Characterization and selection of Japanese electronic health record databases used as data sources for non-interventional observational studies

Yumi Wakabayashi (wakabayashiym@kochi-u.ac.jp)
Kochi University https://orcid.org/0000-0001-9038-4754

Masamitsu Eitoku
Kochi Daigaku

Narufumi Suganuma
Kochi Daigaku

Research article

Keywords: real world, retrospective study, prospective study, observational study, virtual trial, database, medical information

DOI: https://doi.org/10.21203/rs.3.rs-184585/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background

Interventional studies are the fundamental method for obtaining answers to clinical question. However, these studies are sometimes difficult to conduct because of insufficient financial or human resources or the rarity of the disease in question. One means of addressing these issues is to conduct a non-interventional observational study using electronic health record (EHR) databases as the data source, although how best to evaluate the suitability of an EHR database when planning a study remains to be clarified. The aim of the present study is to identify and characterize the data sources that have been used for conducting non-interventional observational studies in Japan and propose a flow diagram to help researchers determine the most appropriate EHR database for their study goals.

Methods

We compiled a list of published articles reporting observational studies conducted in Japan by searching PubMed for relevant articles published in the last 3 years and by searching database providers’ publication lists related to studies using their databases. For each article, we reviewed the abstract and/or full text to obtain information about data source, target disease or therapeutic area, number of patients, and study design (prospective or retrospective). We then characterized the identified EHR databases.

Results

In Japan, non-interventional observational studies have been mostly conducted using data stored locally at individual medical institutions (713/1463) or collected from several collaborating medical institutions (351/1463). Whereas the studies conducted with large-scale integrated databases (195/1463) were mostly retrospective (68.2%), 27.2% of the single-center studies, 46.2% of the multi-center studies, and 74.4% of the post-marketing surveillance studies, identified in the present study, were conducted prospectively.

Conclusions

Our analysis revealed that the non-interventional observational studies were conducted using data stored local at individual medical institutions or collected from collaborating medical institutions in Japan. Disease registries, disease databases, and large-scale databases would enable researchers to conduct studies with large sample sizes to provide robust data from which strong inferences could be drawn. Using our flow diagram, researchers planning non-interventional observational studies should consider the strengths and limitations of each available database and choose the most appropriate one for their study goals.
Trial registration

Not applicable.

Background

During the course of primary-care medical practice, a huge amount of patient data, including laboratory results and diagnoses, administrative data, and health insurance information, are generated and collated as electronic health records (EHRs). Patients’ individual EHRs are then archived in databases that can be accessed by stakeholders throughout the medical field. Because these data arise through actual medical activities, they are considered real-world data; that is, these are observational data obtained through real-world medical practice rather than data obtained in an experimental setting.

Traditionally, interventional studies are the fundamental method for obtaining answers to clinical questions. In such studies, researchers enroll patients, randomize them into two or more groups, provide the groups different medical treatments, and compare the resulting data between groups. However, it is sometimes difficult to conduct interventional studies because of insufficient financial or human resources or the rarity of the disease in question. One means of addressing these issues is to conduct a non-interventional observational study using EHR databases as the data source. EHR such as medical records, claims data, and health insurance data are available at medical institutions, and large-scale integrated EHR databases, organized and maintained by database providers, are also available as study data sources (Fig. 1). Large-scale databases would be advantageous over small-scale databases because they allow researchers to conduct non-interventional observational studies with a big sample size, which affords robust data from which strong inferences can be drawn.

When planning a non-interventional observational study using a EHR database, researchers must first identify the databases that are most suitable for their study purpose. Although many such databases are available, they each have their strengths and limitations that must be considered and weighed against one another. For example, most EHRs, and therefore most databases, lack patient data regarding the pre-symptomatic stage of disease; therefore, many EHR databases will be of limited benefit to researchers who intend to investigate aspects of the early stages of disease onset such as the pre-symptomatic stage of Alzheimer’s disease. This lack of data likely reflects that, despite the potential benefits of early preventive care, patients in the pre-symptomatic stage of disease are rarely seen in hospital.

