Context and Considerations for Use of Two Japanese Real-World Databases in Japan: Medical Data Vision and Japanese Medical Data Center

Thomas Laurent1 · Jason Simeone2 · Ryohei Kuwatsuru3,4 · Takahiro Hirano1,4 · Sophie Graham5 · Ryozo Wakabayashi1,4 · Robert Phillips1 · Tatsuya Isomura1,4

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Abstract
In Japan, an increasing interest in real-world evidence for hypothesis generation and decision-making has emerged in order to overcome limitations and restrictions of clinical trials. We sought to characterize the context and concrete considerations of when to use Medical Data Vision (MDV) and JMDC databases, the main Japanese real-world data (RWD) sources accessible by pharmaceutical companies. Use cases for these databases, and related issues and considerations, were identified and summarized based on a literature search and experience-based knowledge. Studies conducted using MDV or JMDC were mostly descriptive in nature, or explored potential risk factors by evaluating associations with a target outcome. Considerations such as variable ascertainment at different time points, including issues relating to treatment identification and missing data, were highlighted for these two databases. Although several issues were commonly shared (e.g., only month of event occurrence reported), some database-specific issues were also identified and need to be accounted for. In conclusion, MDV and JMDC present limitations that are relatively typical of RWD sources, though some of them are unique to Japan, such as the identification of event occurrence and the inability to track patients visiting different healthcare settings. Addressing study design and careful result interpretation with respect to the specificities and uniqueness of the Japanese healthcare system is of particular importance. This aspect is especially relevant with respect to the growing global interest of conducting RWD studies in Japan.

Key Points
Medical Data Vision (MDV) and JMDC are the most frequently used real-world data sources in Japan.

MDV and JMDC share common limitations with real-world data sources in other countries, though some of them are unique to Japan, including the identification of event occurrence and the inability to follow-up patients visiting different healthcare settings.

Using Japanese real-world data sources requires understanding of the uniqueness of the Japanese healthcare system.

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1 Introduction

In 1961, Japan established a universal medical insurance system that encompasses five public insurance programs. Patients can access clinics and hospitals without a family doctor’s gatekeeper system or insurance-based limitations. Patients frequently visit secondary healthcare facilities with minor symptoms as outpatients, and these facilities can be accessed without a referral from primary healthcare facilities, at an affordable cost. Health insurance typically covers 70–90% of the cost of care, and the rest is paid by the insured. A fee-for-service system is predominantly used for charging medical fees. However, a lump-sum payment system, known as the Diagnosis Procedure Combination (DPC)/Per Diem Payment System (PDPS), was partially introduced for inpatient care. This payment system relies on grouping patients according to DPC categories. Each medical institution submits claims for reimbursement to the Examination and Payment Agency monthly [1].

Since April 2019, Japan has started implementing health technology assessments to address the rising costs of healthcare expenditure by targeting reimbursed drugs or devices that are anticipated to have a substantial impact on healthcare expenditures. Conversely, due to scientific misconduct, regulations on clinical trials have been strengthened after the implementation of the new Clinical Trials Act in 2018 [2]. Other barriers to clinical trials can be mentioned, including the high research and development costs associated with bringing a drug to market, which limit the number of new drug approvals in the Japanese market. Also, the Japanese population has a high proportion of elderly individuals with a high comorbidity burden who are generally not included in clinical trials.

In order to regulate national healthcare expenditures due to ageing, the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) was created in 2008. This database covers about 98% of data on healthcare services and is being used for academic research, but is not accessible to private companies [3]. To generate evidence for use in healthcare decision-making and reduce unmet needs in certain therapeutic areas, Japan aims to leverage real-world data (RWD) for various applications, including informing clinicians on practice patterns, and hypothesis generation for future research. As a consequence, an ongoing increase in the number of studies using RWD is being observed, including in the private sector. The overall landscape of Japanese RWD has been described elsewhere, covering the nature of the databases, their general content, and data governance and access [4]. JMDC, formerly known as Japan Medical Data Center Co., Ltd., and Medical Data Vision (MDV) are the main databases that are accessible to private companies and that do not require any institutional review board (IRB) submission for data access. Previous works have partially covered these databases, but do not provide an overall overview on the practical considerations and the different current applications when using these databases [5–10]. Hiramatsu et al. provided general information on the different types of databases in Japan, including registry, insurance-based, and hospital databases [5]. Lai et al. and Nagai et al. provided detailed information on the variables included in JMDJC, although practical considerations were not addressed [6, 10]. Lee et al. discussed considerations on data collection, transformation, cleansing, and modeling when using MDV [9]. Finally, examples of drug safety and drug utilization studies using either MDV or JMDC have been described in the literature [7, 8]. In this work, we sought to further characterize the concrete advantages and current and future challenges relating to MDV and JMDC databases, particularly with respect to the Japanese healthcare context, given that they are the RWD sources predominantly accessed by pharmaceutical companies.

