ABRIDGED VERSION

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For Users of HTA:
Policy- and Decision-makers,
Industry, and Patient Groups

Use of Real-World Data and Real-World Evidence to Support Drug Reimbursement Decision-Making in Asia.

A non-binding guidance document prepared by the **REAL** World Data **I**n A**S**ia for H**E**alth Technology Assessment in Reimbursement (**REALISE**) working group

NUS National University of Singapore | Saw Swee Hock School of Public Health
HITAP Health Intervention and Technology Assessment Program
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USE OF REAL-WORLD DATA AND REAL-WORLD EVIDENCE TO SUPPORT DRUG REIMBURSEMENT DECISION-MAKING IN ASIA

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Table of Contents

Table of Figures and Tables

Table of Boxes

1 Introduction

A collaboration between global experts and leaders from health technology assessment (HTA) agencies in Asia, the **REAL** World Data **I**n A**S**ia for H**E**alth Technology Assessment in Reimbursement (**REALISE**) working group seeks to develop non-binding guidance that will provide a framework to generate and use real-world data (RWD) / real-world evidence (RWE) in a consistent and efficient manner for decision-making in Asia.[1] The acronym REALISE signifies our desire to realize ('to cause to happen or to facilitate') the potential of RWD/RWE while realizing ('being aware of') its strengths and limitations. The issues to be addressed in the guidance document will include but are not limited to: (a) When is it appropriate to consider RWD/RWE for reimbursement decisions?; (b) What types of RWD should we collect?; (c) What are the data sources for collecting RWD?; (d) How should we collect RWD?; (e) Who should collect RWD?; (f) How will RWD be used to generate RWE?; (g) How should we use RWE in decision making?; (h) What are the potential biases and how to deal with these biases?; and (i) What are the ethical considerations in collecting RWD and generating RWE?

It is our goal that the proposed guidance document will increase the quality of RWD/RWE collected and used in HTA. This abridged version of the guidance is produced for policy and decision-makers, industry, and patient groups who may not be involved in the technical HTA but nevertheless use HTA for decision-making and in their work. This report will focus on the scenarios that one may consider RWD/RWE use; governance, accountability and ethical considerations; and general recommendations for RWD collection.

1.1. Background

1.1.1. RWD and RWE: Definitions

There is growing interest globally in using real-world data (RWD) and real-world evidence (RWE) for regulatory and reimbursement decision-making for health technologies. This is because RWD, defined as *data collected during routine delivery of health care (e.g. from observational studies, electronic medical records (EMR), claims and billing activities, product and disease registries, patient-generated data),*[2 3] and RWE, defined as *evidence that is derived from the analysis of RWD*,[3 4] have shown several potential benefits in informing health-related decision-making. We adopt these definitions from the HTA glossary (htaglossary.net), a collaboration between the International Network of Agencies for Health Technology Assessment (INAHTA), HTA international (HTAi), and other partners to develop a common vocabulary for work in HTA (Box 1.1).[3 5] Benefits of RWE in decision-making include, but are not limited to, reducing time and cost to source relevant information to inform an HTA if population-specific data are required and sufficient local evidence is lacking from available trials,[6] providing evidence with higher external validity compared to randomized controlled trials (RCTs) (see Box 1.2), giving decision makers more certainty of the safety, effectiveness, and cost-effectiveness of technologies in the local setting,[7] and filling the information gap in the absence of clinical trials (e.g. when it is not feasible or ethical to conduct a trial, or there is significant unmet need).[8]

Box 1.1. Differentiating RWD and RWE[9]

In a report by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force created to make recommendations on RWD studies, they state, "The notion was that *data* conjures the idea of simple factual information, whereas *evidence* connotes the organization of the information to inform a conclusion or judgment. Evidence is generated according to a research plan and interpreted accordingly, whereas data is but one component of the research plan. Evidence is shaped, while data simply are raw materials and alone are noninformative."

Box 1.2. Importance of external validity

Constrained study designs with strict inclusion and exclusion criteria for the study population are typically adopted for RCTs, based on severity of illness, comorbidities, use of other medications, and adherence to protocols.[10] This means that the drug is tested for safety and efficacy on a small, non-representative segment of the population.[11] RCTs generally produce more favorable outcomes than observed in real world settings due to lower rates of discontinuation, more frequent protocol driven visits, and exclusion of patients with comorbidities.[10] External validity matters because safety, and effectiveness of a drug over the longer term is what ultimately counts toward drug cost for payers, and in the assessment of its value for money for the payer's specific population. However, external validity should not be pursued at the cost of internal validity.

1.1.2. RWD and RWE: The global context

RWE use in health care decision-making is not new. Regulators have been using routine data to monitor safety in Europe and the US for many years. As an example, the European Medicines Agency used registry and claims data from Denmark and the UK from 2001-2011 to quantify the risk of lactic acidosis following metformin use among patients according to renal function.[12] The contraindications on the product label were consequently modified based on this study, rather than requiring the manufacturers to conduct an expensive post-marketing trial. The United States (US) Food and Drug Administration's (FDA) Sentinel Initiative, launched in May 2008, is another example of a pharmacovigilance program that assesses personal health data of over 223 million US residents to monitor the safety of approved drugs.[13] More recently in 2016, the 21st Century Cures Act required the FDA to develop a framework and guidance for evaluating RWE in the US for regulatory purposes, to standardize the use of RWE to inform regulatory approval of new indications for drugs, and to support post-approval requirements.[14]

In reimbursement and coverage decisions, RWE is increasingly recognized as a tool for accelerated access programs in several European countries. United Kingdom's (UK) National Institute for Health and Care Excellence (NICE) has conditional reimbursement schemes using RWE.[15] US payers (e.g. insurance providers) often use epidemiological data based on claims data, to estimate the proportion of patients that are likely to claim for treatment. Health Canada accepts the use of all relevant data, including RWE, as evidence for a drug's efficacy and safety.[16] Research in the field is still very active and continues to evolve. The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted an environment scan in 2018 on the role of RWE in single-drug appraisal[16] and concluded that new processes and standards globally will develop as more information on the impact of RWE on drug marketing approval and reimbursement becomes available.

1.1.3. RWD and RWE: Early versus late reimbursement in the Asian context

HTA agencies in Asia have used RWE (or sometimes referred to as 'local evidence') to inform coverage decisions in the past without explicit and formal methodological guidelines in place. However, optimal collection, analysis and use of RWD/RWE to inform HTA requires a conceptual framework to standardize processes and ensure consistency. Such a framework is currently lacking in Asia, a region that is likely to benefit from RWD/RWE.

RWD are particularly relevant in Asia where there is greater need and opportunity to use clinical effectiveness data from routine healthcare data sources (such as observational studies or disease registries) for regulatory and reimbursement purposes than in the United States or Europe for two reasons. First, only around 17% of the clinical trials are conducted in Asia[17] due to barriers related to financial and human capacity, ethical and regulatory systems, lack of research environment, and operational issues.[18] Second, there could be an under-representation of Asian populations in pivotal clinical trials.[17 19] In some Asian health systems such as Singapore, Taiwan and South Korea, electronic medical records (EMR) may also be used to generate local clinical effectiveness data. These data are important to demonstrate the efficacy and safety of medical treatments despite biological variations (e.g. because of differences in body weight or pharmacokinetics and/or pharmacodynamics due to different genetic makeups between Caucasians and Asians),[20] and non-biological variations (e.g. clinical trial findings among Caucasians may not be readily generalizable to Asians) seen in the patient populations. At the same time, in view of under-representation of Asians in clinical trials, it is usually unfeasible for most Asian health systems to replicate the RCTs in their local contexts, due to financial, capacity, and resource limitations, thus increasing the potential value of RWD/RWE in estimating the benefits and risks of therapies in Asian populations. Furthermore, there may be differences in local clinical practice guidelines driven by budget and resource constraints. For example, in health systems with larger budgets such as the UK,[21] the use of high cost biologic agents as first- or second-line therapies for rheumatoid arthritis is recommended in line with their registered indications, supported by clinical trial data. However, in Thailand, due to concerns over the sustainability of reimbursing these high cost drugs, biologic agents are only recommended as third line therapies for rheumatoid arthritis.[22] Therefore results from trials conducted in other health systems may not be easily generalizable to countries where these agents are used in a different line of therapy in local clinical practice. A large variety of RWD/RWE can also be used in Asia to inform epidemiology, clinical pathways, healthcare utilization, medication adherence, etc. for HTA decision-making.

In addition, in many Asian health systems (e.g. China, India, Indonesia, Malaysia, Philippines, Singapore, and Thailand), reimbursement decisions are predominantly made up to several years after market entry. Drugs can be prescribed by physicians before reimbursement decisions are made and are paid for like any other non-subsidized drugs, either out of pocket or through private insurance coverage. Other Asian health systems (e.g. Japan, Taiwan and South Korea), make their reimbursement decisions coinciding with or closely after regulatory approval. Here RWD and RWE are used to re-assess initial funding decisions or for price adjustment. In both initial reimbursement and reassessment, RWD and RWE play significant roles and must be carefully collected, managed, and analyzed. An alignment of practices across Asia on how to generate and use RWD/RWE would equip decision makers with context-relevant evidence to inform local reimbursement decisions, provide manufacturers with guidance on evidence they need to deliver, and improve timely patient access to new technologies.

2 Theme one: Scenarios to use RWD/RWE

When is it appropriate to consider RWD/RWE for reimbursement decisions?

2.1. Complementing clinical data

More innovative drugs are entering the market using a combination of data from RCTs and observational studies.[15] In some cases, study sizes decrease as certain patient populations are small to begin with, or as medicine becomes more targeted and personalized. This theme is concerned not only with the absence of data but also when the available data is of low quality and therefore unreliable. RWD in such cases can be utilized as supplementary evidence to RCTs and can enhance decision-making.

2.1.1. RCT data

RWD and RWE may be considered to complement current RCTs and systematic reviews of RCTs if they are lacking or of insufficient quality to inform decision-making. Challenges of some RCTs and systematic reviews include small numbers of patients involved, relatively short follow-up, outcomes that were incomplete or poorly captured, studies that were underpowered, studies with limited external validity (especially for high risk patient groups who are excluded from RCTs such as pediatrics and geriatrics), and inappropriate synthesis of data in systematic reviews. An example of the use of RWD to complement pivotal trial evidence may be found in the NICE technology appraisal guidance of percutaneous vertebroplasty and percutaneous balloon kyphoplasty for treating osteoporotic vertebral compression fractures (TA279; Box 2.1).[23]

Box 2.1. Using RWD when RCT data is lacking: Treating osteoporotic vertebral compression fractures

Percutaneous vertebroplasty and percutaneous balloon kyphoplasty are minimally invasive procedures used to treat spinal compression fractures. They were evaluated with RCTs which measured the efficacy of intervention in reducing mortality from osteoporotic vertebral fractures. Based on a meta-analysis of 3 RCTs over 12 months, the benefit on treatment on mortality had a hazard ratio of 0.68, with no statistical significance.[23] However, the RCT result was initially considered to be uncertain given the 3 RCTs were very small studies, with only 276 patients included in total. RWD, with a much larger sample size, is accepted by NICE to support data from small trials. To confirm the efficacy results, the hazard ratio from the trial data was compared to available RWD and was found to be close to the findings from two large observational datasets. First, the US Medicare Registry, which included 858,979 patients with newly diagnosed vertebral fracture with 4 years follow up, reported a hazard ratio of 0.63 in the treatment group. Second, the German Health Insurance Fund, which recorded data for 3,607 patients with vertebral fractures, reported a hazard ratio of 0.57. Both registry data were not designed to test for mortality, but the results were nonetheless in concordance with the trial data.[23] However, it should be noted that there is still a possibility that the agreement between the trial data and the observational studies may be due to chance.