Researchers also need to consider important database characteristics such as the number of records, accessibility to outcome data, duration of follow-up, and potential biases during data collection. How best to evaluate the suitability of an EHR database when planning a study remains to be clarified.

The aim of the present study is to identify and characterize the data sources that have been used for conducting non-interventional observational studies in Japan and to propose a flow diagram to help
researchers assess the suitability of a potential EHR database for use in their non-interventional observational study.

## Methods

### Determination of the data sources used for non-interventional observational studies in Japan

We used a binary approach to determine the data sources used for past non-interventional observational studies conducted in Japan.

In the first part, we conducted a PubMed search to find articles reporting observational studies conducted in Japan in the last 3 years; the following search settings were used: affiliation field, Japan; article type, observational study; publication date, December 1, 2017 to November 30, 2020; species, human; and language, English. We excluded articles without an abstract or without a structured abstract; articles reporting studies conducted multi-nationally or in a country other than Japan; and articles reporting non-clinical studies, interventional studies, or studies with healthy subjects/controls.

In the second part, we obtained a list of articles reporting observational studies using data from one or more of four large-scale Japanese EHR databases\(^8\)–\(^12\): Japan Medical Data Center Claims Database (JMDC Claim), Medical Data Vision Database (MDV Database), National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB Japan), and Medical Information Database Network (MID-NET). JMDC Claim and MDV Database are the largest EHR databases in Japan\(^1\). NDB Japan and MID-NET are widely known databases in Japan that are provided by the Japanese governmental organization. These four databases all include EHR data generated by the Japanese Diagnosis Procedure Combination/Per-Diem Payment System (DPC; the Japanese medical payment framework); therefore, these databases are sometimes colloquially referred to as “DPC databases”. For example, NDB Japan is frequently called the “DPC database” because it is the most well-known database in Japan.

To obtain this information, we accessed the list of published articles available at the website associated with each of the four databases. For JMDC Claim and MDV Database, the publication lists were very long so we limited our search to the period January 2017 to June 2019. For NDB Japan and MID-NET, the publication lists only included articles published since 2018.

After compiling our list of articles, we reviewed each abstract for information about data source, target disease or therapeutic area, number of patients enrolled in the study, and study design. If the abstract did not include this information, we reviewed the full text of the article. If the full text was not available or lacked enough information, we excluded the article. Classification of each article was conducted using the following criteria:
Data source. Articles were classified into four types based on the source data used: (1) data stored at a medical institution, (2) data collected from several medical institutions, (3) data obtained from a disease registry or database, (4) data obtained from a large-scale integrated database. When the words “single-center study” were included in the abstract or full text, the article was classified as type (1); when an article included the words “in a hospital”, “in our hospital”, “in our institution”, “at XXXX [institution name]”, “in a unit”, “in a center”, or “in a department”, we assumed that this indicated a single-center study, the article was classified as type (1). Similarly, when the abstract or full text included the words “multi-center study” or “in hospitals”, the article was classified as type (2); when they included “registry” or “study database” it was classified as type (3); and when they included “large database” it was classified as type (4). Articles with the words “nationwide database” were also classified as type (3) or (4) after we carefully checked the actual name of the database, if available, in the rest of the abstract and full text. Because post-marketing surveillance (PMS) studies are a kind of multi-center study, these articles should also be classified as (2). However, in Japan, PMS studies are conducted under Good Post-marketing Study Practice regulations\textsuperscript{13}, whereas observational studies are conducted under the ethical guidelines of the Japan Ministry of Education, Culture, Sports, Science and Technology\textsuperscript{14}; thus, PMS studies were considered separately from the other multi-center studies.