2 Overview of Japanese RWD Sources

As is typical with other secondary data sources, RWD data users should bear in mind that data are originally collected for different purposes other than for research. Here, we provide general information on MDV and JMDC data.

2.1 MDV

MDV is a health claims database collecting data from all insurance types containing anonymized outpatient, inpatient, and DPC data and blood test results for a limited number of institutions. MDV data were first made available in 2008, and there is around a 3-month time lag from data collection to data availability. As of September 2021, MDV accumulated data from more than 38 million patients and 23% of acute care hospitals in Japan. The main advantages of the MDV database are that it includes a representative population, has a large sample size, includes medical costs reimbursed by healthcare insurance directly in the data, and includes laboratory test results. Condition-specific hospitalization can be identified using DPC codes, which are attributed for each hospitalization in the DPC data, and allows determination of the major diagnosis associated with a hospitalization. Details on the information available in DPC data, including available clinical data, have been provided by Yasunaga et al. and Lee et al. [9, 11]. In contrast, the absence of information on several clinical outcomes (e.g., death in outpatient settings, disease severity) and the absence of data linkage between prescription and diagnosis are inherent limitations.
Handling Japanese Real-World Databases

[12]. Another limitation is also the impossibility to follow patients outside DPC settings. Although some patient scales (e.g., activities of daily living) or disease staging data might be available, many missing values may be observed for measures that are deemed unnecessary for reimbursement purposes. For example, blood parameter measurements (e.g., glycated hemoglobin [HbA1c] for diabetes and estimated glomerular filtration rate for renal failure) are only available for a small proportion of institutions, and hence, results may not be generalizable to the full study sample. The number of institutions providing laboratory data may change over time since the collection of this information is governed by a contract independent of other data that may be terminated from one year to the next. Also, dosage information is not available in structured data fields, and would require extensive work for data extraction. To identify drug treatment initiation, a lookback window is required considering that MDV only includes DPC hospitals. Only month of event occurrences are provided, and therefore, it is not possible to identify populations or derive algorithms using a daily time component. Moreover, visits to other institutions outside or within the data network cannot be linked given that a unique identifier is allocated to each institution that does not allow data linkage across institutions. Finally, the number of institutions is constantly growing, and reproducing a previous study with the same condition may lead to differences.

2.2 JMDC

JMDC is a claims database that contains anonymized inpatient, outpatient, and dispensing receipts, and also medical examination data, collected from various health insurance associations [3, 7, 10]. As of September 2021, the total number of patients accumulated in the database was 13 million. The claims data include information from 2005 on patient enrollment, medical facilities, diagnoses, procedures, drugs and materials, annual health checkups, and associated costs for each visit, and there is around a 5-month time lag from data collection to data availability. This database presents several advantages, especially the availability of data on medical costs reimbursed by healthcare insurance directly in the data, the possibility of follow-up at different hospitals, and a large sample size. In general, Japanese employees tend to stay with the same employer for many years under the same insurance policy, and thus make this type of RWD more robust when compared to other countries. However, this database presents inherent limitations, including the under-representation of the elderly, since JMDC is sourced from health insurance associations for company employees and their dependents. This database shares common limitations with MDV; in particular, a low level of information on clinical outcomes (e.g., about 80% of deaths occurring outside hospital and clinical outcomes recorded using International Classification of Disease 10 codes) and absence of linkage between prescriptions and diagnoses, and only month of event occurrence is available. Although the date of medical care initiation at a medical facility is available, if an individual goes to another center for the same diagnosis, a different date of medical initiation would be reported. Although not discussed here, JMDC has created a hospital-based database collecting data from more than 460 medical institutions in order to account for the limitations of the health insurance-based JMDC database, by including DPC data and blood parameter measurement data and obtaining data on the elderly population. Further detailed information on the data provided in JMDC was reported by Nagai et al. [10].