Nonetheless, it is essential that RWD and RWE used for national reimbursement decisions represent the target clinical population reflective of the local context, so that the RWD and RWE can be generalized to routine clinical practice. Unfortunately, there are few data sources, including EMRs and claims data, that truly reflect the local population. Delayed reimbursement and launch of drugs first in

the private market, as is common in Asia, may also generate RWD that may not be reflective of the population using the drug once reimbursed. Researchers need to consider the systematic biases that may be present in using certain databases. Using multiple datasets reduces the likelihood of biases. In the Asian context, a list of some of the national-level databases and other sources of RWD available in each country can be found in Appendix 8.1. The representativeness of each source with regards to the local patient population and local clinical practice is variable in each country. An example of RWD that is representative of 99.9% of the population can be found in Taiwan from the Health and Welfare Data Center (HWDC)[24] which centralizes most health-related databases in Taiwan, including comprehensive cross-linkage to claims data, registries, and national surveys.

2.1.2. Rare diseases

Rare diseases are most frequently cited as an area where RWD and RWE need to be collected in the absence of sufficient trial evidence. Conducting RCTs for rare diseases is particularly challenging because of the small numbers of patients available for recruitment, the high variability in clinical presentation and prognosis across patients with the same condition, difficulties in accurately diagnosing patients with specific conditions, and a lack of a consistent definition for what constitutes a rare disease in each country. In the Asian context, South Korea considers a rare disease as a condition where there are fewer than 20,000 patients, or for which the prevalence is unknown owing to difficulties in diagnosing the condition, or that are designated by the procedures and standards set by the Ministry of Health and Welfare.[25] In Singapore, rare disease is defined as <4 in 10,000 people, and ultra-rare is <2 in 50,000 people.[26] Thailand defines a rare disease by the "size of population affected by disease", where a prevalence of 10,000 is considered as the threshold.[27] There is no official definition in Malaysia but the Malaysia Rare Disease Society defines it as 1 in 4000.

Typically, there is no standard of care or treatment for most rare diseases, therefore, comparative trials are typically not feasible. RWD/RWE from patients' medical records and rare disease registries are becoming crucial to demonstrate orphan drugs' long-term safety and efficacy for regulatory and HTA purposes.[15] Several countries and interest groups have advocated for creating a centralized national registry of rare diseases to serve investigators conducting rare disease research, as well as other stakeholder groups (families, clinicians, manufacturers) who may stand to benefit from the repository of information available.[28] To assist with the formation of such a database, the definition of what constitutes a rare disease has to be clearly specified. Individual groups can then deposit de-identified data using a standardized template for diseases that meet the agreed definition.

2.1.3. Surrogate versus final end-points

This working group recognizes that clinical trials cannot continue indefinitely, and it may not always be feasible to capture ultimate endpoints such as overall survival or long-term health-related quality of life (HRQoL). If the manufacturer intends to make a claim regarding the long-term efficacy of the drug based on a surrogate endpoint, the link between the surrogate endpoint and the long-term outcome (e.g. overall survival or long-term HRQoL) would need to be demonstrated. Under such a scenario, well-conducted observational studies that provide convincing evidence for the link between surrogate endpoints and longer term endpoints should be considered (Box 2.2).

Box 2.2. Using RWD in linking surrogate and final end-points: Gastrointestinal stromal tumors

A meta-analysis of 14 RCTs and 5 observational studies of sufficient methodologic quality in patients with unresectable and/or metastatic gastrointestinal stromal tumors and found a strong positive relationship between overall survival (OS) and progression free survival (PFS; served as a surrogate endpoint), especially in later lines of therapy.[29] These findings suggest that PFS could serve as a surrogate marker for OS for this cancer type, although further patient-level data analyses are needed to strengthen its validity. In rare diseases, and for many cancer types, PFS is already reported to be a commonly accepted primary end-point and proxy for longer-term survival benefits of treatment, given the paucity of long-term data.[30]

Surrogate endpoints however, should not be regarded as a replacement for a final endpoint. We advise caution when using RWD/RWE to demonstrate the link between a surrogate and a specific endpoint. Grigore et al. provides a summary of methodological guidelines across international HTA agencies on using surrogate endpoints.[31] A strong sensitivity analysis is recommended to validate the causal link and to omit spurious effects between the surrogate and the endpoint, otherwise, this may lead to false positive conclusions. One method is the analysis of multiple studies of known effective drugs, which assess both the direct and surrogate endpoints, in order to establish and quantitate the relationship.[32] This need not be performed for all surrogate endpoints as regulators such as the US FDA have already established a list of surrogate endpoints that are considered valid for use in drug approval.

2.2. Contextualizing

This section discusses the importance of ensuring that data retrieved is relevant to the local context and situation that it is being used for. Common examples where RWD may be useful include validating the choice of survival curve drawn from studies conducted in other settings, utilizing local data for parameters into economic models, and re-evaluating reimbursement decisions based on data collected retrospectively that have been drawn from the local population/users of the reimbursed drug.

2.2.1. Extrapolating beyond RCTs

In HTAs conducted for drugs, it is common to extrapolate efficacy estimates from short-term trials over the course of the patient's lifetime. The difference in survival between the treatment and control groups is an important measure of clinical efficacy. However, most trials are too short to include accurate information on how long all patients are likely to survive (with and without treatment). There are a variety of statistical methods that can be applied to extrapolate survival beyond a trial's duration, and the predicted differences in survival depend on which statistical extrapolation is used. When survival curves need to be extrapolated, RWD can be used to provide "validation" and determine if the extrapolation method used was appropriate and if results are likely to be clinically plausible (Boxes 2.3-2.4).[33 34]

The biggest caveat in validating the extrapolation of survival is that RWD comprises largely of data from people who have lived a sufficiently long time (survivor bias). The RWD would tend to validate the curve that looks the best when it is in fact invalid to use the RWD to validate the RCT, because the survivor group is different from the trial population and also different from the patients in routine clinical practice.[35] Therefore, despite the use of RWD in practice for such validation, the HTA community agrees that RWD can be used to supplement and not validate clinical trial data as most trials overestimate the true effect.[35 36] The very premise for using RWD is that the real-world and trial populations are different,

contributing to what is known as the 'efficacy-effectiveness gap'[36] and there is no easy way to judge whether the drug will work better, as well, or worse in the real world.

Box 2.3. Extrapolating beyond RCT with RWD. Example 1: Sorafenib for advanced hepatocellular carcinoma

The UK Cancer Drugs Fund reconsidered (TA474) a previously published NICE technology appraisal guidance of sorafenib for treating advanced hepatocellular carcinoma (TA189)[33] following the availability of new data from the manufacturer. The Appraisal Committee reviewed data from three longitudinal observational studies, Palmer et al. 2013, the GIDEON study, and King et al. 2016 and decided that the GIDEON study with a sample matched to the participants of the original RCT (SHARP) was most appropriate to validate the manufacturer's choice of extrapolation method for the survival curve in the original appraisal.[33] Hence, an important prerequisite of using RWD to validate extrapolated curves from RCTs is that the samples should represent the target population.

Box 2.4. Extrapolating beyond RCT with RWD. Example 2: Azacitidine for myelodysplastic syndrome

In another example of using RWD to extrapolate beyond RCT, a prospective observational study was conducted in Ontario from 2010 to 2016 to compare different dosing schedules of azacitidine. Azacitidine is an anti-cancer drug for the Myelodysplastic syndrome (MDS).[34] In 2010, the drug was approved based on an RCT, showing overall survival benefit. The registered dosing regimen required azacitidine to be initially taken 7 days in a row. However, in Canada, clinics usually only open from Monday to Friday, not on Saturdays and Sundays. From a logistical perspective, the intended 7-day regimen was not implementable in Canada. Repeating the RCT with a modified dosing regimen was also not feasible. Hence, a prospective observational study with 3 dosing schedules was proposed: (a) give 5 consecutive doses during the weekdays, skip the weekend, and then give the remaining 2 doses over the next two weekdays, (b) get 6 consecutive doses, by opening the clinics on Saturday mornings to allow for the additional 6th dose and (c) get 7 consecutive doses. The Ontario government provided temporary funding for all 3 regimens from 2010-2016 in order to facilitate the collection of RWD for evaluation. After 6 years, it was shown that the survival curves based on the 3 regimens were similar, suggesting that there was no significant difference in survival. The provincial HTA committee, the Ontario Steering Committee for Cancer Drugs (OSCCD), discussed the RWE with the Ministry of Health, who subsequently converted the temporary funding to permanent funding for all three regimens.

2.2.2. Localizing economic models

RCTs or observational studies conducted in a foreign-country context may not be able to inform policy making in the local Asian contexts, considering differences in current clinical practices, healthcare financing systems, ethics and judicial systems. Local RWD can help to close the gap and this may be one of the most important applications of RWD and RWE in Asia (Box 2.5).

Box 2.5. Examples of localization of economic models using RWD (Taiwan and Malaysia)

Taiwan: With a well-developed national database of registry and claims data, Taiwan was able to utilize RWD to localize their studies across diseases. One example is the evaluation of the long-term cost-effectiveness of different cervical cancer screening strategies in Taiwan.[7] Chow et al. used a natural history model for cervical cancer adopted from the literature, and estimated survival rates for cervical cancer over different time horizons from the Taiwan Cancer Registry. Age-specific mortality was obtained from the Department of Statistics for Taiwan's female population; local direct medical costs from the Bureau of National Health Insurance (NHI) and another local publication. With these findings, the authors recommended a screening strategy for combined human papillomavirus (HPV)-Pap smear every 5 years for the publicly financed healthcare system, over the other 8 strategies evaluated.

Malaysia: Epidemiology and resource utilization evidence generated from the Malaysian Dialysis & Transplant Registry was used in an HTA conducted by the Malaysian HTA Section (MaHTAS), which compared single use vs reusable dialyzers in hemodialysis. The model structure was simplified from a published Canadian model.[37] The study found that reuse was more cost-effective than single use dialyzers.[37]

2.2.3. Re-evaluation of initial reimbursement decisions

As new technologies or policies are introduced into the health system, the opportunity cost and marginal effectiveness of some existing technologies might change, calling for a re-evaluation of the existing technologies. Under such circumstances, the original RCTs might not be able to represent the updated real-world settings. Thus, if the relevant health data system is developed, countries can utilize the rich information from RWD to inform the re-evaluation (Box 2.6).

Box 2.6. Example of reassessment using RWE: Australia's National Cervical Cancer Screening Program

RWE were used to inform revisions to the National Cervical Cancer Screening Program (NCSP) in Australia.[38] NCSP was established in 1991, providing bi-yearly conventional Pap tests for 18- to 69-year-old women. Registers were established within each jurisdiction. NCSP significantly reduced cervical cancer incidence and mortality rates in 1990s. However, in recent years, evidence from RCTs has shown that HPV DNA testing is more effective than traditional cytology-based screening.[39] [40] The former might also save costs by allowing patients' self-collection of testing samples. Meanwhile, a nationwide free HPV vaccination program, introduced in 2007, has high coverage across Australia and has significantly reduced cervical abnormalities for vaccinated women, especially for youngest women.[41] The development in new testing technologies, together with the success of HPV vaccination program, inspired a revision of NCSP, proposed as: a 5-yearly testing with a HPV test (with partial genotyping) and reflex liquid-based cytology, for 25- to 74-year-old women. Based on registry and immunization data, the Medical Services Advisory Committee (MSAC) in Australia evaluated the original NCSP and the revised NCSP, taking into account the effect of vaccination. While the default position of the MSAC is that RCT data remains the gold standard for evidence generation, MSAC agreed that the registry data were useful to demonstrate that with vaccination offered, the revised NCSP, compared to the original NCSP, saved both costs and life-years. As a result, the revised NCSP was implemented from December 2017.

2.2.4. Leveraging RWD/RWE for price negotiations or managed entry schemes

RWD/RWE can be leveraged by pharmaceutical manufacturers to support flexible subsidy arrangements with payers, and can help to balance the need for early access to innovative drugs with the need for evidence-based decision making (see Box 2.7 for an example). One payment model involves paying the manufacturer in annual installments over several years, with the annual payment contingent on the real-world performance of the product. For example, if the treatment efficacy is expected to last for 10 years, then the reimbursement is divided into 10 annual installments, with each installment being paid out contingent on the patient still being alive and responding to treatment. This payment model needs to be supported with the development of a registry to collect patient outcomes so that the manufacturer can be duly reimbursed, or the use of other RWD sources such as EMRs or claims data. Economic models that informed the original cost effectiveness analysis using trial data, can then be updated with RWD collected for a more accurate assessment of the ICER in the local context. In other situations, price negotiations between payers and pharmaceutical manufacturers based on cost-effectiveness analyses may fail and require RWE for outcomes-based agreements. This is because, for treatments with a small market size or which address a high unmet need (such as in the case of treatments for rare diseases), manufacturers may try to justify setting a higher price irrespective of the ICER. Another example of leveraging RWE, although less common, is in price re-negotiations or managed exit (disinvestment) of drugs, especially in settings where the evidence to support initial market entry is very weak.