Target disease or therapeutic area: Articles were classified by using the following 19 classes with reference to the 10th revision of the International Statistical Classification of Disease and Related Health Problems\textsuperscript{15}: (1) infectious and parasitic diseases other than coronavirus disease 2019 (COVID-19), (2) COVID-19, (3) cancer and neoplasm, (4) diseases of blood and blood forming organs, (5) endocrine, nutritional and metabolic diseases, (6) diabetes, (7) mental disorder, (8) nervous system, (9) disease of the eye and adnexa, (10) disease of the ear and mastoid process, (11) circulatory system, (12) respiratory system, (13) digestive system, (14) Disease of the skin and subcutaneous tissue, (15) disease of the musculoskeletal system and connective tissue, (16) disease of the genitourinary system, (17) pregnancy, childbirth, and perinatal, (18) injury or other consequences of eternal causes, (19) others, including surgery, transplantation, hemodialysis, dental, and pain.

Number of patients enrolled in study

The number of patients included in the final analysis was obtained by reviewing the abstract or full article text.

Study design

Studies were classified as either prospective or retrospective, depending on which word was used in the abstract or full article text.

Characteristics of the large-scale integrated databases

By contacting the relevant organizations through their websites, we solicited information regarding the procedures through which the four large-scale databases were established. JMDC Claim was constructed
by the Japan Medical Data Center Inc. and comprises EHR data collected through daily medical practice since 2005. MDV Database and related services have been maintained by Medical Data Vision Co., Ltd., since 2008. NDB Japan was constructed by the Japan Ministry of Health, Labour and Welfare in 2009. MID-NET has been offered through a governmental organization (under the Ministry of Health, Labour and Welfare) and the Pharmaceuticals and Medical Devices Agency since 2018. In characterizing these databases, we focused on the (1) data sources and procedures for processing data, (2) data items available, and (3) anonymization of data. We also contacted the companies responsible for two of the databases (Japan Medical Data Center and Medical Data Vision) to ask for general information regarding the construction and maintenance of their databases; the same questions regarding data cleaning, data standardization, and database construction were sent to both companies.

Results

Determination of the data sources used for non-interventional observational studies in Japan

Of 2513 articles identified (2318 through PubMed and 195 through the websites of the large-scale database providers), 1463 articles met the eligibility criteria (Fig. 2). The data sources used in the identified studies are shown in Table 1, stratified by study type.
| Study type                                  | Data source                                      | Database example | Strengths                                      | Limitations                                      |
|--------------------------------------------|--------------------------------------------------|------------------|-----------------------------------------------|-------------------------------------------------|
| Single-center study                        | Data stored at a single medical institution      | -                | Medical practice well-known                   | Limited volume of data                           |
|                                            |                                                  |                  | Flexible approach                              |                                                  |
| Multi-center study                         | Medical records collected from collaborating medical institutions | -                | Study team collaboration                       | Medical practices can differ by institution     |
| Post-marketing surveillance study<sup>a</sup> | Medical records collected from collaborating medical institutions | -                | Controlled under GPSP regulations              | -                                               |
| Study using a disease registry/database    | Disease registry                                 | All Japan Utstein Registry<sup>16,17</sup> | Disease-specific test results available       | Data usually related to a single disease        |
|                                            | Disease database                                 | NinJa<sup>18,19</sup> |                                              |                                                  |
|                                            |                                                  | KCHF Registry<sup>20,21</sup> |                                              |                                                  |
| Study using a dataset from a large-scale integrated database | Integrated large-scale database                | JMDC Claim<sup>b</sup> | Data volume                                   | -                                               |
|                                            |                                                  | MDV Database<sup>c</sup> |                                              |                                                  |
|                                            |                                                  | NDB Japan<sup>d</sup> |                                              |                                                  |
|                                            |                                                  | MID-NET<sup>e</sup> |                                              |                                                  |
| Study type | Data source | Database example | Strengths | Limitations |
|------------|-------------|------------------|-----------|-------------|
| PMS: Post-marketing surveillance; GPSP: Good Post-marketing Study Practice; NinJa: National Database of Rheumatic Diseases in Japan; KCHF: Registry: Kyoto Congestive Heart Failure Registry; JMDC: Japan Medical Data Center; MDV: Medical Data Vision; NDB Japan: National Database of Health Insurance Claims and Specific Health Checkups of Japan; MID-NET: Medical Information Database Network. | | | | |
| a A PMS study is a kind of multi-center study initiated by a sponsor and conducted under GPSP regulations. | | | | |
| b JMDC Claim is provided by Japan Medical Data Center, Inc. | | | | |
| c MDV Database is provided by Medical Data Vision Co., Ltd. | | | | |
| d NDB Japan is provided by the Ministry of Health, Labour and Welfare of Japan | | | | |
| e MID-NET is sponsored by the Pharmaceuticals and Medical Devices Agency of Japan | | | | |