3 Use Cases for Studies Based on MDV or JMDC Databases

We conducted a literature search using (Japanese AND “administrative claims data”) or “Medical data vision” or JMDC within PubMed, and included articles published by March 2021. Overall, we found 68 and 105 articles for MDV and JMDC, respectively. We concluded that a broad scope of research questions has been addressed by leveraging the MDV and JMDC databases. A non-exhaustive list of examples of studies conducted using MDV or JMDC databases is provided in Table 1, covering a large set of research questions and therapeutic areas. Many studies focused on either product utilization patterns or descriptions of patient characteristics [17, 18]. Interestingly, two studies focused on describing drug prescriptions among hyperlipidemic patients using both databases. The authors concluded that lipid-lowering drug prescription trends were similar across databases, though some differences were observed, mainly explained by a higher proportion of elderly patients and a higher degree of poly-comorbidities among the patient population in the MDV database [23, 24]. In some cases, associations between intervention or risk factors and outcomes have been explored to generate hypotheses, but studies based on a clearly defined causal framework or focusing on a causal effect were not conducted using these databases. Although descriptive studies and studies exploring potential risk factors based on associations can be informative to generate new hypotheses, a causal inference framework is needed for multiple purposes, including replication of randomized clinical trials in the real world, comparative effectiveness and comparative safety, support of regulatory and reimbursement decisions, and clinical adoption decisions. Hypothesis generation studies are likely to continue to play an important role in RWD, because this type of evidence is much less demanding in terms of resources considering that knowledge on the data generation process is needed in causal frameworks, as

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| Research question                        | References            | Database | Method                                                                 | Strength/impact                                                                 | Limitations                                                                 |
|----------------------------------------|------------------------|----------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Disease epidemiology/pharmacoepidemiology | Kobayashi 2020 [13]   | MDV      | Population: Inflammatory bowel disease patients                        | Impact of non-Hodgkin lymphoma associated with thiopurine or anti-tumor necrosis factor-α treatment in Japanese patients with inflammatory bowel disease | Lack of information on important confounders (disease duration and severity) |
|                                        |                        |          | Exposure: Thiopurine/anti-tumor necrosis factor-α                      |                                                                                   |                                                                             |
|                                        |                        |          | Outcome: Incidence of malignancies                                      |                                                                                   |                                                                             |
|                                        |                        |          |                                                                 |                                                                                   | Very few outcome events were observed                                      |
|                                        | Chang 2018 [14]        | JMDC     | Population: All patients with sufficient enrollment                    | Impact of norovirus as an important cause of MA-AGE in Japan, not only in children, but also in other age groups | The number of elderly individuals included in the analysis is relatively small, especially for women |
|                                        |                        |          | Exposure: None                                                          |                                                                                   | No information on 75 years and older                                        |
|                                        |                        |          | Outcome: MA-AGE, MA-NGE                                                |                                                                                   | Restrictive assumption of the residuals modeling method since all cause unspecified MA-AGE episodes in the database were considered due to norovirus |
|                                        |                        |          |                                                                 |                                                                                   |                                                                             |
| Research question | References            | Database | Method |
|-------------------|-----------------------|----------|--------|
| Healthcare resource use/economic burden | Yamazaki 2019 [15] | MDV      | Population: Chronic hepatitis C patients, Exposure: Antiviral treatment, Outcome: Medical cost, healthcare resource use (including inpatient and outpatient visits) |
| Impact            | This study generated evidence that delaying antiviral treatment initiation for Japanese patients with chronic hepatitis C may increase the clinical and economic burden associated |
| Strength          | Use of an algorithm to identify delayed treatment and early treatment cohort based on cirrhosis diagnosis record |
| Limitations       | Validation of the algorithm was performed with another claims database, but not in MDV, Sustained virologic response status was not observed and thus could not be used for subpopulation analyses |
| Inoue 2019 [16]   | JMDC                  | Population: Asthma patients, Exposure: Asthma severity (Japanese Society of Allergology guidelines), Outcome: Healthcare resource utilization (including direct costs) |
| Impact            | The results highlight a potential deviation from consensus care guidelines, and present an opportunity for further examining real-world clinical practices |
| Strength          | Healthcare resource use data were generated in a large Japanese population, severe and non-severe asthma cohorts were characterized, and confirmation of age and comorbidities as relevant variables for asthma outcomes |
| Limitations       | Drug treatment was used as a proxy for disease severity since the information on disease severity was not available, Smoking behavior and body mass index were not included in the analysis |
| Research question            | References | Database | Method                                                                 | Strength/impact                                                                 | Limitations                                                                 |
|------------------------------|------------|----------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Product utilization pattern  | Tanabe 2017 [17] | MDV      | Population: Type 2 diabetes patients Exposure: Alpha-glucosidase inhibi- | Impact Cardiovascular disease history was not associated with treatment choice | Analyses were restricted to patients with HbA1c, and these patients may present different characteristics when compared to those without HbA1c measurement |
|                              |            |          | tor, biguanide, dipeptidyl peptidase-4 inhibitor, thiazolidinediones vs sulfonylurea | Strength Large population of diabetic patients allowed selection of patients with HbA1c data and capture of the elderly population | Specialty of physicians administering treatment and some clinical information that may affect treatment selection were not available |
|                              |            |          | Outcome: Treatment choice and adherence | Outcome: Treatment choice and adherence |                                                                              |