Box 2.7. Example of a managed entry scheme: Australia

The Australian government introduced the managed entry scheme (MES) in 2010 to accelerate patient access to innovative drugs.[42] Conditions for an MES in Australia include high and unmet need for the drug and evidence that can be gathered within a suitably short time frame to resolve any initial uncertainties in the evidence base. One product that went through this process in 2013 was crizotinib for the treatment of ALK positive non-small cell lung cancer (NSCLC). The Pharmaceutical Benefits Advisory Committee (PBAC) initially deferred the reimbursement decision due to uncertainty with the incremental 12-month OS proposed. A resubmission was subsequently made by the manufacturer in March 2014 with a MES proposal. To address the uncertainty surrounding the survival benefit of crizotinib, the manufacturer agreed to collect 12 month survival data for the first 50 patients receiving crizotinib after it was listed on the Pharmaceutical Benefits Scheme (PBS). A price reduction was agreed if the claimed survival benefit was not realized, and the manufacturer agreed to rebate the government a prespecified (confidential) percentage of the cost of treatment depending on the OS outcomes. In 2017, the manufacturer successfully provided survival outcomes collected from patients receiving treatment that were consistent with their original survival claims. The PBAC subsequently allowed crizotinib to continue to be listed on the PBS at the initial MES entry price and further data collection was no longer required to support the listing.[42]

2.3. Using RWE with caveats

While many see value in RWE and are exploring ways to utilize routine health data sources, there are inherent limitations associated with RWE application. We conclude the chapter with certain situations in which caution is needed when using RWD/RWE.

2.3.1. Biases arising from RWD/RWE

Biases may be introduced by confounding and/or selection bias in the RWD that may not have been adequately dealt with. Confounding represents a mixing of effects between the treatment group and external factors that may also influence the outcome, potentially obscuring or distorting the relationship that can be inferred.[43] These factors that influence the association between a treatment and the effect may either be known or unknown.[44] The most common concern in observational studies and real-world sources, like patient registries, is of confounding. Selection bias occurs when the observed subgroup of patients is not representative of the broader population of interest,[45] when using patient-level data from real-world sources and is a threat to both the internal and external validity of the study and its generalizability to a larger population. It is important to note the difference between confounding and selection bias and that methods to control for the former may not address the latter.

Box 2.8. Biases arising from RWD: Lesinurad for treatment of chronic hyperuricemia

An example where bias was introduced into an HTA through the use of RWD was in NICE's technology appraisal of lesinurad for treating chronic hyperuricemia in people with gout (TA506)[46]. In RCTs, lesinurad was found to improve serum uric acid level, without any evidence in reducing flares, increasing tophi healing, or delaying death. However, the manufacturer presented a meta-analysis of 6 observational studies showing that people who took uric acid lowering therapies lived longer than those who did not, which conflicted with findings in the RCTs. The RWE was not accepted by the NICE, which noted that (a) no evidence from RCTs validated the relationship between lowering serum uric acid levels and life expectancy, even with drugs other than lesinurad, (b) the observational studies from the UK did not suggest that uric acid-lowering treatment extended life and (c) known and unknown confounders, e.g. renal function and socioeconomic status, were not well controlled for in the observational studies.

2.3.2. RWD data quality

Fit-for-use RWD for HTA is a challenge because the data is not originally intended for research. Noise in routinely collected data can be caused by coding inaccuracies and inconsistent naming conventions over time and across sites.[47] Study sites may lack data management protocols, are subject to human errors in data entry, and omit important variables needed for HTA. To overcome this issue, a study in Malaysia for example, required extensive primary data collection to supplement data from the Asian-Heart Failure (HF) Registry Data in order to estimate the cost of heart failure in Malaysia.[48] Validation of the collected RWD can be addressed with quality management/assurance plans, e.g. one that periodically checks a subset of the extracted data for accuracy, consistency, completeness and plausibility.

The following chapter, Theme 2 ('Collecting RWD') will discuss more of these data quality and validation issues by each type of RWD source, methods of collection, and introduce suggestions for best practices in data collection in Asia.

2.4. Conclusion

RWE is already utilized in many countries as supplementary evidence to inform reimbursement decisions. Because of limitations and/or the lack of RCT-generated efficacy data, HTA agencies have been exploring the benefits and limitations of using RWD to supplement and enrich primary evidence to demonstrate the cost-effectiveness of drugs in each local context. Examples when RWE may be useful to inform decision making includes disease areas where RCTs are limited and/or of poor quality, or impossible to conduct for ethical reasons or due to small numbers (e.g. rare diseases). RWE can also be used to contextualize and localize economic models, extrapolate RCT data beyond trials, and for price setting and negotiations with manufacturers based on real-world outcomes. In Asia the drivers of RWD adoption are the availability of good quality data in the public domain and the expertise of HTA researchers.

While RWD and RWE are useful in the stipulated scenarios, it is important to remain cautious in their application as they can be subject to various forms of bias and generate misleading conclusions. The recommendations in this chapter relate to use of RWD and RWE with the following caveats:

Box 2.9. Recommended caveats while using RWD and RWE

1. RWD and RWE are generalizable to routine clinical practice only if the data represents the target clinical population reflective of the local context;
2. Trial and real-world populations are, by definition, different and any comparisons made, even 'validations', should be cognizant of the efficacy-effectiveness gap;
3. Observational studies can link surrogate and final end points, but sensitivity analyses should be used to validate the causal link and avoid spurious conclusions; and lastly,
4. Limitations and threats to validity from confounding, missing data, and overall low-quality data should be noted.

Evidence should only be accepted to inform decision making if it is considered robust and generalizable to the local context.

3 Theme two: Collecting RWD

3.1. Introduction

Many concerns raised about the value of RWD to inform reimbursement decisions relate to the perceived quality and validity of the RWD collected, which is heightened by the lack of, and difficulties establishing, universally accepted methodological standards or principles for the design, conduct, and/or reporting of RWD/RWE.[49] Despite growing interest from stakeholders involved in HTA, these concerns reduce the incentive to generate and use it.

However, users of RWE can exercise caution over the potential quality concerns and review validation processes for data collected from different sources. To do that, this theme discusses the common sources for RWD in Asia ('Where to collect?'), their pros and cons, and the good practices associated with using them.

We conclude with a case study illustrating the importance of contextualizing the ethical and legislative issues associated with collecting RWD to each local setting ('Who to collect?') and a set of recommendations to improve the process of RWD collection.

3.2. Where to collect? Sources of RWD and good practice guidelines

RWD can be collected from various sources including product or disease registries, routine administrative data sets such as claims databases, electronic medical records (EMRs), health surveys, or from daily wearables and personal tracking devices. When presented with RWE, users of the evidence should deliberate the benefits and limitations of various sources in the local context. It is critical to understand the potential reimbursement questions that may or may not be answerable because of the availability, access, and quality of the RWD sources. The strengths and limitations of these common RWD sources, as well as recommendations in the literature will be discussed below. In many cases the best solution to a policy question requires integrating sources and leveraging the strengths of each.

3.2.1. Disease registries

Disease-specific, and other public health-relevant registries such as for births, deaths, immunization records etc., consist of structured datasets that can be made available for analysis. They can be used for understanding natural history, assessing or monitoring real-world safety and effectiveness, assessing quality of care and provider performance, and as inputs for cost-effectiveness analyses. Disease registries involve prospective data collection that reflect everyday clinical decision making. Rare disease registries in particular play a key role in providing RWD to inform decisions regarding clinical effectiveness because evidence cannot be easily obtained through clinical trials due to limited patient numbers typically recruited. A non-exhaustive list of registries in Asia can be found in Appendix 8.1.

Data quality issues

Data quality is a major issue with disease registries when study sites are not experienced in data collection intended for research.[9] One example was the use of the ASIAN-Heart Failure (HF) registry to estimate the cost-of-illness of heart failure in Malaysia. The authors raised challenges in obtaining sufficient information on resource utilization because medication profiles were overwritten each time

the registry electronic data was updated, deleting the information on medications previously prescribed.[48] In other cases poor data management, compounded by constraints in manpower and funding, can lead to valuable data loss.

Registries do not always include all patients in the target population. For example, some of the existing cancer patient registries in Japan only include patient information that is registered voluntarily, making it unclear whether the data are entirely representative of the populations under evaluation. Hence, it is sometimes difficult to justify the use of such data for reimbursement decisions at national level.

Table 3.1. Pros and cons of registries

Registries: Pros	Registries: Cons
• Patients are often followed over a longer time frame, allowing for an assessment of longer-term outcomes • Most registries have very few required visits, evaluations, or procedures. Treatment patterns reflect the everyday clinical decision-making that is most relevant to providers and payers • Rare disease registries record and increase understanding of specific diseases among a very limited patient population	• Registries sometimes include study sites that are not as experienced in data collection intended for research, affecting data quality • Selection bias can occur, especially for patients who did not or could not provide consent to enter registry,[50] i.e. data does not include the entire patient population • May lack control group within the same registry, increasing risk of bias because of systematic differences in the sources for selecting cases and controls

How are registry data used in drug reimbursement decisions in Asia?

A successful example of RWD from registries used in initial reimbursement decisions is the use of Malaysia's National Obstetric Registry to evaluate the cost-effectiveness of carbetocin compared to oxytocin as prophylaxis against post-partum hemorrhage during cesarean deliveries.[51] Data from the registry contributed by 14 major hospitals confirmed that compared to oxytocin, administration of carbetocin was simpler and its longer-acting nature reduced the need for additional medications. Taking this evidence into consideration, carbetocin was found to be cost effective.

Taiwan conducts post-market reassessment of reimbursement, and registries are frequently used to collect outcomes data especially for high cost oncology drugs with high uncertainty of clinical effectiveness, e.g. in managed entry agreements for direct-acting antiviral (DAA) medications for hepatitis C and immunological drugs for various cancers. Payments and claims data from the National Health Insurance Administration (NHIA) are directly contingent on patient's clinical response. Among Asian countries, Taiwan is exceptional in its accessibility policy for disease registries and other national databases. Access to the Health and Welfare Data Center (HWDC) that links many sources of national health data can be granted to anyone conditional upon prior approval of the research or industry-sponsored project by an Institutional Review Board (IRB). Safeguards to data privacy include deidentified datasets only accessible on-site, having statistical analysis syntax reviewed before access, and analyzed results examined before data export.

Despite these examples, access to disease registries is a commonly cited challenge in Malaysia, South Korea, Japan, and Singapore. The National Institute of Health (NIH) Centers for Disease Control and Prevention (KCDC) in Korea accept registration for clinical research in their CRIS system (cris.nih.go.kr). Publicly funded research, including many disease registries funded by KCDC are available, but most of

them are considered investigator-initiated rather than public as researchers view the registries as their own. Public access to disease registries is therefore limited and potentially requires the individual to know the researchers or have contacts in the NIH/KCDC. A similar situation occurs in Japan whose registries have been implemented by medical societies and parties and are hence researcher-owned. National registries in Singapore produce standard public reports of aggregated outcomes periodically, but they often have limited use as evidence to inform reimbursement decisions, given the data is not disaggregated and may not be relevant to inform estimates for particular subgroups or disease types. Several disease registries are also established in different public healthcare institutions, but they are often investigator-led and data are not readily shared between hospitals or with the public.

Health-relevant registries like for births and deaths are sometimes separately curated outside the Ministries of Health and are typically requested for separately (e.g. from the Internal Ministry in Taiwan and the Immigration Checkpoint Authority in Singapore). Data linkage between such data and patient registries can be an enormous challenge.

