently 1, with additional clinical outcomes and endpoints being added in 2024 and beyond
Data quality and reliability	Data from prospective randomized studies conducted for drug approval Onsite and central monitoring, source document verification (SDV), and audits have been already conducted in several studies.	Efficacy data were prospectively collected. Onsite and central monitoring, SDV, and audits have been conducted for regulatory use.	Data were collected as an observational study. Data were cleaned annually.	structured and unstructured data were collected from electronic health record. Data will be updated every 3 mo. Procedures, including abstraction procedures, education for abstractors, and automatic verification on the system, are performed to ensure reliability.
Evaluation of efficacy	Imaging evaluations (computed tomography scan) were performed every 6-8 wk. Efficacies were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), allowing evaluations of efficacies, such as response rate (RR), progression-free survival (PFS), and overall survival (OS), at the patient level.	Imaging evaluations were performed at 8 ± 2 wk. Efficacies were evaluated using the RECIST, and evaluations of efficacies, such as RR, PFS and OS, can be performed.	Image evaluations were performed in clinical practice at the discretion of the attending physician. No evaluations using the RECIST have been conducted. PFS and OS can be evaluated.	Image evaluations were performed based on standard of care. No evaluations using the RECIST have been conducted. OS, time to therapy discontinuation, RR, and PFS can be evaluated at the patient level.
Evaluation of adverse events	Data of adverse events are stored in the ARCAD database as raw data, and they can be analyzed at the patient level.	Data of adverse events are not collected in principle.	Data of adverse events are not collected in principle.	Data of adverse events are not collected as part of the standard data points, but Flatiron has standard methodologies to extract adverse events, so that rwAE can be analyzed at the patient level, if required.
Informed consents	Consent has been provided by a documented consent form describing secondary use of data. Consents for secondary use, including use by industry, have not been obtained.	Consent has been obtained in a documented consent form describing secondary use, including use by industry.	Consent has been obtained in a documented consent form describing secondary use, including use by industry.	Consent has been obtained in a consent document describing secondary use, such as third-party provision and use by industry.
Legal compliance for regulatory submissions	Under the current Personal Information Protection Law, data may not be possible to use for regulatory approval.	Data can be used for regulatory approval.	Data can be used for regulatory approval.	Data can be used for regulatory approval.

Figure 1 The design of the REALISE study. In the REALISE study, we aim to compare the "relevance" and "reliability" of data derived from various databases. These databases include the ARCAD global database and the SCRUM-Japan Registry, both of which have been utilized for regulatory approvals. Additionally, we examine data from the SCRUM-Japan observational study and the Flatiron Health Real-World Data (RWD) study.



has joined the project since 2021. As of January 2024, the ARCAD database project has collected and integrated the IPD of 45,224 cases from 63 Western and Eastern studies. Regarding ARCAD Asia, the IPD from 13 Asian trials, encompassing a total of 4218 cases, have been collected and integrated.

SCRUM-Japan Registry

The SCRUM-Japan Registry is a prospective multicenter study that creates external control data for the application of regulatory approval by prospectively accumulating the treatment effects of standard therapies (UMIN000028058). Candidates for the SCRUM-Japan Registry are solid tumors with specific gene alterations for whom a new drug development study has been conducted. Patients with specific genetic alterations detected in the SCRUM-Japan observational studies are registered with the individual patient's informed consent. As of January 2024, the SCRUM-Japan Registry has collected 546 cases.

SCRUM-Japan Observational Study

Since 2015, we have accumulated both clinical and genomic data from patients with solid tumors under the SCRUM-Japan project. For the REALISE study, we have converted the data of the SCRUM-Japan observational study to the Study Data Tabulation Model (SDTM) format, and 14,325 cases of data from GI-screen 2013-01-CRC (UMIN000016343), GI-screen 2015–01-Non CRC (UMIN000016344), GOZILA study (UMIN000029315), and MONSTAR-SCREEN (UMIN000036749) have been integrated.

Flatiron Health Real-World Data Study

Flatiron Health Japan, in collaboration with the NCCHE, currently processes structured and unstructured data to produce high-quality real-world datasets on gastrointestinal, breast, and hematological malignancies.