| Matsuoka 2021 [18] | JMDC      | Population: Patients diagnosed with ulcerative colitis Exposure: Corticosteroids, thiopurine, biologics | Impact The study showed corticosteroid use became more appropriate as use of thiopurine and biologics increased, although there were still many cases of inappropriate use | Strength This study captured the changes in corticosteroid use from 2006 to 2016 and the difference in characteristics of patients with long-term and non-long-term corticosteroid use, and identified factors associated with long-term corticosteroid use in ulcerative colitis patients | The population of elderly patients was limited Due to the unavailability of the information, the study did not address the differences in disease severity, which probably influenced corticosteroid use The reason for drug prescription could not be determined when more than one disease code was recorded |
| Research question                                      | References          | Database | Method | Strength/impact                                                                                                                                                                                                                                                                                                                                 | Limitations                                                                                                                                                                                                                       |
|--------------------------------------------------------|---------------------|----------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Characteristics of the patient population              | Fuji 2017 [19]      | MDV      | Population: Patients with orthopedic surgeries Exposure: Multiple risk factors (including type of surgery, gender, history of venous thromboembolism, thrombophilia, age) Outcome: Pulmonary thromboembolism and deep venous thrombosis | Impact The incidence of thromboembolism and deep venous thrombosis, and the risk factors for thromboembolism and deep venous thrombosis were comparable to data obtained in previous studies
Strength Validation of the outcome definitions was performed based on the clinical laboratory data from a sample of medical records and a high positive predictive value could be obtained | Inherent broader definitions of orthopedic surgeries in the database
Lack of information to identify the cause of death
No information on bleeding event date that was identified based on date of diagnostic imaging or examinations                                                                                                                                                                       |
|                                                        | Yamada-Harada 2019 [20] | JMDC   | Population: Diabetic patients Exposure: Number of risk factors (blood pressure, LDL-C, HbA1c, current smoking) Outcome: Coronary artery disease | Impact The study suggested that composite control of modifiable risk factors is important in patients with and without diabetes
Strength Large sample size and long follow-up (at least 3 years). Use of health examination data (not only hospital data) | Issue of population sampling considering that only patients who had undergone physical examinations with blood tests were included
Presence of unmeasured confounders such as undetected comorbidities, severity, duration of diabetes, and socio-economic status
Lack of information on the symptomatic nature of coronary artery disease
Target blood parameter values were assessed based on a single measurement |
| Research question          | References          | Database | Method                                                                 | Strength/impact                                                                 | Limitations                                                                 |
|---------------------------|---------------------|----------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Comparative effectiveness/safety | Kobsaka 2020 [21]   | MDV      | Populations: Patients with non valvular atrial fibrillation Exposure: apixaban, dabigatran, edoxaban and rivaroxaban versus warfarin Outcome: Risks of stroke and systemic embolism | Impact This study suggested that exposures were associated with a significantly lower risk of major bleeding and stroke/systemic embolism compared with warfarin Strength Large population and various treatment groups identified. Balancing among treatment group using stabilized inverse probability of treatment weighting was performed. Sensitivity analyses on time horizon and an alternative balancing method were used to assess the robustness of the results | Patients may present poorer health compared to the average population Due to the lack of information on the follow-up loss, the incidence of stroke may have been underestimated |
|                           | Hashimoto 2020 [22] | JMDC     | Population: Pregnant women with allergic conjunctivitis Exposure: Topical ophthalmic corticosteroids Outcome: Congenital anomalies, preterm birth, low birth weight, and the composite of these three outcomes | Impact The study showed the use of topical ophthalmic corticosteroids in pregnant women with allergic conjunctivitis was not associated with congenital anomalies, preterm birth, or low birth weight Strength Availability of family identifiers to link newborn data to mother data | No possibility to confirm whether ophthalmic corticosteroids were actually used Daily frequency, duration of treatment, and dosage could not be accounted for |