Box 3.1. Good practices when collecting data for registries

How a system collects, cleans, monitors, and reports registry data determines whether the data can be useful toward the registry's goals. Critical factors relating to the quality of the data collection include how data variables are defined, whether personnel are adequately trained to enter the data, and verification checks targeting errors during collection resulting in out-of-range and logically inconsistent values.[52]

Registries should be carefully planned with clear objectives and extensive clinical input. These data collection, management, and quality assurance procedures should be defined in a detailed manual when establishing the registry and not after.[53] Registries may also be required to comply with local guidelines or legislation (e.g. Singapore's National Registry of Diseases Act). Quality assurance ensures that data are collected in accordance with the pre-defined procedures and that they meet the requisite standards of quality to meet the registry's intended purpose.

Importantly, as certain requirements may have significant cost implications, a risk-based approach to developing a quality assurance plan is recommended.[53] It should be based on identifying the most likely sources of error or potential lapses that affect the quality of the registry in its intended use of the data.

For more recommendations on data collection and quality assurance for registries, see:

- Gliklich RE, Dreyer NA, Leavy MB: Registries for Evaluating Patient Outcomes: A User's Guide[53]
- Blommestein HM, Franken MG, Uyl-de Groot CA: A Practical Guide for Using Registry Data to Inform Decisions about the Cost Effectiveness of New Cancer Drugs[52]
- China Real world Evidence (ChinaREAL) Consortium: Technical Guidance for Developing Patient Registry Databases (in Mandarin Chinese)[54]
- Singapore: National Registry of Diseases Act[55]
- Japan: Guidelines for setting up registries in Japan are now under development and planned to be published in 2020 or 2021. These guidelines relate more to privacy and data sharing than how to scientifically use the data. The government is planning to make RWD from registries available for research purposes in 5 to 10 years' time (2025-2030).

Box 3.2. Good practices when collecting data for rare disease registries

Rare disease registries can be a valuable tool for increasing understanding of the disease and supporting the development of orphan drug therapies but have their unique challenges due to limited patient population. Expert opinion from stakeholders such as patient advocacy groups, payers, patients, and their caregivers/families should be collected.[53] This requires the registry administrators to also effectively educate stakeholders about how they can meaningfully contribute to the data capture and the type of experiences or information that they should share.

Unique features of rare disease registries include:

- Limited number of patients with conditions of interest (either due to low incidence or large number of undiagnosed patients due to clinicians' lack of familiarity with the condition in their local context);
- Limited information available on the disease to guide development of a research and data collection plan. Diagnostic criteria may be complex or evolving;
- Disease-specific patient reported outcome measures may not be available. Long-term and even lifelong follow-up may be needed;
- Need to adapt and change over time as knowledge increases or treatments become available; and
- Limited treatment options (95% of rare diseases do not have effective treatments) and many of the available treatments are unaffordable for patients.

Thus, a key focus is on engagement and retention of patients/providers over the duration of the registry, closely monitoring follow-up rates over time to identify potential issues that may shape the data structure and definitions. Developing clear policies are recommended for governance of the registry and data access if multiple stakeholders are involved.

3.2.2. Claims databases

Compared to disease registries that are disease-centric, claims databases are focused on data that is generated from payment activities. Claims databases are also called billing and administrative databases. They consist of bills that health care providers submit to public (e.g. National Health Insurance Administration, Taiwan) or private insurance entities for reimbursement of covered services. Claims data are especially rich as an RWD source for countries/regions like Japan, South Korea, and Taiwan with national payers because of the breadth and comprehensiveness of all patient encounters across the full continuum of care. Variables and data types recorded can be diagnoses and procedure codes, dates of service and lengths of stay, pharmacy dispensing data, clinical data, and patient demographics. The purpose of claims data is for payment, making it convenient for researchers to establish the cost for certain diagnoses by consulting fee schedules and reimbursement data for CEAs.[56]

The data has the benefit of relatively structured data fields and lend themselves well to retrospective analyses of clinical and economic outcomes, which can be conducted in a relatively short period of time and at lower cost compared to prospective data collection.[9] In terms of scope, claims databases tend to capture a more holistic view of utilization and cost information from all providers caring for a single patient as long as they have made claims submissions. An exception is the Japanese healthcare system that does not consolidate submitted claims by patient. An additional benefit given the large volume of historical data is being able to identify outcomes of patients with rare events more easily in order to assess the economic impact of various interventions.

Data quality issues

Claims data are designed to hold only pieces of information relevant to facilitate payment. It requires diagnosis, services, and cost data but is otherwise limited in clinical information and may not collect all variables of interest (e.g. symptoms, health status). Retrospective billing and claims data, however, often face issues of data quality (missing data, unintentional miscoding, and intentional miscoding or 'upcoding'). There is also often a lack of distinction between cost and charges,[9] which can be an issue if claims data does not represent the economic value of resources used to provide services, and is influenced by monopolies or monopsony, then its utility for costing as part of a CEA is limited. Claims-based reporting also has latency of data refresh at varying intervals depending on the provider and are hence not updated in real time.

Table 3.2. Pros and cons of claims databases

Claims databases: Pros	Claims databases: Cons

• Comprehensive billing record covering all medical claims of a population except for the medical services that are self-paid, useful in measuring and estimating resource use and costs for economic evaluation
• More structured, and standardized format than EMRs
• Holistic view of all interactions of patient with health care services (Vs EMRs, which are provider specific)
• Analyses can be performed at low overall cost and in a short period of time
• Claims databases lend themselves well to retrospective longitudinal and cross-sectional analyses of clinical and economic outcomes at patient, group, or population levels
• Researchers can identify outcomes of patients with rare events given the large number of people captured in the database
	• Latency of data refresh for claims data (versus EMRs that are updated in real-time)
	• Depending on the comprehensiveness of coverage, the claims database may have limitations in terms of utility
	• May not allow granular assessment of cost components, which may be relevant for the CEA
	• Validity of retrospective claims database analyses in terms of:
	  ○ limited clinical information on health outcomes, health status, and symptoms (only captures data relevant to billing such as diagnosis and procedures)
	  ○ data quality (missing data, coding errors)
	• Availability of claims data for analysis is subject administrative approvals, and generally may not be available in public domain
	• Privacy of patient data is a priority in many countries. Potential difficulties in access and obtaining consent if data privacy is not adequately enforced

How are claims data used in drug reimbursement decisions in Asia?

As part of an economic evaluation in Indonesia to determine whether pneumococcal conjugate vaccine (PCV)10 or PCV13 should be included in the national benefits package, all country-specific health care costs used in the CEA were obtained from local clinical and billing databases.[57] In Korea, a cost utility analysis (CUA) of the Prostate Specific Antigen (PSA) test which included local cost estimates from Health Insurance Review and Assessment (HIRA) claims data, and effectiveness data from linked data from HIRA claims, NCI central cancer registry, vital statistics, and a tertiary hospital laboratory, provided evidence against the inclusion of PSA in the national screening program compared to the current opportunistic screening. The study results showed the PSA test was cost-ineffective as part of the National Cancer Screening program in Korea.[58]

Box 3.3. Good practices when collecting data for claims databases

Claims databases are also integral to providing local resource use and costs as long as the research population and comparison groups are clearly defined, identified, and addressed by an appropriate study design.[9 10] Recommendations to minimize threats to validity include:

- *Consistency of study design and conclusions with the claims database*. Before conducting a study, the degree to which the required data elements are captured by the claims database should be investigated.[10] Designs that require very specific diagnostic codes or lab data cannot be fulfilled with claims databases. Conclusions should not go beyond the capabilities of the database.
- *Use of a study design that includes comparisons.* Comparison groups are constructed to be as similar as possible except for the treatment of interest. Also, conducting both pre-post (in same group of patients) and cohort (different groups) comparisons is a stronger design than either alone.[10]
- *Use of appropriate constructs*. This relates to the translation of concepts into variables that are captured by the claims database, dependent on diagnostic codes and other criteria.[59] Claims database analyses rely heavily on proxies and constructs; results can vary drastically depending on how methodology is translated into technical algorithms. These decisions should be documented carefully and undertaken by those with specific expertise.

For further reading, see:

- Motheral BR, Fairman KA: The Use of Claims Databases for Outcomes Research: Rationale, Challenges, and Strategies[10]
- Birnbaum H, Cremieux P, Greenberg P, LeLorier J, Ostrander J, Venditti L: Using Healthcare Claims Data for Outcomes Research and Pharmacoeconomic Analyses[59]

3.2.3. Electronic medical records (EMRs)

While claims data have broad scope and coverage, EMRs provide a much richer dataset that is generated in real time (no latency), allowing for rapid response. EMRs contain structured and unstructured data fields that include real-time patient demographic and health information from clinical encounters, including diagnoses, symptoms, treatments, patient habits and surveys, lab results, and prescriptions. In addition to these core data elements, EMRs include peripheral documents such as imaging data, pathology reports, and patient history documents. That said, while detailed longitudinal data in EMRs and at a patient-level is a rich RWD source, critical data may not be stored in a readable format and transforming the said information that is originally intended for clinical purposes to RWE can be challenging. In contrast to claims databases, EMRs also tend to be provider specific and are limited in scope to patients who access the provider's services.

Data quality issues

EMR data collected in routine clinical care for non-research purposes is often incomplete and must be cleaned before it can be used. Noise in the data is caused by coding inaccuracies and inconsistent naming conventions over time and across sites, etc.[47] Biased sampling may occur when the same patient visits different providers for medical help who do not share information between each other.

Table 3.3. Pros and cons of EMRs

EMRs: Pros	EMRs: Cons
• Generates real time data about clinical treatment and outcomes. Evaluating real time EMR data can allow for a more rapid response (no latency) • Contains rich, longitudinal information if patient stays with the same provider, including disease-specific symptoms, patient vital signs, habits, etc. at the person-level	• EMR may be hospital/provider specific, and does not capture patients who access health services outside of the provider's health system • Logistical challenges even in accessing own data • Critical unstructured data may be stored in non-machine-readable formats (like handwritten notes) • Transforming the information meant for a clinical workflow to a format for research purposes requires further data management

How are EMR data used in drug reimbursement decisions in Asia?

RWD from the EMR has also been used in Bhutan to determine whether adding the rotavirus (RV) vaccine in the National Immunization Program would be cost effective, with relevant hospitalization and death statistics extracted from Bhutan's Health Management and Information System (HMIS).[60] In the near future, Bhutan also has plans to roll out an electronic patient information system (ePIS) to all levels of health facilities, from sub-posts, primary health care centers, to district, regional, and national referral hospitals. Policy makers and researchers are expected to be able to use integrated EMR data for future evidence-based decision making on health benefit package development.

Box 3.4. Good practices when collecting data for EMRs

There are practical challenges to the interoperability of EMR systems, which have to do with diverse systems used across providers, as well as diverse clinical data standards used by the health care and research communities. Some of these can be addressed if there are existing local requirements for open data standards or EMR data standardization. For data extraction, a protocol-defined data collection plan should define the 'when' and 'how' of measurement (timing and method of measurement).[61] Extra attention should be paid to the reliability and quality of unstructured EMR data and how they are translated into formats ready for analysis. Like registries, a quality management plan (e.g. standard operating procedures) should address validation of collected data, for example to periodically check a subset of the extracted data for accuracy, consistency, completeness and plausibility with the EMR source data.[61 62] The quality of EMR data must be ascertained in order to ensure their appropriateness for use to inform reimbursement decision making.

For further reading on data collection and quality assurance for EMRs, see:

- U.S. FDA Guidance for Industry: Use of Electronic Health Record Data in Clinical Investigations[61]
- ChinaREAL Consortium: Technical Guidance for Developing Research Databases Using Existing Health and Medical Data (in Mandarin Chinese)[63]

Box 3.4. (continued)

For further reading on specific verification checks for EMR data, see:

- Duke Margolis RWE Collaborative RWD Quality Working Group, for verification recommendations adapted from database level checks used in PCORnet and Sentinel: Determining Real-World Data's Fitness for Use and the Role of Reliability[62]

3.2.4. Health surveys

Population, household, and health surveys are designed to collect health related information from a target sample of the community, which can inform disease epidemiology, health status and well-being, health care utilization, health care expenditures, and treatment patterns. With rigorous study designs, surveys can provide information on a large group of the population, unlike data collection from limited participants in a RCT. Some examples from Asia include India's National Sample Survey Office (NSSO) that collects population-wide data on morbidity rates, health seeking behavior, and social consumption related to health, such as expenditure on healthcare.[64] This can be used to estimate costs in HTA. In Japan, health check-up data has been routinely collected for the population and includes information about basic health indices and non-communicable diseases, which can be used to derive epidemiological estimates for specific conditions. The National (Population) Health Surveys and National Health Surveillance Surveys have been collected on a regular basis in Singapore which, among other things, track the health and risk factors, as well as lifestyle practices of Singapore residents. Other similar surveys include Thailand's National Health Examination Survey[65] and Taiwan's National Health Interview Survey. Health surveys may also include patient reported outcome instruments that are administered to patients in order to gather data on their quality of life. However, population health surveys as stand-alone sources of data can be challenging to use without the ability to link them to other RWD databases. Other limitations of health survey data for initial coverage and reimbursement decisions include the lack of a representative population and lack of relevant data on specific products.