A total of 713 (48.7%) studies were single-center studies. In these studies, the sample size was < 100 in 316 (44.3%) studies and 100–299 in 214 (30.0%) studies (Table 2). Thus, 64.3% of the single-center studies used a sample size < 300. The single-center studies were conducted in various target diseases and therapeutic areas.
A total of 351 (24.0%) studies were multi-center studies. In these studies, the sample size was < 100 in 84 (23.9%) studies, 100–299 in 94 (26.8%) studies, and 300–999 in 89 (25.4%) studies. Thus, 76.1% of the multi-center studies used a sample size < 1000. The multi-center studies were also conducted in various target diseases and therapeutic areas.

A total of 39 PMS studies were identified. Generally, PMS studies are used to gather information about a new medicinal product or medical device after it has been granted marketing authorization; thus, 29 of
the 39 PMS studies (74.4%) were conducted prospectively. In the 39 PMS studies, the sample size was 1000–2999 in 9 (23.1%) studies, 3000–9999 in 14 (35.9%) studies, and ≥ 10,000 in 2 (5.1%) studies.

A total of 165 studies conducted for the construction of a disease registry or database were identified. Such studies are usually conducted prospectively, although the disease registries or databases themselves are sometimes used for retrospective secondary analysis. In the identified studies, three Japanese registries/databases were used by researchers of different studies: All-Japan Utstein Registry\textsuperscript{16,17}, National Database of Rheumatic Diseases in Japan (NinJa)\textsuperscript{18,19}, and Kyoto Congestive Heart Failure (KCHF) Registry\textsuperscript{20,21}. In addition, although our focus was on studies conducted in Japan, we identified seven registry studies conducted by using the Surveillance, Epidemiology, and End Results (SEER) program of the US National Cancer Institute.

Finally, we identified 195 studies using large-scale integrated databases, 133 (68.2%) of which were conducted retrospectively. The sample size was 10,000–99,999 in 59 (30.3%) studies and ≥ 100,000 in 54 (27.7%) studies. In the identified studies, the following large-scale integrated databases were used: MDV Database, 65 studies; JMDC, 84 studies (10 were studies using both MDV Database and JMDC); NDB Japan, 17 studies; MID-NET, 2 studies. In the remaining articles, the databases used were referred to only as “DPC database” and the actual names of the databases were not mentioned.

**Characteristics of large-scale integrated databases**

Summaries of the four large-scale integrated databases are shown in Table 3. NDB Japan is one of several Japanese DPC databases. MID-NET was launched 2018 and includes laboratory data as well as DPC information. The data sources, available data items, and anonymization status were obtained from the websites of the respective databases\textsuperscript{8–12}.
### Table 3
Japanese large-scale integrated databases and their characteristics