Difference of "Relevance" and "Reliability" in 4 Databases

For the "relevance" and "reliability," the data of ARCAD database are the data from prospective randomized studies (Table 1). In general, onsite and central monitoring, source document verification, and audits have been already conducted. Efficacy data were prospectively collected from the SCRUM-Japan Registry. Central monitoring, sampling-based source document verification, and audits have been conducted for regulatory submissions. In contrast, in the SCRUM-Japan observational study, the efficacy data were collected as an observational study. Data were cleaned annually. In the Flatiron Health RWD study, data were collected from EHRs, and the data will be updated every 3 months. Abstraction procedures, education for abstractors, standardization of unstructured data using defined Flatiron methodologies, and automatic verification of the system are performed to ensure reliability.

Regarding the evaluation of efficacy, as the data from the ARCAD database are from randomized trials, imaging evaluations were performed every 6 to 8 weeks based on the trial protocol. The evaluations were performed based on the Response Evaluation Criteria in Solid Tumors (RECIST). In the data of the SCRUM-Japan Registry, imaging evaluations were performed at 8 ± 2 weeks. The evaluations were performed based on the RECIST. In contrast, in the SCRUM-

Japan observational study and Flatiron Health RWD study, image evaluations were performed in clinical practice at the discretion of the attending physicians based on the standard of care. The evaluations using the RECIST were not conducted. The data on adverse events are stored in the ARCAD database at the IPD level, and the collection of adverse events is planned in the Flatiron Health RWD study. However, no data on adverse events have been collected from the SCRUM-Japan Registry and SCRUM-Japan observational study.

For informed consent and usage for regulatory submission, the documented consents describing secondary use, including use by industry, have been obtained from the SCRUM-Japan Registry, SCRUM-Japan observational study, and Flatiron Health RWD study. However, in the ARCAD database, consents, including for use by the industry, have not generally been obtained. Therefore, under the current Personal Information Protection Law in Japan, the data may not be applicable for regulatory submissions.

Planned Statistical Methods for Data Analysis

All analyses will be descriptively summarized using the SCRUM-Japan observational studies, SCRUM-Japan Registry, Flatiron Health RWD study, and ARCAD. The similarity of patient characteristics and efficacy endpoints, such as response rate, progression-free survival, overall survival, and all available endpoints, will be evaluated according to the cancer type, treatment line, and standard treatment. For colorectal cancer, data extracted from the RWD-DB will be compared with data extracted from RCTs in the ARCAD database to examine its availability as an external control for RWD. The Kaplan–Meier method will be used to estimate the survival distribution of the time-to-event data. No imputation method for missing data will be used, and the frequency of missing data will also be summarized. The details of the analysis will be described in a separate statistical analysis plan.

Discussion

The utilization of RWE generated from RWD has been discussed and promoted, especially for regulatory applications, such as external control data for rare cancers or rare molecular subtypes for which RCTs are difficult. In this field, we have already obtained the regulatory approval of trastuzumab plus pertuzumab for unresectable HER2-positive colorectal cancer using an external control group generated from the SCRUM-Japan Registry.[15,20] We also have the ARCAD global database, the database of the SCRUM-Japan observational study, and the RWD database created in collaboration with Flatiron Health. Of these 4 databases, data from the ARCAD global database and SCRUM-Japan Registry have been utilized for regulatory approval. In addition, as summarized in Table 1, the 4 databases have different data "reliability" systems (Table 1).

We expect that the reason why RWD/RWE has not been actively utilized for the application of regulatory approval is that the required "relevance" and "reliability" of data for regulatory uses are unclear. For these reasons, pharmaceutical companies, which are users of RWE, cannot make decisions to utilize RWE for regulatory submissions. In our REALISE study, we will compare the "relevance" and "reliability" of the 4 databases and statistically analyze the differences and similarities, especially between the ARCAD database and SCRUM-Japan Registry, which have already been used for regulatory approval, the database of SCRUM-Japan observational study, and the Flatiron Health RWD database, which is aimed to be used for the regulatory approvals in the next few years based on Flatiron Health's expertise and precedents for successful regulatory submissions utilizing Flatiron Health US RWD. We will also examine the methodology for extracting sufficiently relevant data from the SCRUM-Japan observational study. In addition, if the "reliability" of RWD/RWE does not reach the required level, the necessities of retrospective "reliability" assurance will be assumed. However, a specific methodology for this purpose has not yet been developed. In this study, we will also examine methodologies to ensure the "reliability" of the SCRUM-Japan observational study for regulatory approval. The obtained results will be submitted to the "Consultation for Development of Registry" at the PMDA, and we will discuss the standard methodology with the regulatory authorities. The procedures and findings identified in our study will be organized from the perspectives of "database construction," "data analysis," and "outcome evaluation," and will be issued as "the evaluation sheets" and "the draft guidelines."