Data quality issues

Surveys are subject to issues of subjectivity and recall bias from respondents.[66]

Table 3.4. Pros and cons of health surveys

Health surveys: Pros	Health surveys: Cons
• Health surveys typically collect information on representative individuals in the target population • Can be methodologically rigorous • With well-designed sample surveys, can provide information about all members of the target population, not just those who are participating in a given RCT • Can make unique contributions about generalizability of treatments and their impacts and about use of and expenditures for health services	• Lack of relevant data on specific treatments/products to guide reimbursement decisions • Relevance of health surveys is dependent on periodicity of survey. If done infrequently, the data may not be relevant • Surveys are subject to issues of subjectivity and recall bias • Can be more resource intensive to distribute survey, follow up on responses and collate data

How are survey data used in drug reimbursement decisions in Asia?

A national level population-based survey in India has been used to answer a policy question of interest, whether to reimburse a new pan-genotypic direct antiviral, sofosbuvir/velpatasvir for the treatment of hepatitis C virus (HCV) instead of standard treatment.[67] This is motivated by the effectiveness of sofosbuvir/velpatasvir regardless of genotype, unlike in standard of care where drug treatment was previously dependent on HCV genotype. Removing the need for genotyping prior to treatment initiation had potential to improve patient outcomes as HCV patients in some districts could not access genotyping facilities and did not continue treatment. The demographic data in this study was obtained from census data, and out-of-pocket costs estimated using the National Sample Survey Office's population-based measure of social consumption in health, across 65,932 sampled households.[64] Despite the utility of readily available statistics, one limitation was the lack of control over degree of data disaggregation and unable to be broken down further, which is a common challenge in extracting RWD relevant to reimbursement from health surveys. The effectiveness of treatment among HCV patients was derived based on analysis of the routine program data. The authors showed that treating HCV patients was cost saving and strongly recommended that schemes targeting Universal Health Coverage should include the treatment of HCV in their benefit packages. Secondly, the authors also showed that while the budget impact of a universal application of the new drug maybe be very high, it could be initially introduced for HCV patients with cirrhosis with the greatest clinical need. This led to a change in the standard treatment guidelines for treatment of HCV, not just in the state but also in the national HCV control program.

Box 3.5. Good practices when collecting data using health surveys

Key factors found in the literature to promote survey data collection from diverse populations are: (a) awareness of the importance of the research, (b) acceptability of participation through social support and community, and (c) access to participation through transportation provision, translation for multilingual populations, and financial incentives.[68] In addition, documentation of the following information improves rigor of health survey data collection and ensures that data is gathered in an ethical manner:[69]

- *How, where, how many times, and by whom were potential respondents contacted?*
- *How many people were approached and how many of those agreed to participate?*
- *How did those who agreed to participate differ from those who refused with regard to characteristics of interest in the study?* For example, their gender, age, and features of their illness or treatment (if any); how they were identified?; where they were approached? Sufficient information on demographics and characteristics of groups and individuals should be available, that would provide fair estimations that address the cost-effectiveness question of interest
- *How the survey was administered*? Self-administered (by post, internet, in person), face-to-face (computer assisted or paper-and-pencil), and telephone interview all are associated with their own pros and cons[68]
- *What the response rate was?* The number of usable responses as a proportion of the number of people approached is the best indicator to measure how much confidence can be placed in the results for the specific instrument, which reduces potential for bias as the response rate increases.

Box 3.5. (continued)

For further reading, see:

- Eurostat: Guidelines for the Development and Criteria for the Adoption of Health Survey Instruments. Eurostat 2005. Luxembourg[68]
- Kelley K, Clark B, Brown V, Sitzia J: Good Practice in the Conduct and Reporting of Survey Research[69]

3.2.5. Wearables and personal tracking devices

Wearables and personal tracking devices (including mobile technologies, health apps) capture person-generated health data (PGHD), which are defined as wellness and/or health-related data created, recorded, or gathered by or from patients to help address a health concern.[62] PGHD offers a rich RWD source of patient characteristics and outcomes collected during the course of individuals' normal routines and daily life. Examples range from patches for electrocardiogram monitoring, wrist-worn devices for activity monitoring and sleep assessment, to sensors with subcutaneous probes for continuous glucose monitoring. The different types of PGHD can be grouped into person-reported data, task-based measures, active sensor data, and passive sensor data.[62] The sources of RWD continue to expand and pose new possibilities for use in reimbursement and reassessment.

An example of the untapped potential of RWD from PGHD was the finding that Fitbits, wearable devices that measure resting heart rate and sleep time, hold promise in real-time flu surveillance at the US state level.[70] The weeks during which de-identified Fitbit users in five states had elevated heart rates and more sleep time tended to be those when influenza-like illnesses were most common in those states. When the Fitbit data were included in flu-intensity prediction models, correlations of the final models with the actual Centers for Disease Control and Prevention (CDC) influenza rates were excellent (0.97).

In the ongoing novel coronavirus (COVID-19) pandemic, human mobility studies have shown that aggregate and anonymized mobile phone location data can assist the modeling of the geographical spread of epidemics.[71] Digital contact-tracing technologies have also been deployed, such as Korea's smartphone app Corona 100m and Singapore's TraceTogether.[71]

Data quality issues

Despite the promise of these evolving technologies, the accuracy, usability, and robustness of these relatively novel sources of RWD need to be established, especially for acceptance of data collected in this way for regulatory or reimbursement purposes.

Table 3.5. Pros and cons of wearables and person-generated health data

Wearables and personal trackers: Pros	Wearables and personal trackers: Cons
• Routine collection of objective real-world data on the impact of an intervention, from individuals during their everyday life • Scalable data collection and extensive reach • Reduced barriers to participation • Lower costs than manual data collection	• Lack of completeness of data when patients fail to consistently wear, charge or sync a device • Accuracy, usability, and robustness needs to be established • Generalizability of data from persons who have or wear these devices compared to those who do not • Various law implemented by national and state governments to protect data collected through apps and sensors, which could affect information on data provenance

How are PGHD used in drug reimbursement decisions in Asia?

The use of PGHD to inform reimbursement decision remains uncommon worldwide. Effort is required to explore ways to protect patient privacy and need for additional regulatory approval for wearables data collection. In Japan, wearable devices for fall prevention among elderly people have been introduced.[72] While still a private sector service, it has potential to be reimbursed in the public through Long-term Care Insurance due to the care needs of a rapidly aging Japanese population.

Box 3.6. Good practices when collecting data using personal tracking devices

PGHD is an emerging field with massive data volume collected through a constantly increasing number of devices, apps, and websites. Lack of standard data definitions or formats and data validation are key challenges. Several sets of recommendations have been made for quality PGHD data collection. For instance, biostatisticians and relevant data scientists should be involved in all decisions involving protocol design and collection.[73] Only a minimum set of necessary data that can address the study endpoints should be collected, and the protocol should include strategies to monitor and optimize data quality. Devices and wearables should have suitable measurement properties that can measure the concept of interest in the target population. Hence, verification and validation checks of tools related to PGHD collection focus on establishing content validity, intra-device and inter-device reliability, concurrent validity, responsiveness of data, usability of device, and interpretability.[74]

For further reading, see:

- The Clinical Trials Transformation Initiative (CTTI) Mobile Clinical Trials Program: Advancing the Use of Mobile Technologies for Data Capture and Improved Clinical Trials[73]
- Duke Margolis RWE Collaborative RWD Quality Working Group: Determining Real-World Data's Fitness for Use and the Role of Reliability, Chapter 3[62]
- Critical Path Institute's Electronic Patient-Reported Outcome (ePRO) Consortium: Selection of and Evidentiary Considerations for Wearable Devices and their Measurements for Use in Regulatory Decision Making[74]

3.2.6. Prioritization of RWD variables in the local setting

Many health systems in Asia face challenges in collecting RWD due to the lack of infrastructure and human capacity to support data collection; lack of clinician, institutional or legislative support for data collection; and lack of experience in its quality assessment and assurance. The working group agrees that RWE should be considered as supplementary evidence and is unlikely to replace evidence generated from clinical trials for reimbursement decisions. While the preceding sub-sections have discussed what RWD to collect and where to collect, not all RWD is feasible to collect in each local context, therefore, data collection efforts are likely to be more targeted to address specific research needs in each country. The REALISE working group was surveyed on the top locally-collected variables that their countries would prioritize over regional or international data. Overall, variables with high uncertainty or that are key drivers of cost effectiveness (such as costs and epidemiological data) are typically collected in the local context. Survey findings are presented in Table 3.6.

Table 3.6. Prioritization of RWD variables in reimbursement decisions for REALISE members

RWD variables	Q1. Top 5 variables preferred not to be taken from Europe, US, and outside of Asia (We would like to know which *region-specific* data are acceptable to you)	Q2. Top 3 variables preferred not to be taken from Europe, US, and Asia (We would like to know which *country-specific* data are most important to you)
Population characteristics	IN5, KR, TL	KR, MY, SG, TW3
Intervention and control	IN4, JP, MY, TL, TW(I)	TL, TW3(C)
Outcomes – Effectiveness	MY, SG, TW	
Outcomes – Patient reported outcomes (PROs)	JP, KR, MY, SG, TL, TW	JP, KR, TL
Outcomes – Safety	JP, MY, SG, TL, TW	JP
Outcomes – Cost	IN1, KR, TL	IN1, JP, KR, MY, SG, TL, TW1
Epidemiological	IN2, KR, SG	IN2, KR, MY, SG, TW2
Adherence	IN3, KR, MY	IN3, KR, TW3

Notes:

- IN: India, JP: Japan, KR: South Korea, MY: Malaysia, SG: Singapore, TL: Thailand, TW: Taiwan. Some countries responded with variables in ranked order, indicated by numbers after their country code.
- In Japan, the official guideline does not give any clear restriction on using international data. Japan does not differentiate between regions and treats all other countries as international data.
- In Korea, Top 5 cannot be reduced to Top 3 as all five are necessary.
- In Singapore, regional/international data is acceptable to inform Singapore's HTA if it is considered generalizable to the local context. Collection of local data is not mandatory and is not required in most instances except for local costs because Singapore is a small country and there is limited incentive for companies to collect local data when patient populations are small. Local comparators may differ from comparisons in the trial, therefore indirect comparison may be required. Local epidemiological data/drug utilization patterns etc. may be collected by the HTA agency (ACE) to validate clinical trials and demonstrate whether they are generalizable to the local setting.
- In Thailand, local data is preferred if available. There are exceptions.

3.2.7. RWD sources for key RWD types

Table 3.7 summarizes the link between common RWD types (3.6) and their sources (3.2). For the interested reader, a list of real-world data sources available in Asia is provided in Appendix 8.1.

Table 3.7. RWD sources for common RWD types. Shaded areas indicate sources that could be used for given types of RWD.