| Characteristics of the database | JMDC Claim<sup>a</sup> | MDV Database<sup>b</sup> | NDB Japan<sup>c</sup> | MID-NET<sup>d</sup> |
|--------------------------------|------------------------|-------------------------|------------------------|----------------------|
| **Characteristics of the database** | Information regarding health insurance claims and DPC collected from institutions through standardized procedures since 2005. | Claim information, DPC information, and laboratory data collected from institutions through standardized procedures since 2008. | Claim information on medical treatment, dental treatment, medications, and DPC. | Medical records, health insurance claims, and DPC information. |
| **Data volume** | 5.6 million subjects (as of June 2018) | 2.8 million subjects (as of May 2019) | All Japanese citizens (not clearly described) | 4 million subjects (as of November 2018) |
| **Available data** | Information regarding health insurance claims, DPC; medical products' information coding; diagnosis; number of patients; complications; surgery; medication information; and events. Data from healthy subjects are available. Data are updated monthly according to pre-defined processes. | Information on claims and DPC and laboratory data are available. Data updated monthly according to pre-defined processes. | Claim information on medical treatment, dental treatment, medications, and DPC. Use of NDB Japan is permitted for evaluated researchers only. NDB Open Data Japan, partial dataset, is freely available. | Demographic data; hospital visits/admissions; disease and injury diagnoses; medical treatment, laboratory data, results of physiologic tests; pharmacologic data; and medications. |
| JMDC Claim<sup>a</sup> | MDV Database<sup>b</sup> | NDB Japan<sup>c</sup> | MID-NET<sup>d</sup> |
|----------------------|-----------------------|----------------------|----------------------|
| Number of published articles | 185 articles published (as of July 2019) | 116 articles published (as of July 2019) | 78 articles published<sup>e</sup> (as of October 2020) | 11 articles published (as of April 2020) |
| Anonymization? | Anonymized | Anonymized | Subjects’ personal information is not available. Anonymization is up to the individual researcher. | Anonymized |

JMDC: Japan Medical Data Center; MDV: Medical Data Vision; NDB Japan: National Database of Health Insurance Claims and Specific Health Checkups of Japan; MID-NET: Medical Information Database Network; DPC: Diagnosis Procedure Combination/Per-Diem Payment System (Japanese medical payment framework).

<sup>a</sup> JMDC is provided by Japan Medical Data Center, Inc.<sup>8</sup>

<sup>b</sup> MDV is provided by Medical Data Vision Co., Ltd.<sup>9</sup>

<sup>c</sup> NDB Japan is provided by the Ministry of Health, Labour and Welfare of Japan<sup>10</sup>. NDB Open Data Japan<sup>11</sup>.

<sup>d</sup> MID-NET is sponsored by the Pharmaceuticals and Medical Devices Agency of Japan<sup>12</sup>.

<sup>e</sup> The article list of NDB Japan shows 119 items including technical reports and congress abstracts for oral or poster sessions as well as published articles.

Health insurance companies transfer claims data derived at medical institutions to JMDC Claim according to pre-defined procedures once a month. Similarly, MDV receives anonymized data from medical institutions on a monthly basis; the data managers then check the data and update the database. According to the MID-NET website, medical records and claims data are transmitted to the Integrated Data Source of MID-NET through pre-defined procedures. The MID-NET system and data are monitored and verified at variable intervals.

The detailed data processing procedures for NDB Japan are not shown on the information website offered by the Ministry of Health, Labour, and Welfare (MHLW)<sup>10</sup>. Although, the website states that the use of the NDB Japan data is usually permitted for academic researchers only, MHLW does extract part of the NDB Japan data to create a small dataset called NDB Open Data Japan, which is freely available at the MHLW website<sup>11</sup>.

**Discussion**
We investigated the data sources that have been used for conducting past non-interventional observational studies in Japan. We also characterized four Japanese large-scale integrated EHR databases by summarizing their data sources, available data, and anonymization status.

We found that non-interventional observational studies in Japan are mostly conducted by using data stored at individual medical institutions or collected from several collaborating medical institutions. This approach provides a limited volume of data, so such studies have a limited sample size. To increase the sample size, researchers should consider using a disease registry, disease database, or large-scale integrated EHR database. Such registries and databases have the advantage that the data are already anonymized and cleaned.