All studies listed adopted a cohort design

HbA1c glycated hemoglobin, LDL-C low-density lipoprotein cholesterol, MA-AGE medically attended acute gastroenteritis, MA-NGE medically attended norovirus-attributable gastroenteritis, MDV Medical Data Vision
reported by Ho et al. [25]. Moreover, hypothesis generation studies would allow the identification of potential variables to be included in a causal modeling framework as a preliminary step before conducting a causal inference study using RWDs [26]. Hence, we believe that there will be an important interplay between studies for hypothesis generation and causal inference studies.

4 Challenging and Practical Considerations when Using MDV or JMDC

The development of appropriate research questions requires researchers to take into account several aspects of these data sources to ensure that the question can be addressed when using MDV or JMDC. Several issues relating to various domains of the study should be considered when using MDV or JMDC (Table 2). In particular, those particularly relating to the specificity of the Japanese healthcare system should be carefully considered.

The nature of institutions from which data were collected is an important aspect to consider. For example, large hospitals and DPC-designated hospitals over-represent patients with severe conditions. As mentioned above, the MDV database is based on DPC data, a payment system unique to Japan, and knowledge about the patient that may regularly visit these institutions is of importance when designing a study using this database. In general, patients in MDV present more severe conditions when compared to JMDC, and thus, understanding the nature of Japanese medical institutions is crucial to clarify data coverage, and carefully considering the target population in a study before selecting a data source is advisable. Moreover, in Japan, the concept of primary care is absent, and patients can access any institution and visit doctors when they have minor ailments, without any restriction. From this perspective, the individual patient journey may not be captured entirely; also, it is for the researcher to identify whether the data for a particular therapeutic area are comprehensive enough, on a case-by-case basis. We would advise checking whether a variable is available for a specific target population before the design stage.

Although not specific to a Japanese context, few Japanese studies have implemented sequence symmetry analysis (SSA) that is underpinned by a case-only design, similarly to the case crossover design, accounting for non-time-varying confounders; this approach was shown to enable the observation of drug-related adverse event signals [27]. Considering that MDV generally does not present sufficient lookback data, we would recommend using the JMDC database for this application (Table 2). In addition, for studies requiring long-term outcome assessment, such as long-term effectiveness or safety, patient tracking may be difficult. In JMDC, it is possible to track patients across multiple institutions as patients retain the same identifier if they maintain the same insurance policy. Hence, if continuous follow-up of patients is required, the use of insurance-based claims would be recommended. The study conducted by Yamada-Harada et al. [20] in Table 1, based on JMDC, is an example of when this type of data can be more useful. Finally, for a long study period, medical practices may change overtime and may affect the relationship between the medical treatment and the outcome, for example, by redefining the recommendations for the population that may be prescribed the medical treatment. We would recommend identifying the absence of any major change in patient management guidelines, for example, by checking specific disease guidelines.

Importantly, there are different aspects to take into account at baseline for correct identification of the study sample, and for mitigating confounding (e.g., disease severity) (Table 2). Some studies implemented algorithms to handle this latter issue [28, 29]. Further, the linkage between treatment and diagnosis and the identification of treatment initiation requires assumptions, as encountered in other RWDs (Table 2). Time-related bias has been reported to be an important issue, potentially more important than randomization itself, as reported by Hernán et al. [30], and the absence of guidance for defining time zero can make the assessment inconsistent across different studies. Finally, JMDC and MDV may contain missing data for specific clinical outcomes, and we would recommend checking observed patient characteristics among patients with and without data to clarify whether using complete cases only may introduce selection bias.