What? RWD type (2.2)	Where? Source (2.3)				
	Disease and other registries	Claims databases	Health surveys	Electronic medical records	Wearables, personal tracking
Population characteristics	IN, JP, MY, SG, TH, TW	IN, JP, KR, MY, SG, TH, TW	IN, JP, KR, MY, SG, TH, TW	IN, JP, MY, SG, TH, TW	IN, JP, MY, SG, TW
Intervention and control	IN, JP, KR, MY, SG, TH, TW	IN, JP, KR, MY, SG, TH, TW	TH	IN, JP, KR, MY, SG, TH, TW	IN, JP, MY, SG, TW
Outcomes – Effectiveness	IN, JP, KR, MY, SG, TH, TW	IN, JP, KR, MY, SG, TH, TW	TH	IN, JP, KR, MY, SG, TH, TW	IN, JP, MY, SG, TW
Outcomes – Patient reported outcomes (PROs)	IN, JP, KR, MY, SG, TH, TW		IN, JP, KR, MY, SG, TH, TW	TH	IN, JP, MY, SG, TW
Outcomes – Safety	IN, JP, KR, MY, SG, TH, TW	IN, KR, MY, SG, TH, TW	TH	IN, JP, KR, MY, SG, TH, TW	TW
Outcomes – Cost		IN, JP, KR, MY, SG, TH, TW	KR, TH	IN, JP, KR, MY, SG, TW	
Epidemiological	IN, JP, KR, MY, SG, TH, TW	IN, JP, KR, MY, SG, TH, TW	IN, JP, KR, MY, SG, TH, TW	IN, JP, KR, MY, SG, TH, TW	TW
Adherence	TH, TW	IN, JP, KR, MY, SG, TH, TW	IN, JP, KR, MY, SG, TH	IN, JP, KR, MY, SG, TH, TW	IN, JP, MY, SG, TW

Notes:

- IN: India, JP: Japan, KR: South Korea, MY: Malaysia, SG: Singapore, TH: Thailand, TW: Taiwan.
- In Thailand, the above are just the common sources of RWD. Besides claims, databases may include other types of administrative databases (e.g. special health promotion and prevention databases, chronic diseases databases).

3.3. Who to collect? Governance and accountability considerations for country adaptation

Box 3.7. Case study: Taiwan's National Health Insurance Research Database

The Taiwan National Health Insurance (NHI) Research Database covers more than 23 million residents (99.9% of the population) and is one of the largest nationwide population databases in the world. In 1995, a single-payer National Health Insurance plan was established by the government to provide Universal Health Coverage for its population.[75 76] This system's claims data are released as the National Health Insurance Research Database (NHIRD), and all data from primary outpatient departments and inpatient hospital care settings after 2000 are included. Some civil groups have filed lawsuits against the use of the NHIRD by the Ministry of Health and Welfare (MOHW) due to data privacy concerns, which led to the setup of the Health and Welfare Data Center (HWDC) to further strengthen the protection of health data. HWDC is a data repository that centralizes the NHIRD and other health-related databases. Cross-linkage of registries is comprehensive and linked to national surveys. Researchers and government alike are aligned in recognizing the utility of real-world health data as practical tools in medical research. Access can be granted to anyone conditional upon prior approval of the research or industry-sponsored project by an Institutional Review Board (IRB).[76] Safeguards to data privacy include deidentified datasets only accessible on-site, having statistical analysis syntax reviewed before access, and analyzed results examined before data export. There are no known NHIRD data breaches or leaks to date. [75]

The challenges of RWD collection in many countries extend beyond study design and data quality. Also relevant are issues of access and linkage involving data security, permissions from populations and database owners, and multiple stakeholders. Although the extensiveness and quality of Taiwan's database can answer a wide variety of research questions, not all in Taiwan are supportive of use of their personal information (Box 3.7) due to data privacy concerns, which led to the setup of the Health and Welfare Data Center (HWDC) to further strengthen the protection of health data.[75 76] Taiwanese patients cannot opt out of inclusion in the database and this requirement is currently under review. This makes a strong case for the need to recognize that the standards and enforcement of privacy protection laws are country dependent. South Korea has some of the strongest data privacy laws in Asia, covering a person's image or voice, and linkage of health data is prohibited or limited to government operational purposes. Other countries may prefer an opt-in health records system.

Decisions made about the use, sharing, and re-use of RWD data are complex and laden with values. Interested individuals may refer to the Ethics Framework for Big Data in Health and Research (the 'Framework') for further consideration. The Framework, developed by the SHAPES initiative[77], describes ethical considerations underpinning decisions related to the use of big data, including the use of RWD to generate evidence about healthcare interventions[78]. It aims to support decision-makers to identify underlying values that should be taken into consideration by articulating and describing a set of substantive and procedural values that are relevant to the use of big data. Other key components of the Framework include:

• the articulation of three broader considerations that influence decisions made using the Framework*: respect for persons*, *social licence*, *and issues of vulnerability and power*; and

• a six-step deliberative balancing process which aims to guide users' thinking during decision-making, the most challenging aspect of which is weighing up values which conflict with each other to reach a consensus decision.

As the issues related to governance and ethics are contextual, the working group encourages consideration of the following questions in the local adaptation of recommendations for data collection, including:[79]

- Which stakeholders are responsible for RWD collection, for which RWD source?
- Who bears the cost of RWD collection?
- Who manages and controls access to RWD?
- Who approves the ethics for research conduct, and who protects the privacy of RWD?
- Who can have access to RWD?
- What is the public's opinion on the use of their medical records for reimbursement and reassessment purposes?
- What is the impact of not granting access of these data for research purposes?

3.4. Conclusion: General recommendations to improve RWD collection

3.4.1. Standardization of RWD variables between sources

Improvements to the collection and potential standardization of RWD variables will encourage further applications of RWE in reimbursement decision making. RWD format, completeness, and quality across registries, EMR vendors, and healthcare providers can vary significantly, and appropriate curation and validation are needed. In Malaysia, the Ministry of Health has initiated the Telemedicine Blueprint in 1996 and established National Health Data Dictionary to promote health information management and standardize health information in the country. Its terminology provides a common language that enables a consistent way of indexing, storing, retrieving, and aggregating clinical data across specialties and care settings. Thereafter, the Malaysian Health Data Warehouse Project in 2010 acts as a platform for the standardization and integration of health data from a variety of sources to better manage the health system, provide surveillance information and in addition provide a valuable source of data for research. The project is integrated into the ICT Strategic Plan in 2019. Taiwan has also set up the EMR Exchange Center (EEC) as an EMR gateway to facilitate the exchange of EMRs between different hospitals to avoid duplicating medications or examinations. Patients' informed consent are required to exchange the EMR. By the end of 2015, more than 80% of hospitals or clinics provide EMR exchange service through EEC.

Common data models that determine data fields of relevant capture can be implemented within specific disease areas to establish a broader consistency in data capture across providers and databases. An example of this is ASCO's CancerLinQ, which uses the National Cancer Institute (NCI) Metathesaurus and other vocabularies.[80] CancerLinQ aggregates data from EMRs through direct feeds and processes it through a series of transformations to standardize data elements across EMR systems.[81] Taiwan has also built common data models for collecting the clinical health information from clinical visits, discharge notes, surgery, pathology, examinations, blood tests, medical images, etc. The EEC and common data models are used as platforms for exchanging EMR and do not directly serve as sources of RWD. In Asia, national standardization of RWD can and should be an important consideration among countries that are already making plans for country-wide EMR systems (e.g. Bhutan, China).

3.4.2. Assess the costs and benefits of data collection

Evidence costs money. There are concerns in every resource constrained setting about whether the resources dedicated to an effort will be worthwhile. There is a need to prioritize RWD such that the

benefits of collecting additional information can be expected to outweigh the costs. In Asian settings where data can be fragmented and incomplete, balance should be struck between the relevance of a new registry (or any other data) in relation to the burden of collection. The 'value-of-information (VOI) analysis' framework offers one approach to decision making, for when and what types of data to collect (see Box 3.8, for an example of VOI analysis in Thailand for coverage decision-making).[82] Decision analysis and VOI analysis provide information on whether an intervention should be adopted, whether it is worthwhile gathering additional evidence to further inform that decision, and what kinds of information is of most value to collect. The analysis evaluates the extent to which new evidence might improve expected benefits by reducing the chance for error and compares that improvement to the cost of the information.[9]

Box 3.8. Example of VOI analysis: Expected value of perfect information in palliative management vs peritoneal dialysis and hemodialysis for End Stage Renal Disease coverage decisions in Thailand

A study by Teerawattananon et al. examined the value for money of including peritoneal dialysis (PD) or hemodialysis (HD) for coverage in the universal health insurance scheme.[83] The results indicated that the government should not include dialysis services unless the social willingness to pay increases three times higher (700-750,000 Baht per QALY) than recommended by the commission on Microeconomics and Health. With uncertainty around input parameters of alternative treatment modalities, Figure 3.1 shows the expected opportunity loss of making a wrong decision for patients aged 50. The overall expected value of perfect information (EVPI) of treating 10,000 new ESRD cases per year and for a 10-year time period was highest (260,000 million Baht) at a ceiling ratio of 650,000 Baht per QALY.

The study also explored the effects of uncertainty around input parameters by looking at the value of obtaining further information on chosen parameters (partial EVPI) (Figure 3.2). Among the parameters, cost of PD and HD had the highest partial EVPIs.

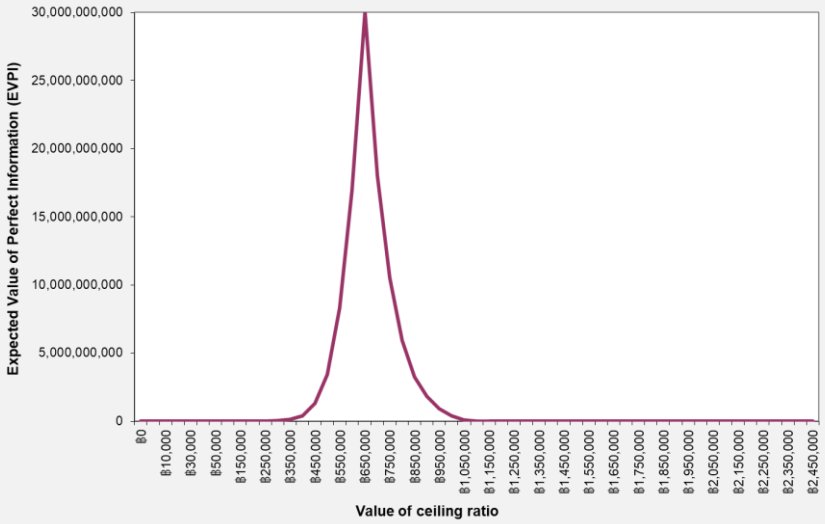

Figure 3.1. Population EVPI for a model using the 50 years age group

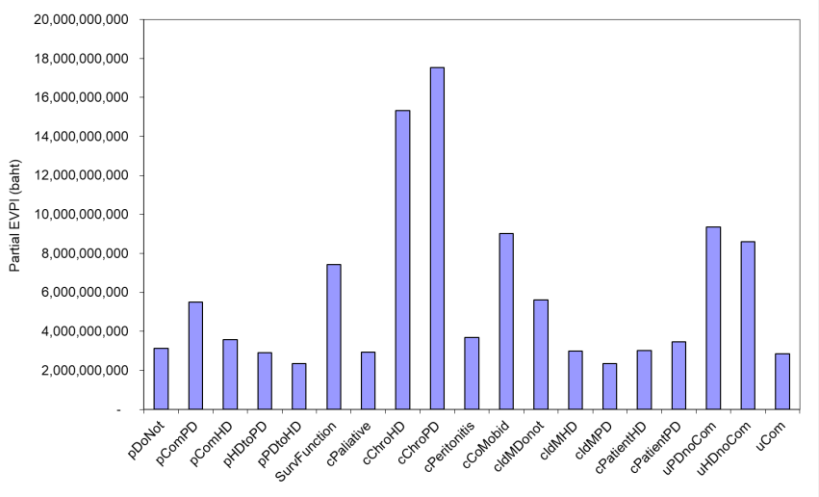

Figure 3.2. EVPI for input parameters. cChroHD: health care cost of HD, cChroPD: cost of PD

3.4.3. Develop incentives for quality capture of RWD

Incentives need to be developed for physicians and other providers, health care systems, payers, and patients to become invested stakeholders in the development and use of RWD and RWE.[84] These include financial incentives from public and private insurance payers for quicker processing of reimbursement claims if accurate data are captured by the EMRs;[85] for hospitals if they submit laboratory and test results efficiently; for reporting on patient outcomes; providing RWD for studies; and for further adoption of payments based on outcomes. In Korea, public funding for clinical research can be used to collect RWE such as pragmatic clinical trials / prospective cohort / retrospective cohort and others. NECA (Korea) manages US$20 million of research funding each year for extramural clinical research helpful from the public perspective.