Observational studies using large-scale databases are usually conducted retrospectively. However, we found that 27.2% of the single-center studies, 46.2% of the multi-center studies, and 74.4% of the PMS studies, identified in the present study, were conducted prospectively. When a researcher focuses on a new parameter as a study endpoint, they must take a prospective approach because no data for the parameter is yet included in medical records at their medical institution or in integrated large-scale databases. However, if the target parameter data is expected to be collected and added to EHRs and EHR databases in the future, the researcher may wait for further data accumulation.

Based on our present findings, we developed a flow diagram that can be used to assess the suitability of a registry or database for use in a non-interventional observational study (Fig. 3). In this context, it is crucial that the EHR database contains data related to the study endpoints, such as laboratory findings and the treatments (exposures) the patients received. The database should also contain demographic information as well as patients’ medication, surgery, and hospitalization histories. When the target database lacks appropriate reference (comparison) population data, this information might be available in other databases.

When planning a non-interventional observational study, it is helpful for researchers to know how a database is constructed and what anonymization processes have been applied to the data. Appropriate anonymization of data is important to adhere to current ethics and quality guidelines. Also, the database should have been established through data-processing procedures that are satisfactorily explained and reproducible. The database construction and data anonymization processes of JMDC Claim, MDV, and MID-NET are explained on their websites.

Having sufficient data to support an appropriate sample size is crucial to obtain robust outcomes. Even when a potential database lacks a sufficient volume of data initially, a researcher might still consider using the database when the data-processing approach is known and the volume of data is expected to increase. If the patient follow-up period is too short to extract relevant data to cover the duration of the intended study, researchers have the option of waiting for data updates to accumulate longer-term data.
However, missing data might ultimately be unavoidable. For JMDC Claim database, data has been collected since 2005. For MDV Database, since 2008. For NDB Japan, since 2009.

PMS studies are performed by taking a prospective approach to gather information about a new medicinal product or medical device after it has been granted marketing authorization. Data related to exposure to a new medicinal product is very limited in EHRs at the time when planning a PMS study, but will be collected and added to EHRs at medical institutions and then collated into large-scale integrated databases over time. If it is possible for a PMS researcher or sponsor to wait for the data to be accumulated, they can use a large-scale database to conduct their study with less financial or human resource costs. In fact, a researcher who intends to conduct a prospective study can use a large-scale database by employing the tactic of waiting for data accumulation of the database. Prospective clinical studies are rigidly managed, which usually means huge amounts of human and financial resources are needed \(^{24, 25}\).

We acknowledge several limitations to the present study. First, we identified the articles reporting observational studies through PubMed search and database providers’ publication lists, instead of accessing to clinical trial registration sites. That means we didn’t focus on all studies those have been planned and initiated in Japan, but our analysis was based on information about completed and published studies. Second, our group has not yet conducted an observational study using the EHR databases evaluated in the present study; in the next phase of our research, we intend to conduct a study using an appropriate EHR database. Finally, we do not discuss limitations regarding linking Japanese EHR data stored on different platforms, such as the various health insurance databases.

### Conclusion

Our analysis revealed that the non-interventional observational studies were mostly conducted using data stored local at individual medical institutions or collected from collaborating medical institutions in Japan. Disease registries, disease databases, and large-scale integrated EHR databases would enable researchers to conduct studies with big sample sizes to provide robust data from which strong inferences could be drawn. Using our flow diagram, researchers planning non-interventional observational studies should consider the strengths and limitations of each available database and choose the most appropriate one to their study goals. Whereas observational studies using large-scale databases are usually retrospective, a researcher, even planning a prospective study, can leverage a large-scale database by employing the tactic of waiting for data accumulation of the database.