To expand the procedures and findings in our study to RWD/RWE from EHRs, standard specifications and terminology of medical records for system vendors will be required. Next-generation EHRs should be constructed according to Health Level Seven Fast Healthcare Interoperability Resources to facilitate data integration. In addition, a certification program for medical information systems, which is common in the United States, should be established. Registering data through an appropriate process using a reliable system facilitates various studies. The data format for the study should also be constructed based on the Observational Medical Outcomes Partnership Common Data Model, which is the de facto international standard format for observational studies. In Japan, data collection currently relies on a proprietary standard known as SS-MIX2. However, its limited use in global studies and the challenges in managing data quality have led to its restricted application in oncology. To address these issues, efforts are underway to develop a data exchange mechanism using FHIR, with the Japanese government taking a lead role in setting the standards and criteria for exchanging EHR data. Furthermore, to enhance global research collaboration, there is consideration for adopting the Observational Medical Outcomes Partnership framework.

Conclusion

The REALISE study will elucidate the "relevance" and "reliability" of RWD/RWE necessary for regulatory approval. It seeks to define clear guidelines for "database construction," "data analysis," and "evaluation of results." Furthermore, through the PMDA "Consultation on Registry Utilization" and extensive discussions with pharmaceutical companies, common understanding among all relevant stakeholders will be promoted.

Disclosure

Hideaki Bando reports research funding from Ono Pharmaceutical and honoraria from Ono Pharmaceutical, Taiho Pharmaceuti-

cal, and Eli Lilly in Japan. Yasutoshi Sakamoto reports no conflict of interests. Toshihiro Misumi reports honoraria from Chugai, AstraZeneca, and Miyarisan. Yuriko Takeda reports no conflict of interests. Yoshiaki Nakamura reports honoraria from Chugai Pharmaceutical, Merck Biopharma, and Guardant Health AMEA and research grants from Taiho Pharmaceutical, Chugai Pharmaceutical, Guardant Health, Genomedia, Daiichi Sankyo, Seagen, and Roche Diagnostics. Kazuya Mizuguchi and Yoshihiro Aoyagi reports no conflict of interests. Takayuki Yoshino reports honoraria from Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Merck Biopharma, Bayer Yakuhin, Ono Pharmaceutical, and MSD and research funding from Taiho Pharmaceutical, Ono Pharmaceutical, Chugai Pharmaceutical, Amgen, Parexel International, MSD, Daiichi Sankyo, Pfizer, Genomedia, Sysmex, Nihon Boehringer Ingelheim, and Sanofi. Atsushi Ohtsu reports research funding from BMS and honoraria from Chugai and Ono Pharmaceutical.

CRediT authorship contribution statement

Hideaki Bando: Writing – original draft, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Toshihiro Misumi:** Writing – original draft, Resources, Investigation, Conceptualization. **Yasutoshi Sakamoto:** Writing – original draft, Resources, Investigation. **Yuriko Takeda:** Writing – original draft, Conceptualization. **Yoshiaki Nakamura:** Writing – original draft, Conceptualization. **Kazuya Mizuguchi:** Writing – original draft, Conceptualization. **Yoshihiro Aoyagi:** Writing – original draft. **Izumi Miki:** Writing – original draft. **Tomohiro Kuroda:** Writing – original draft. **Ryu Kasai:** Writing – original draft. **Takuya Suzuki:** Writing – original draft. **Takayuki Yoshino:** Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Atsushi Ohtsu:** Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Ethics Statement

The trial protocols of the REALISE study were approved by the institutional review board of each participating site before study initiation (2023-148). This study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

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