Non-financial incentives include ensuring that RWD meets research needs and have clear value for those who collect them. The burden of RWD collection should be reduced by choosing meaningful RWD elements required for collection and that can be easily integrated into the workflow, thereby reducing errors due to time and resource constraints at the point of care. Clinicians must be convinced of the importance of the collected RWD in benefiting their patients and the delivery of clinical care.

3.4.4. Increase credibility of RWE relevant study designs (observational studies, PrCTs)

While many may perceive observational approaches as lacking credibility, researchers can exercise greater caution to overcome these concerns and improve the overall rigor of such studies. The use of checklists for good reporting practices is strongly encouraged (e.g. STROBE, RECORD for observational studies), and submission of completed checklists is now required by some journals to validate manuscripts. Another way to increase credibility is by publishing detailed protocols of real-world studies in a public and online repository (as has been done for clinical trials, on ClinicalTrials.gov). This will enable researchers to see the study population, exposure and outcome variables, other key covariates, and the analysis plan that will be utilized before the study begins and can increase the validity of study results by ensuring that decisions made during the study process are not arbitrary, and that no data was mined to produce consequent study findings.[4] Study registration, particularly for RWD studies intended to formally test hypotheses around comparative effectiveness, has been proposed by a ISPOR and ISPE (International Society for Pharmacoepidemiology) joint task force to improve transparency

and trust in RWE.[2] A public record encourages careful deliberation and accountability. Some observational studies have been registered on ClinicalTrials.gov, but not without some difficulty as the site is designed for RCTs.[4] One suggestion is to establish an online repository specific to RWE relevant study designs that an international audience can access. Comprehensive published protocols also allow for replication, where similar conclusions are derived from different data or with different analytical methods.

3.4.5. Balance patient data privacy protections and RWD as public good

Any consideration of patient medical records as a public good calls into question the safety and security of individual data. Data privacy laws are enforced to varying degrees in Asian countries, from requiring individual patient consent for every real-world study in South Korea, to permitted usage of de-identified and anonymized patient data in Taiwan and Singapore. Given that Japan is extremely conservative about data sharing, the process of anonymization before data can be shared with researchers or policymakers (e.g. the degree of disaggregation of registry data that is required before sharing) is an area of significant concern. We recommend that individual countries comply with their own countries' guidelines but at the same time, to promote active discussion of the tensions between access to RWD while ensuring adequate data protection, in order to arrive at a compromise between two needs. Block chain technology can be considered to link up patient consent such that it is required only once. In South Korea, a privacy law was passed in 2012 that prohibits the linkage of data but permits government agencies to link limited data for their operational purposes.[86] This challenge of data privacy is mitigated in Korea by allowing researchers or industry to purchase anonymized sample claims datasets, and by amendments to data privacy laws for allowing more flexibility in using deidentified health data generated from hospitals. It is also possible to apply masking techniques to create a synthetic dataset that replicates the key information needed for the specific research or policy question.[87] The Centers for Medicare and Medicaid Services (CMS) Data Entrepreneurs' Synthetic Public Use File (DE-SynPUF) is an example of a synthetic claims database which reflects real patient data but in a format that protects patients' identities so that the data can be used to train individuals in the appropriate use of claims data.[87]

4 Conclusion and moving forward

We conclude by affirming the need for better quality RWD and RWE to inform HTA in Asia. There are several opportunities to use RWD/RWE that can provide clear advantages for understanding outcomes of drug therapies in the real-world setting, especially in diseases areas involving diverse patients whose treatment regimens and clinical needs are not driven by trial protocols. Many RWD sources can contribute to RWE efforts but steps for mitigating erroneous data, standardizing its collection, and ensuring quality management/assurance will need to be developed and applied across efforts in the Asian setting. A summary of recommendations can be found below:

Table 4.1. Summary of recommendations

Theme one

Recommendations on when to use RWD/RWE:

1. Consider RWD/RWE when RCTs are of poor quality, or impossible to conduct for ethical reasons or due to small numbers (e.g. for rare diseases)
2. Consider use of RWD/RWE to contextualize and localize economic models, extrapolate RCT data beyond trials, and for price negotiations based on real world outcomes
3. Note that RWD and RWE is generalizable to routine clinical practice only if the data represents the target clinical population reflective of the local context

Theme two

Recommendations on where to collect:

1. Deliberate over the benefits and limitations of various sources in the local context, such as product or disease registries, claims databases, electronic medical records (EMRs), health surveys, or use of daily wearables and personal tracking devices.
2. Understand the potential reimbursement questions that may or may not be answerable because of the availability, access, and quality of the RWD sources. It may require integrating sources and leveraging the strengths of each

Recommendations on who to collect:

1. Consider data governance and accountability in your local context, e.g. which stakeholders are responsible for RWD collection, who bears the cost of RWD collection, who manages and controls access to RWD, and who can access the data

Recommendations on improving the process of RWD collection:

1. Standardize RWD variables between sources
2. Assess the costs and benefits of data collection
3. Develop incentives for quality capture of RWD
4. Increase credibility of RWE relevant study designs
5. Balance patient data privacy protections and RWD as public good

The aim of this guidance is to provide a framework for anyone involved in HTA in Asia to generate and use RWD/RWE and improve the quality of such evidence when used to inform reimbursement activities. Recommendations from this guidance may be useful for some countries to include in their local HTA methods and process guidelines to clearly explain the role of RWD/RWE in informing HTAs. As noted by the ISPOR-ISPE 2017 special task force, the involvement of key stakeholders (e.g., patients, clinicians, clinical administrators, HTA/payers, regulators, and manufacturers) would be meaningful in designing, conducting, and disseminating RWD research. The key to optimal uptake of RWE is transparency of the

research process to enable decision-makers to evaluate the quality of the methods used and the applicability of the evidence that results from the RWE studies. It is important to promote transparent and honest dialogue among stakeholders regarding the use of RWD/RWE, and to have commitment from research funders as well as providers and professional associations at all levels (national and regional) to support the development of infrastructure for collecting and analyzing RWD in the region.

Therefore, this abridged report has been developed with policy- and decision-makers, industry, patient groups and other users of HTA in mind, to address the concerns of different audiences in the conversation who may have different expectations and needs.

While this guidance attempts to be as comprehensive as possible, there are other aspects of RWD use that we have not covered in detail. For example, in reimbursement for medical devices and companion diagnostics. These topics may be considered in future work of the REALISE working group. Experiences of the REALISE working group members in using this guidance will also be documented so that future updates of this guidance document will reflect the feasibility and outcomes of our recommendations.

Figure 4.1. REALISE guidance document infographic

5 About the REALISE Working Group

5.1. The REALISE Working Group: Who are we?

A collaboration between global experts and leaders from health technology assessment (HTA) agencies in Asia, the **REAL** World Data **I**n A**S**ia for H**E**alth Technology Assessment in Reimbursement (**REALISE**) working group seeks to develop non-binding guidance that will provide a framework to generate and use real-world data (RWD) / real-world evidence (RWE) in a consistent and efficient manner for decision-making in Asia. The acronym REALISE signifies our desire to realize ('to cause to happen or to facilitate') the potential of RWD/RWE while realizing ('being aware of') its strengths and limitations. The issues addressed in the guidance document include but are not limited to: (a) When is it appropriate to consider RWD/RWE for reimbursement decisions?; (b) What types of RWD should we collect?; (c) What are the data sources for collecting RWD?; (d) How should we collect RWD?; (e) Who should collect RWD?; (f) How will RWD be used to generate RWE?; (g) How should we use RWE in decision making?; (h) What are the potential biases and how to deal with these biases?; and (i) What are the ethical considerations in collecting RWD and generating RWE?

5.1.1. Scope and position

The REALISE working group regards RWD and RWE as complementary to RCT, the current gold standard for generating evidence on treatment efficacy.

The approach for this guidance document, given the interest area and experience of the REALISE working group, is to focus on the use of RWD and RWE to inform drug assessments. Other technologies where HTA is applicable, such as medical devices or companion diagnostics, are not covered by this guidance. This document, which is the beginning of a series of projects the REALISE working group will be undertaking is intended to be a living document that will be updated over time as new approaches to optimize the generation and use of RWD and RWE emerge.

5.1.2. Organizational structure

The REALISE working group comprises three subgroups: the (a) International Advisory Panel (IAP), (b) HTAsiaLink working group, and (c) Core Team. The IAP are prominent experts from leading HTA organizations in Australia, Canada, the UK and the US, where the use of RWD/RWE in HTA is already established. They provide guidance on how RWD/RWE are collected, analyzed and assessed in their countries. The HTAsiaLink working group includes representatives from 11 Asian health systems (Bhutan, China, India, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan and Thailand), who share their experiences and perspectives on opportunities and challenges in using RWD/RWE in their local contexts. The core team comprises staff from Saw Swee Hock School of Public Health (SSHSPH), National University of Singapore (NUS), and Health Intervention and Technology Assessment Program (HITAP), Ministry of Health, Thailand. Figure 5.1 shows the organizational chart of the WG.

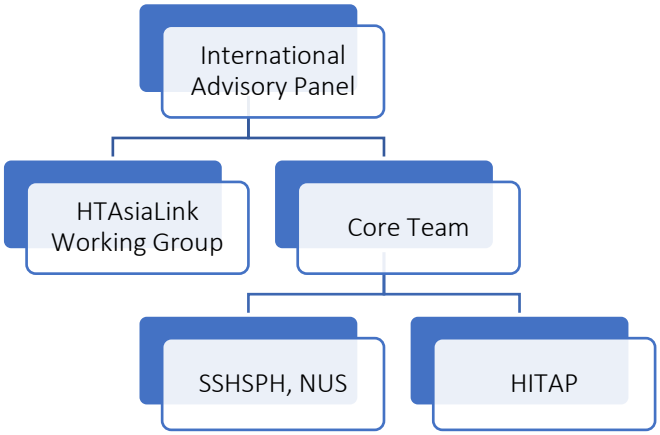

Figure 5.1. REALISE organizational chart

5.1.3. Grant information

This work is supported by an unrestricted grant from The International Decision Support Initiative (iDSI, www.idsihealth.org), a global network of health, policy and economic expertise, working to achieve Universal Health Coverage and the health Sustainable Development Goal (SDG 3), and which supports countries to get the best value for money from healthy spending. iDSI receives funding support from the Bill & Melinda Gates Foundation, the UK Department for International Development, and the Rockefeller Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The findings, interpretations and conclusions expressed in this document do not necessarily reflect the views of the aforementioned funding agencies.

5.2. Content development: How were the contents of this guidance document developed?

In preparing this guidance document, we supplemented a review of the literature with in-person meetings, stakeholder surveys, interviews with country representatives, and teleconferences with the working group representatives. A draft guidance was launched online for public feedback between 1st to 31st October 2020, and revisions integrated into this version of the document.

The literature review was designed to be pragmatic rather than exhaustive, and was used to identify key papers and examples for illustration, rather than to identify all papers on RWD/RWE. The working group had two in-person meetings to deliberate on the scope and content for the document; the first meeting was in April 2019 following the 8th HTAsiaLink conference and the second meeting was a 2-day symposium in Singapore in October 2019. A survey circulated to REALISE members focused on: (a) background of respondent; (b) current practice with regards to the use of RWD/RWE for HTA for reimbursement decisions; (c) current practice with regards to pragmatic clinical trials; (d) challenges encountered in RWD/RWE generation; and (e) availability of a local guidance document on RWD/RWE generation. Working group members were also invited for an hour-long interview to understand the health care context in their individual countries and how RWD is collected and used, with 8 countries interviewed in 2019. Regular teleconferences for the collective group were held to gather opinions on the document and also individually on select topics (e.g. to obtain country examples, consult on specific themes of the document, etc.).