### Abbreviations

COVID-19: coronavirus disease 2019; DPC: Diagnosis Procedure Combination/Per-Diem Payment System; EHR: electronic health record; GPSP: Good Surveillance Practice; JMDC: Japan Medical Data Center; KCHF: Kyoto Congestive Heart Failure; MDV: Medical Data Vision; MHLW: Ministry of Health, Labour, and Welfare of Japan; MID-NET: Medical Information Database Network; NDB Japan: National Database of
Health Insurance Claims and Specific Health Checkups of Japan; NinJa: National Database of Rheumatic Diseases in Japan; PMS: Post-marketing surveillance; SEER: Surveillance, Epidemiology, and End Results program.

**Declarations**

**Ethical approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and/or analyzed during the present study are available from the corresponding author of reasonable request.

**Competing interests**

All authors have declared they have no competing interests. This study was externally funded. No funding/assistance was received from a commercial organization.

**Funding**

This work was supported by an “Initiative for Realizing Diversity in the Research Environment” grant from the Japan Science and Technology Agency.

**Authors’ contributions**

YW contributed to the conception of the work and the acquisition and analysis of the data. YW, ME, and NS contributed to the interpretation of the data and to the drafting and revising of the manuscript. NS, ME, and YW contributed to the final version of the manuscript.

**Acknowledgements**

We thank Mr. Takashi Itagaki for his helpful comments from his experiences with registries construction. We also thank the experts from Medical Data Vision and Japan Medical Data Center for providing information regarding their database establishment processes.

This study was presented in part during the poster sessions of the 15th Drug Information Association Japan Annual Meeting (November 2018 in Tokyo, Japan) and the 40th Annual Meeting of the Society for Clinical Trials (May 2019 in New Orleans, Louisiana, USA).
References

1. Saokaew S, Sugimoto T, Kamae I, Pratoomsoot C, Chaiyakunapruk N. Healthcare databases in Thailand and Japan: potential sources for health technology assessment research. ProsOne 2015; 10(11): e014199

https://doi.org/10.1371/journal.pone.0141993

2. Kimura T, Koide D, Orii T. Large, automated administrative and clinical databases available for pharmacoepidemiology studies in Japan [in Japanese]. Jpn J Pharmacoepidemiol 2012; 17: 135-144.

3. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade. Lancet Neurol 2010; 9(1); 119.

https://doi.org/10.1016/S1474-4422(09)70299-6

4. Sperling RA, Jack CR, Aisen PS. Testing the right target and the right drug at the right stage. Sci Transl Med 2011; 3 (111).

https://doi.org/10.1126/scitranslmed.3002609

5. Bateman RJ, Xiong C, Benzinger TLS, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer’s disease. N Engl J Med 2012; 367: 795–804.

https://doi.org/10.1056/NEJMoa1202753

6. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer’s disease. N Engl J Med 2014; 370: 322–333.

https://doi.org/10.1056/NEJMoa1304839

7. Dreyer NA. Advancing a framework for regulatory use of real-world evidence: when real is reliable. Therapeutic Innovation & Regulatory Science 2018; 52(3): 362-368.

https://doi.org/10.1177/2168479018763591

8. Japan Medical Data Center. Company website. https://www.jmdc.co.jp/ (Accessed 1 July 2019)

9. Medical Data Vision. Company website. https://www.mdv.co.jp/ (Accessed 1 July 2019)

10. Ministry of Health, Labour, and Welfare. National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB Japan). https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/reseputo/index.html (Accessed 12 Oct 2020)
11. Ministry of Health, Labour, and Welfare. NDB Open Data Japan. 
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177182.html (Accessed 12 Oct 2020).

12. Pharmaceuticals and Medical Devices Agency. MID-NET (Medical Information Network) 
https://www.pmda.go.jp/safety/mid-net/0001.html (Accessed 8 Jan 2019)
https://www.pmda.go.jp/safety/mid-net/0005.html (Accessed 18 Apr 2020)

13. Ministry of Health, Labour, and Welfare. Good Post-Marketing Study Practice. 
https://www.pmda.go.jp/files/000161574.pdf (Accessed 15 Jan 2021).

14. Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour, and 
Welfare. Ethical Guideline. 2014. https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000- 
Daijinkanbokouseikagakuka/0000069410.pdf (Accessed 15 Jan 2021).

15. The 10th revision of the International Statistical Classification of Disease and Related Health 
Problems (ICD-10). https://icd.who.int/browse10/2019/en

16. Matsuyama T, Komukai S, Izawa J, Gibo K, Okubo M, Kiyohara K, et al. Pre-hospital administration of 
epinephrine in pediatric patients with out-of-hospital cardiac arrest. J Am Coll Cardiol 2020;75:194–204. 
https://doi.org/10.1016/j.jacc.2019.10.052

17. Suematsu Y, Zhang B, Kuwano T, Sako H, Ogawa M, Yonemoto N, et al. Citizen bystander–patient 
relationship and 1-month outcomes after out-of-hospital cardiac arrest of cardiac origin from the All- 
Japan Utstein Registry: a prospective, nationwide, population-based, observational study. BMJ Open 
2019;9:e024715. 
http://dx.doi.org/10.1136/bmjopen-2018-024715

18. Mori H, Sawada T, Nishiyama S, Shimada K, Tahara K, Hayashi H, et al. Influence of seasonal 
changes on disease activity and distribution of affected joints in rheumatoid arthritis. BMC 
Musculoskeletal Disorders 2019; 20:30. https://doi.org/10.1186/s12891-019-2418-2.

19. Hirata A, Suenaga Y, Miyamura T, Matsui T, Tohma S, Suematsu E, et al. Effect of early treatment on 
physical function in daily management of rheumatoid arthritis: a 5-year longitudinal study of 
rheumatoid arthritis patients in the National Database of Rheumatic Diseases in Japan. International 
Journal of Rheumatic Diseases 2018; 21: 828–835. 
https://doi.org/10.1111/1756-185X.12877

20. Yoshikawa Y, Tamaki Y, Morimoto T, Yaku H, Yamamoto E, Inuzuka Y, et al. Impact of left ventricular 
ejection fraction on the effect of renin-angiotensin system blockers after an episode of acute heart 
failure: from the KCHF Registry. PLoS ONE 2020; 15(9): e0239100. 
https://doi.org/10.1371/journal.pone.0239100.
21. Yaku H, Kato T, Morimoto T, Inuzuka Y, Tamaki Y, Ozasa N, et al. Association of mineralocorticoid receptor antagonist use with all-cause mortality and hospital readmission in older adults with acute decompensated heart failure. JAMA Netw Open 2019; Jun 2(6): e195892.

https://doi.org/10.1001/jamanetworkopen.2019.5892

22. Becker JC, Lorenz E, Ugurel S, Eigentler TK, Kiecker F, Pfoehler C, et al. Evaluation of real-world treatment outcomes in patients with distant metastatic Merkel cell carcinoma following second-line chemotherapy in Europe. Oncotarget 2017; 8(45): 79731-79741.

https://doi.org/10.18632/oncotarget.19218

23. Cowey CL, Mahnke L, Espirito J, Helwig C, Oksen D, Bharmal M. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. Future Oncol 2017; 13(19): 1699-1710.

https://doi.org/10.2217/fon-2017-0187

24. Wakabayashi Y, Matsui H, Ikai K, Hayashi M, Wakabayashi H, Yamamoto K. Developing a practical method for validation of computerized systems integrated with smart and/or wearable devices for regulatory compliance of clinical t Therapeutic Innovation & Regulatory Science 2017; 51: 118-124.

https://doi.org/10.1177/2168479016666585

25. Wakabayashi Y, Matsui H, Hayashi M, Ikai K, Yamamoto K. Clinical trial management adaptation to ICH E6 (R2): Good Clinical Practice. Pharmaceutical Engineering 2019; 39: 66–70.

https://ispe.org/pharmaceutical-engineering/january-february-2019/clinical-trial-management-adaptation-ich-e6-r2