To identify pharmacological treatments, MDV and JMDC databases provide information on prescription date, the medical department, the dose and the number of days of supply, cost information for claims reimbursement, and date of hospitalization. Although patients in MDV cannot be tracked outside the network of institutions included in the database, Nishimura et al. conducted a study in type 2 diabetes patients and found that the proportion of days covered for fixed-dose combinations and two-pill combinations was similar between MDV and JMDC [31]. Thus, we can suppose that the lack of data capture for other institutions in MDV may not be an issue at least in some specific applications. Overall, we would recommend collaborating with local researchers who are experienced using these data.

5 Future Challenges for RWD in Japan

Japanese real-world research studies are subject to limitations that are relatively typical of RWD sources as well as those that are Japanese specific. At present, few validation studies of diagnosis in claims databases have been conducted.
| Domain            | Issue                                | Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
in Japan [32], and key elements to consider when planning a validation study are under discussion [33]. MDV may provide data collection on demand, such as clinical data, to compensate for limitations and address a specific research question in the near future. Although rarely conducted, in the context of RWE use for decision-making, conducting sensitivity analyses, such as quantitative bias analysis, would be informative to the decision maker to characterize the uncertainty associated with systematic errors [34].

MDV and JMDC may present potential applications to complement clinical trials. Firstly, both allow for the characterization of subpopulations of patients, based for instance on comorbidities or age, in real-world settings that are generally excluded from clinical trials based on the eligibility criteria. Secondly, we expect that clinical trial replication using RWD could provide information on the generalizability of clinical trials in terms of eligibility criteria and treatment adherence, even though the studies conducted so far lack consistency, as reported by Bartlett et al. [35]. However, identifying patients for recruitment in a clinical trial is not possible using MDV or JMDC since these databases are anonymized. In contrast, the Clinical Innovation Network, a national project for registry-oriented clinical research that includes several patient registry databases, can be leveraged for patient recruitment for clinical trials [36].

In Japan, a particular effort is being made to develop novel data sources. For instance, there is a growing need for central data aggregation of genomic and clinical information in oncology; the Center for Cancer Genomics and Advanced Therapeutics database, a repository database storing the genomic data and clinical information of patients receiving cancer gene panel tests under the national health insurance system, is under development. This is believed to be an important step to establish the next-generation infrastructure for medical care and innovation in cancer research [37]. However, at present, it is not clear whether data access will be guaranteed to private companies.

The Pharmaceuticals and Medical Devices Agency (PMDA) guidance expansion in 2018 has helped to enhance the relevance of scientific rigor of the research. In particular, this expansion has fostered discussions between PMDA and pharmaceutical companies from the design stage of studies to provide an external source of expertise, revealing the need of specific educational programs [38].

Finally, following the recent outbreak of the coronavirus disease 2019 (COVID-19) pandemic, the Japanese
government has communicated the importance of promoting RWD collection to stimulate drug development and approval processes. For example, a recent study using MDV showed a sharp drop in asthma-related hospitalizations during the COVID-19 pandemic and brought to light the importance of patient behavior and environmental factors for asthma patients [39].

In conclusion, although several data sources are available to conduct real-world research in Japan, MDV and JMDC are the main data sources that have been used by the pharmaceutical industry. Japan is the third-largest spender in health expenditure after the USA and China, and hence, growing interest in generating Japanese real-world evidence is present, especially for assessment of treatment patterns and healthcare resource utilization, though MDV and JMDC can be leveraged for other types of RWD studies. However, the importance of a careful assessment of each database’s strengths and the need for sufficient knowledge on Japan’s unique healthcare system were noted, especially at the study design stage. For this reason, the way that care is provided to patients differs from that in Western countries, and thus, it is particularly important to understand the differences that could be impactful on study design and interpretation, in particular, through collaboration with local researchers.

Declarations

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Conflict of interest TL, TH, RW, and RP are employees of Clinical Study Support Inc. SG is an employee of Evidera. JS was an employee of Evidera during the time this manuscript was developed. TI is the founder/CEO of Clinical Study Support Inc. RK has no conflicts of interest to report.

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