6 Glossary of terms and list of abbreviations

6.1. Glossary

Accuracy: In the context of a study, the quality of a measurement (e.g. the mean estimate of a treatment effect) that is correct or that reflects the actual effectiveness of the treatment.[3]

Clinical effectiveness: The benefit of using a technology, program or intervention to address a specific problem under general or routine conditions, rather than under controlled conditions, for example, by a physician in a hospital or by a patient at home.[3]

Confounding: A mixing of effects between the treatment group and external factors that may also influence the outcome, potentially obscuring or distorting the relationship that can be inferred. These factors that influence the association between a treatment and the effect may either be known or unknown.[43]

Economic evaluation: The comparative analysis of the costs and consequences of two or more possible options. Depending on whether the consequences are expressed as monetary, physical or qualitative variables, the analysis may be a cost-benefit, cost-effectiveness or cost-utility analysis.[3]

Efficacy: The benefit of using a technology, program or intervention to treat a particular problem under ideal conditions—for example, in the context of research in a laboratory or a rigorous protocol for a randomized clinical trial.[3]

Efficacy-effectiveness gap: The difference in benefit–risk between effectiveness and efficacy.[3]

External validity: The ability of a research design to provide findings that can be generalized to other populations, contexts and periods.[3]

Health-related quality of life: The measures of the impact of an intervention on patients' health status, extending beyond the traditional measures of mortality and morbidity to include dimensions such as physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception and general life satisfaction.[3]

Health technology assessment: The systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies. HTA is conducted by interdisciplinary groups that use explicit analytical frameworks drawing on a variety of methods.[3]

Medication possession ratio: The sum of the days' supply for all fills of a given drug for a specified time period divided by the number of days in the period.[88]

National Health Insurance Research Database, Taiwan: One of the largest nationwide population databases in the world, covering approximately 23 million residents in Taiwan. The NHI program was established in 1995 to deliver universal coverage provided by a government-run, single-payer compulsory insurance plan, covering more than 99.9% of the population. This system's claims data are released as the National Health Insurance Research Database (NHIRD), and all data from primary outpatient departments and inpatient hospital care settings after 2000 are included. The Health and Welfare Data Center (HWDC) was set up by the Ministry of Health and Welfare (MOHW) to further strengthen the protection of health data. HWDC is a data repository that centralizes the NHIRD and

other health-related databases. Cross-linkage of registries is comprehensive and linked to national surveys.[76]

Observational studies: A study in which the investigators do not intervene, but only observe subjects who are (and sometimes who are not, for comparison purposes) exposed to a given factor, and interpret the outcomes. This type of study is more subject to bias than is an experimental study such as a randomized controlled trial.[3]

Orphan drug: A drug used to treat, prevent, or diagnose an orphan disease.[89]

Pharmacovigilance: The pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products.[90]

Pragmatic trials: A trial that measures the effects of an intervention in routine clinical practice, to evaluate the intervention's actual effectiveness.[3]

REALISE: A working group comprising the (a) International Advisory Panel (IAP), (b) HTAsiaLink working group, and (c) Core Team. The IAP are prominent experts from leading HTA organizations in Australia, Canada, the UK and the US. The HTAsiaLink working group includes representatives from 11 Asian health systems (Bhutan, China, India, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan and Thailand). The core team comprises staff from Saw Swee Hock School of Public Health (SSHSPH), National University of Singapore (NUS), and Health Intervention and Technology Assessment Program (HITAP), Ministry of Health, Thailand.

Real-world data: Data collected during the routine delivery of health care. Sources may include observational data, administrative data, research data, patient-generated data or professional-generated data. These data may be collected in administrative datasets, case notes, surveys, product and disease registries, social media, electronic health records, claims and billing datasets, or mobile health applications.[3]

Real-world evidence: Evidence derived from the analysis of real-world data. Real world data are primarily analyzed through observational study designs. Real world evidence is characterized by the actual use of the technology in practice and by findings that are generalizable to the target population for the technology.[3]

Single arm trials: An analysis or evaluation of a study with only one branch, i.e. a trial in which there was no parallel comparison group and all the subjects received the same intervention.[91]

Surrogate endpoint: An indicator that, while not being of direct interest for the patient, may reflect important outcomes. For example, blood pressure is not of direct clinical interest to the patient, but is often used as an evaluation criterion in clinical trials because it is a risk factor for stroke and heart attacks.[3]

US Food and Drug Administration and EU European Medicines Agency: Regulators that are responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices[92]

Validity: The ability of a measurement or a study to estimate the true value free of systematic errors (bias).[3]

6.2. Abbreviations

AD	Aggregate data
ADE	Adverse drug event
CEA	Cost effectiveness analysis
CUA	Cost utility analysis
CTTI	Clinical Trials Transformation Initiative (US)
EE	Economic evaluation
EMR	Electronic medical records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration (US)
HIRA	Health Insurance Review and Assessment Service (Korea)
HITAP	Health Intervention and Technology Assessment Program (Thailand)
HPV	Human papillomavirus
HRQoL	Health-related quality of life
HMIS	Health Management and Information System (Bhutan)
HTA	Health technology assessment
HWDC	Health and Welfare Data Center (Taiwan)
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Individual patient-level data
IPW	Inverse probability weights
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	Instrumental variable
KCDC	Korea Centers for Disease Control and Prevention
MDS	Myelodysplastic syndrome
MES	Managed entry scheme
MI	Multiple imputation
MPR	Medication possession ratio
MSAC	Medical Services Advisory Committee (Australia)
NBR	Net-benefit regression
NCSP	National Cervical Cancer Screening Program (Australia)

NHIRD	National Health Insurance Research Database (Taiwan)
NICE	National Institute for Health and Care Excellence (UK)
NKTI	National Kidney and Transplant Institute (Philippines)
NSCLC	Non-small cell lung cancer
NSSO	National Sample Survey Office (India)
OS	Overall survival
OSCCD	Ontario Steering Committee for Cancer Drugs
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PCV	Pneumococcal conjugate vaccine
PFS	Progression free survival
PGHD	Person-generated health data
PICO	Patient, Intervention, Comparators and Outcomes (framework)
PRO	Patient reported outcomes
PrCT	Pragmatic clinical trial
PSA	Prostate Specific Antigen
PSM	Propensity score matching
QALY	Quality-adjusted life year
REALISE	REAL World Data In ASia for HEalth Technology Assessment in Reimbursement
RCT	Randomized clinical trial
RWD	Real-world data
RWE	Real-world evidence
SDG	Sustainable Development Goal
SEER	Surveillance, Epidemiology, and End Results database (US)
VOI	Value of information (analysis)
WHO INTDIS	World Health Organization International Drug Information System

7 References

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8 Appendix

8.1. List of real-world data sources available in Asia (non-exhaustive)

Table 8.1. Adapted from: Milea et al.[93] RWD sources supplemented by the REALISE guidance authors.

Country / RWD source	RWD source
Bhutan	
• Bhutan cancer Registry	Registry
• DHIS-2 (District Health Information System)	EMR
• Mother and Child Health tracking system	EMR
• Lab Information system	EMR
• e-BMSIS (Electronic Bhutan Medical Supplies Inventory System)	EMR
China	
• Zhongnan Hospital	EMR
• West China Hospital	EMR
• Jinhua Municipal Central Hospital database	EMR
• The 306th Hospital of PLA, Beijing	EMR
• Chinese People's liberation army general hospital database	EMR
• Soochow University Affiliates Children's Hospital database	EMR
• Urban Employee Basic Medical Insurance database (UEBMI) (Tianjin)	Claims database
• UEBMI (Guangzhou)	Claims database
• UEBMI (Hebei)	Claims database
• Urban Resident Basic Medical Insurance database (URBMI) (Guangzhou)	Claims database
• China Health Insurance Research Association (CHIRA) database	Claims database
• Zhongshan Hospital	EMR
• New Rural Cooperative Medical Scheme (NRCMS)	Claims database
• Electronic Health Records (EHR) system - Minhang, Shanghai	EMR
• Guangzhao Psychiatric Hospital	EMR
India	
• National Health System Cost Database	Claims database
Japan	
• Convergence CT Global Research Network (CGRN)	EMR
• Medical Data Vision (MDV) EBM Provider	Hospital administration

• Hamamatsu Medical University Database	EMR
• Osaka University Database Computer Operating System Database Dokkyo Medical University	EMR
• EMR Retrieval System-Kyoto University Hospital	EMR
• Nihon University School of Medicine Clinical Data Warehouse	EMR
• Japan Medical Data Centre (JMDC) Claims database	Claims database
• JammNet	Claims database
• Diagnosis Procedure Code Database	EMR
• NHI Database	Claims database
• Medi-Trend	Prescription
• Nihon-Chouzai Pharmacy Claim Database	Prescription
• JMIRI Pharmacy Claims Database	Prescription
• Long term care insurance (Kaigo Hoken)	Claims database
Malaysia	
• United Nations University (UNU)-Casemix database	Hospital administration (discharge records)
• Electronic Health Management Information System	Hospital administration
• Acute Stroke Registry Malaysia	Registry
• Malaysian Thalassaemia Registry	Registry
• National Dermatology Registry	Registry
• Malaysian Gastrointestinal Registry	Registry
• Malaysian National Neonatal Registry	Registry
• National Cardiovascular Disease Database	Registry
• National Cancer Patient Registry	Registry
• National Cardiovascular and thoracic surgical database	Registry
• National Eye Database	Registry
• National Inflammatory Arthritis Registry	Registry
• National Neurology Registry	Registry
• National Obstetrics Registry (NOR) Malaysia	Registry
• National Renal Registry	Registry
• Malaysian Registry of Renal Biopsy	Registry
• National Transplant Registry	Registry
• National Trauma Database	Registry
• National Orthopaedic Registry Malaysia	Registry
• National Suicide Registry Malaysia	Registry
• Malaysian Registry of Intensive Care	Registry

Philippines	
• Philippine Health Insurance Corporation (PhilHealth) Claims Database	Claims database
• Philippine Health Insurance Corporation (PhilHealth) Cost Database for Z-Benefits	Claims database
• Philippine Integrated Disease Surveillance and Response (PIDSR)	Registry
• Philippine Renal Disease Registry (PRDR)	Registry
• Field Health Service Information System	Database
• National Injury Surveillance System	Database
Singapore	
• Casemix database	Hospital
• Medisave database	Claims database
• National Electronics Health Records Database	EMR
• National Immunization Registry	Registry
• Various condition-specific registries including Singapore Acute Myocardial Infarction Registry, Singapore Cancer Registry, Singapore Diabetes Registry, Singapore Stroke Registry, Singapore Renal Registry, etc.	Registry
South Korea	
• National Health Insurance Corporation (NHIC) database	Claims database
• Health Insurance Review and Assessment (HIRA) database	Claims database
• NCI Central Cancer Registry	Registry
• National Institute of Health Clinical Research Information System (CRIS)	Registry (only publicly funded research registries)
• All hospitals have EMR systems compliant to HL7 and connected with PACS and OCS for various research	EMR (with image data)
Taiwan	
• National Health Insurance (NHI) Database	Claims database
• NHI DAA-treated patients registry	Registry/Claims database
• NHI immune oncology drugs treated patient registry	Registry/Claims database
• Taiwan Cancer Registry	Registry
• Cancer screening registries	Registry
• Adult preventive health information file	Registry
• Rare disease data	Registry
• Data of genetic disease	Registry
• Notifiable disease dataset of confirmed cases	Registry
• Symptom Surveillance and Reporting System Database	Registry

• Infectious diseases database (tuberculosis, HIV/AIDS)	Registry
• Database of National Immunization Information System	Registry
• Birth certificate application	Registry
• Survey for three-hypers series	Health survey
• National Health Interview Survey	Health survey
• Chang Gung Research Database (CGRD)	EMR
• China Medical University Hospital Clinical Research Data Repository (CMUH-CRDR)	EMR
• National Taiwan University Hospital Integrated Health Care Information System (NTUH-IHIS)	EMR
• Taipei Medical University Healthcare System Clinical Data	EMR
• Taipei Veterans General Hospital Big Data Center (Taipei VGH BDC)	EMR
Thailand	
• Universal Coverage Scheme	Claims database
• Civil Servant Medical Benefits Scheme	Claims database
• Social Security Scheme	Claims database
• Ramathibodi Hospital Database	EMR
• Buddhachinaraj Hospital Database	EMR
• Sunpasitthiprasong Hospital	EMR
• Nakhon Thai Crown Prince Hospital	EMR